THE LANCET

Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Silverberg JI, Rosmarin D, Bieber T, et al. Rezpegaldesleukin treatment of moderate-to-severe atopic dermatitis (REZOLVE-AD): final results from the 16-week induction period of an international, double-blind, placebo-controlled, randomised phase 2b study. *Lancet* 2026; published online Aug 21. https://doi.org/10.1016/S0140-6736(26)01143-8.

Nektar Therapeutics

CLINICAL PROTOCOL

Protocol Number:	23-358-05
Title:	A Phase 2b, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rezpegaldesleukin in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis (REZOLVE-AD)
Protocol Amendment Number:	3.0 (Global)
Date:	06 June 2024
Supersedes:	Protocol Amendment 2.1 (European Union), dated 13 March 2024 Protocol Amendment 2.0, dated 27 September 2023 Protocol Amendment 1.0, dated 09 August 2023 Original Protocol, dated 31 May 2023
US IND No.:	143086
EU CT No.:	2023-507456-69-00
Investigational Product:	Rezpegaldesleukin
Indication:	Treatment of moderate to severe atopic dermatitis
Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA
Sponsor's Medical Contact and Study Medical Monitor:	PPD Nektar Therapeutics PPD

CONFIDENTIALITY STATEMENT

The confidential information in this document is provided to you as an Investigator or consultant for review by you, your staff, and the applicable Institutional Review Board/Independent Ethics Committee and applicable Regulatory Authorities. Your acceptance of this document constitutes agreement that you will not disclose the information herein to others without written authorization from Nektar Therapeutics except to the extent necessary to obtain informed consent from persons who participate as patients in this study.

PRINCIPAL INVESTIGATOR COMMITMENT

Protocol Number:	23-358-05
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Sponsor:	Nektar Therapeutics 455 Mission Bay Boulevard South San Francisco, CA 94158 USA

I, the undersigned Principal Investigator, submit this statement of commitment as evidence that I understand my responsibilities pursuant to the Code of Federal Regulations (21 CFR § 312) and ICH E6 Good Clinical Practice guidelines, as well as with any and all applicable federal, state and/or local laws and regulations, and agree to conduct the study in accordance with the protocol referenced herein.

_____ _____

Principal Investigator Signature **Date**

Printed Name: _____

Institution: _____

Address _____

PROTOCOL APPROVAL PAGE

Protocol Number:	23-358-05
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PPD

Signature

Printed Name:	PPD
Position:	PPD

LIST OF STUDY CONTACTS

PPD

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ACRONYMS AND ABBREVIATIONS

Abbreviation or Term	Definition
CCI	[redacted]
CCI	[redacted]
AD	atopic dermatitis
ADA	antidrug antibodies
ADCT	Atopic Dermatitis Control Tool
ADL	Activity of Daily Living
ADSS	Atopic Dermatitis Sleep Scale
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine transaminase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
anti-HCV	antibodies to HCV
APA	American Psychiatric Association
AST	aspartate transaminase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-}14\ day}$	area under the plasma concentration versus time curve from time zero to 14 days
BCG	Bacillus Calmette-Guerin
BSA	body surface area
CBD	cannabidiol
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum observed plasma concentration
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRS	cytokine release syndrome
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DCI	data collection instrument
DLQI	Dermatology Life Quality Index

Abbreviation or Term	Definition
DNA	deoxyribonucleic acid
DSC	Drug Safety Committee
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
EASI	Eczema Area and Severity Index
EASI-XX	patient's EASI is reduced by at least XX% relative to their baseline score
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCOA	electronic clinical outcomes assessments
eCRF	electronic case report form
ED	early discontinuation
eGFR	estimated glomerular filtration rate
ER	emergency room
ERCP	endoscopic retrograde cholangiopancreatography
FDA	Food and Drug Administration
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
CCI [redacted]	[redacted]
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRQoL	health-related quality of life
IB	investigator's brochure
ICE	intercurrent events
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IFN-γ	interferon gamma
IgA	immunoglobulin A
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug application
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
ISR	injection site reaction

Abbreviation or Term	Definition
ITT	intent-to-treat
IV	intravenous
JAK	Janus kinase
KFAC	Study J1P-MC-KFAC
KFAD	Study J1P-MC-KFAD
KFAI	Study J1P-MC-KFAI
KFAJ	Study J1P-MC-KFAJ
KFAL	Study J1P-MC-KFAL
KFAN	Study J1P-MC-KFAN
kg	kilogram
l or L	liter
LSMEAN	least squares mean
LTBI	latent tuberculosis infection
CCI	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MI	Multiple Imputation
min	minute(s)
mIU/mL	milli-international units per milliliter
mL	milliliter
MMRM	mixed models for repeated measures
MRCP	magnetic resonance cholangiopancreatography
µg	microgram
N/A	not applicable
nAb	neutralizing antibodies
NK	natural killer
NOAEL	no-observed-adverse-effect-level
NONMEM	nonlinear mixed effects modeling
NRS	numerical rating scale
PC	product complaint
PCR	polymerase chain reaction
PD	pharmacodynamic
PDE4	phosphodiesterase type 4
PEG	polyethylene glycol
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
POEM	Patient-Oriented Eczema Measure
PT	preferred term

Abbreviation or Term	Definition
q12w	every 12 weeks
q2w	every 2 weeks
q4w	every 4 weeks
QoL	quality of life
QTcF	corrected QT interval by Fridericia's formula
RBC	red blood cell
rezpeg, REZPEG	abbreviation for rezpegaldesleukin, the International Nonproprietary Name
rhIL-2	recombinant human interleukin 2
RNA	ribonucleic acid
SAE	serious adverse event
CCI	[redacted]
SAP	statistical analysis plan
SC	subcutaneous
SCORAD	SCORing Atopic Dermatitis Index
SCORAD-50/75	patient's SCORAD is reduced by at least 50%/75% relative to their baseline score
SD	standard deviation
SLE	systemic lupus erythematosus
CCI	[redacted]
SOC	system organ class
SoE	Schedule of Events
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TARC	thymus and activation-regulated chemokine
TB	tuberculosis
TBL	total bilirubin level
TCI	topical calcineurin inhibitor
Tcon	conventional T cell
TCS	topical corticosteroid
CCI	[redacted]
TEAE	treatment emergent adverse event
THC	tetrahydrocannabinol
TRAE	treatment-related adverse event
Tregs	regulatory T cells
TST	tuberculin skin test
UC	ulcerative colitis
ULN	upper limit of normal
US, USA	United States of America

Abbreviation or Term	Definition
CCI [redacted]	[redacted]
vIGA-AD	Validated Investigator Global Assessment for Atopic Dermatitis
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of childbearing potential

1.0 STUDY SYNOPSIS

<table>
<tr><td>Title of Study:</td><td colspan="2">A Phase 2b, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Rezpegaldesleukin in the Treatment of Adult Patients with Moderate-to-Severe Atopic Dermatitis (REZOLVE-AD)</td></tr>
<tr><td>Sponsor:</td><td colspan="2">Nektar Therapeutics</td></tr>
<tr><td>Name of Finished Product(s):</td><td colspan="2">Rezpegaldesleukin (REZPEG, NKTR-358, formerly known as LY3471851)</td></tr>
<tr><td>Name of Active Ingredient(s):</td><td colspan="2">Rezpegaldesleukin (REZPEG, NKTR-358, formerly known as LY3471851)</td></tr>
<tr><td>Phase of Development:</td><td colspan="2">Phase 2b</td></tr>
<tr><td>Objectives and Endpoints:</td><td colspan="2">
<table>
<tr><th>Primary Objective</th><th>Primary Endpoint</th></tr>
<tr><td>To compare the efficacy of each dose regimen of rezpegaldesleukin versus placebo as measured by the percent change from baseline in EASI in the treatment of biologic-naive patients with moderate-to-severe AD.</td><td>Mean percent change in EASI from baseline at Week 16</td></tr>
<tr><th>Secondary Objectives</th><th>Secondary Endpoints</th></tr>
<tr><td>To compare the efficacy of rezpegaldesleukin versus placebo as measured by improvement in signs and/or symptoms in the treatment of biologic-naive patients with moderate-to-severe AD.</td><td>Proportion of patients from baseline at Week 16 achieving
• vIGA-AD of 0 or 1 and at least a 2-point reduction.
• EASI-75
• EASI-90
• EASI-50
• ≥ 4-point improvement from baseline in Itch NRS in the subset of patients with ≥ 4-point Itch NRS at baseline.
• SCORAD-75
• SCORAD-50

Mean change/percent change from baseline over the period between Week 0 and Week 16 in
• EASI
• SCORAD
• BSA involvement

In addition, all of the above efficacy assessments will be further evaluated at other time points during induction therapy, maintenance therapy, and follow-up.</td></tr>
</table>
</td></tr>
</table>

	In the subpopulation of patients with baseline EASI of at least 18.0, to compare the efficacy of rezpegaldesleukin versus placebo as measured by improvement in signs and/or symptoms in the treatment of biologic-naive patients with moderate-to-severe AD	In the subpopulation of patients with baseline EASI of at least 18.0, proportion of patients from baseline at Week 16 achieving • **vIGA-AD of 0 or 1 and at least a** 2-point reduction. • EASI-75 • EASI-90 • EASI-50 • ⩾ 4-point improvement from baseline in Itch NRS in the subset of patients with ⩾ 4-point Itch NRS at baseline. • SCORAD-75 • SCORAD-50 Mean change/percent change from baseline over the period between Week 0 and Week 16 in • EASI • SCORAD • BSA involvement In addition, all of the above efficacy assessments will be further evaluated at other time points during induction therapy, maintenance therapy, and follow-up.
	To characterize the PK of rezpegaldesleukin in patients with moderate-to-severe AD.	Rezpegaldesleukin plasma concentrations at various time points assessed throughout the study.
	To describe the observed safety of rezpegaldesleukin in patients with moderate-to-severe AD.	Incidence of • Serious adverse events • Treatment-emergent adverse events
	Exploratory objectives and endpoints may include, but not be limited to, evaluations of the following at various study time points:	
	Exploratory Objectives	**Exploratory Endpoints**
	To evaluate signs and symptoms (including efficacy and patient-reported outcomes measures) at each time point collected in all patients.	Mean change/percent change as well as proportion of patients from baseline at Week 16 achieving • Improvement in DLQI • Improvement in POEM • Improvement in ADCT • Improvement in ADSS • Improvement in Skin Pain NRS CCI [redacted]


CCI

	ADSS = Atopic Dermatitis Sleep Scale; BSA = body surface area; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-50/75/90 = patient's EASI is reduced by at least 50%/75%/90% relative to their baseline score; CCI [redacted]; NRS = numerical rating scale; PD = pharmacodynamics; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetics; POEM = Patient-Oriented Eczema Measure; CCI [redacted]; SB = suicidal behavior; SCORAD = SCORing Atopic Dermatitis Index; SCORAD-50/75 = patient's SCORAD is reduced by at least 50%/75% relative to their baseline score; SI = suicidal ideation; CCI [redacted] vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis
Rationale:	Rezpegaldesleukin (REZPEG: NKTR-358, formerly known as LY3471851) is a polyethylene glycol (PEG)-conjugated recombinant human interleukin 2 (rhIL-2) with the ability to promote the activation and expansion of regulatory T cells (Tregs) with relatively minimal effect on conventional T cells (Tcons). As compared to rhIL-2, rezpegaldesleukin has prolonged systemic exposure and favors binding to the high affinity interleukin (IL)-2 receptor more highly expressed on Tregs. In a Phase 1b study evaluating the safety, tolerability, pharmacodynamics, and pharmacokinetics of multiple subcutaneously administered doses of rezpegaldesleukin in adult patients with moderate-to-severe atopic dermatitis (AD), robust and durable efficacy was demonstrated in the majority of patients (Eli Lilly Study J1P-MC-KFAD). Study 23-358-05 is a Phase 2b study to evaluate the efficacy and to describe the safety of rezpegaldesleukin in adult patients with moderate-to-severe AD. Results of this study will be used to guide the dose selection for future studies and to further characterize the benefit/risk profile of rezpegaldesleukin.
Duration of Treatment:	Approximately 12 months
Study Population:	Patients from at least 18 years of age with moderate-to-severe AD as measured by Eczema Area and Severity Index (EASI) ≥ 16.0, Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score ≥ 3, and ≥ 10% of body surface area (BSA) involvement at randomization.
Number of Patients (Planned):	Approximately 396 patients
Number of Study Sites:	Approximately 130 sites
Study Design:	This is a Phase 2b, multicenter, randomized, double-blinded, parallel-group, placebo-controlled, outpatient dose-ranging study to evaluate the efficacy and safety of multiple rezpegaldesleukin induction and maintenance dosing regimens in adult patients with moderate-to-severe AD. The study population includes biologic-naive patients with diagnosed AD which is moderate to severe as measured by EASI ≥ 16.0, vIGA-AD score ≥ 3, and ≥ 10% of BSA involvement at randomization. **Screening Period** The Screening Period begins with Visit 1, which occurs from 15 to 35 days before the Randomization Visit (Visit 2). Patients with severe AD (vIGA-AD score of 4) may have a Screening Period of a minimum of 7 days before the Randomization Visit (Visit 2) if all other eligibility criteria have been met. Informed consent will be obtained at Visit 1 before any other study procedures are performed, and a patient identification number will be assigned. The Schedule of Events (SoE; Section 1.2) lists the screening procedures for Visit 1. Eligible patients will be randomized to one of the induction dosing regimens listed here, using a 3:3:3:2 ratio.

Induction regimen	Approximate number of patients planned
Rezpegaldesleukin 24 µg/kg q2w	108
Rezpegaldesleukin 24 µg/kg q4w	108
Rezpegaldesleukin 18 µg/kg q2w	108
Placebo q2w	72

Abbreviations: q2w = every 2 weeks, q4w = every 4 weeks

Patients randomly assigned to rezpegaldesleukin 24 µg/kg every 4 weeks (q4w) during induction will be administered placebo on Weeks 2, 6, 10, and 14 to satisfy every 2 weeks (q2w) induction dosing schedule.

The randomization stratification factors are as follows:

- At Visit 2 (Week 0 Day 1) for the Induction Period
  - Disease severity measured by vIGA-AD (vIGA-AD score of 3 [moderate] vs 4 [severe])
  - Region (North America vs rest of world)
- At Visit 10 (Week 16 Day 1) for the Maintenance Period
  - Disease response measured by % EASI reduction from baseline (patient's EASI is reduced by at least XX% relative to their baseline score, where XX is 50% [EASI-50] to 74% [EASI-74] vs 75% [EASI-75] to 89% [EASI-89] vs 90% [EASI-90] to 100% [EASI-100])
  - Region (North America vs rest of world)

Blinded Induction Period

Randomized patients will begin the double-blinded, placebo-controlled, 16-week induction period when the initial dose is administered at Visit 2 (Study Day 1).

Rescue medications for AD will not be allowed after Day 14 (ie, after the first 2 weeks).

During the first two weeks (ie, between Days 1 and 14), patients experiencing intolerable AD symptoms may receive rescue treatment for AD, at the discretion of the Investigator, with the following restrictions:

- Up to 5 days of consecutive use of topical corticosteroids (TCS) or topical calcineurin inhibitor (TCI) will be allowed.
- Only a mid-potency TCS (eg, triamcinolone acetonide ointment 0.1%) or a low-potency TCS (hydrocortisone 1% cream), or TCI (for use on sensitive skin areas, eg, face) is to be used by the patient.
- High potency TCSs (eg, fluocinonide, clobetasol) are not allowed.
- All patients who adhere to the topical rescue medication stipulations during the Induction Period, and who complete the study through Week 16 will be eligible to proceed to the Maintenance Treatment Period. Failure to comply with the topical rescue medication stipulations will render a patient ineligible to participate in the Maintenance Treatment and/or Escape Arm; these patients should complete Posttreatment Follow-up Visits per the SoE for up to 12 months from the last dose.
- Systemic rescue treatments (eg, oral corticosteroids, phototherapy, cyclosporin) are prohibited. If systemic rescue therapy is used, study drug must be discontinued. The patient should continue participation by attending all study visits through Week 16. In addition, the Early Discontinuation visit and Posttreatment Follow-up Visits per the SoE for up to 12 months from the last dose should be completed. Patients who required systemic rescue medication are not

eligible to participate in the Maintenance Treatment and/or Escape Arm component of the study.

The schedule of study treatments administered in the Induction Period is provided in Table 9.

Blinded Maintenance Treatment Period

The blinded 36-week Maintenance Treatment Period begins with the dose administered at Week 16. Patients having at least an EASI-50 response at Week 16, will receive a maintenance dosing regimen, as listed here:

Week 16 responders (ie, achieved EASI-50) who were originally randomized to this induction regimen…	**will receive this maintenance regimen:**
Rezpegaldesleukin 24 µg/kg q2w	by rerandomization in 1:1 ratio: Rezpegaldesleukin 24 µg/kg q4w, or Rezpegaldesleukin 24 µg/kg q12w
Rezpegaldesleukin 24 µg/kg q4w	by rerandomization in 1:1 ratio: Rezpegaldesleukin 24 µg/kg q4w or Rezpegaldesleukin 24 µg/kg q12w
Rezpegaldesleukin 18 µg/kg q2w	by rerandomization in 1:1 ratio: Rezpegaldesleukin 18 µg/kg q4w, or Rezpegaldesleukin 18 µg/kg q12w
Placebo q2w	Placebo q4w

Abbreviations: EASI-50 = patient's Eczema Area and Severity Index is reduced by at least 50% relative to their baseline score; q12w = every 12 weeks; q2w = every 2 weeks, q4w = every 4 weeks

Patients assigned to every 12 weeks (q12w) arms during maintenance will be administered placebo on Weeks 20, 24, 32, 36,44, and 48 to satisfy the q4w maintenance dosing schedule.

The schedule of study treatments administered in the Maintenance Treatment Period is provided in Table 11.

Patients who have adhered to the rescue medication rules and who do not achieve EASI-50 at Week 16 may receive escape therapy. In addition, the Maintenance Period includes an Escape Arm for patients who, despite use of topical TCS, have an acute exacerbation (ie, drop in EASI to a less than 25% improvement relative to baseline [<EASI-25]) suggesting the need for an active or more frequently administered dose as determined in consultation with the Medical Monitor. The Escape Arm therapy is rezpegaldesleukin 24 µg/kg q2w. A patient will receive this Escape Arm therapy under the conditions listed here:

Begin rezpegaldesleukin 24 µg/kg q2w as escape therapy…	**if the patient:**
At Week 16 following induction	has not achieved an EASI-50 response.
At Week 20, 24, 28, 32, 36, 40, 44, 48, 50 or an unscheduled visit for patients on maintenance therapy	has dropped to less than an EASI-25 response and with Medical Monitor consultation.

Abbreviations: EASI-25 = patient's Eczema Area and Severity Index is reduced by at least 25% relative to their baseline score; EASI-50 = patient's Eczema Area and Severity Index is reduced by at least 50% relative to their baseline score; q2w = every 2 weeks

A patient assigned to the Escape Arm will continue receiving escape therapy through the last dosing visit of the study (Week 52) unless the patient is discontinued from study therapy per protocol. Additionally, any patient on the Escape Arm who does not

achieve an EASI-50 at any point through Week 32 assessment will discontinue from study therapy. Patients in the Escape Arm will follow the Maintenance Period schedule, with an additional study drug administration visit between each Maintenance Period study drug administration visit to increase the frequency of study drug administration to q2w (Table 2).

The schedule of study treatments administered for patients receiving Escape Arm therapy is provided in Table 13.

In the Maintenance and Posttreatment Follow-up Period, intermittent use of topical rescue medication is permitted (not required) for patients who demonstrate need based on clinical judgment. Systemic rescue treatments (eg, oral corticosteroids, phototherapy, cyclosporin) are prohibited. If systemic rescue therapy is used or other prohibited concomitant medication is used, study drug must be discontinued. Completion of the Early Discontinuation visit and a 30-Day safety follow-up visit are required. These patients will be requested to continue the early discontinuation Induction or Maintenance scheduled visits per SoE Table 1 or Table 2, respectively, prior to starting the Posttreatment Follow-up Visits approximately every 3 months.

Posttreatment Follow-up Period

For patients who have completed treatment per protocol, the last visit in the Maintenance Period is Week 52. Five subsequent follow-up visits will also occur, as listed here:

Condition	**First Posttreatment Safety Follow-up Visit**	**Posttreament follow-up visits every three months (q3m)**
If the patient **did not** discontinue study intervention early…	occurs approximately 4 weeks and ≥ 30 days [+ 7] after the last dose of study drug (ie, Week 56) or before a new atopic dermatitis regimen (Table 15) starts	occurs approximately every 13 weeks (± 14 days) from the last dose of study drug (ie, Week 65, 78, 91, and 104) or until a new atopic dermatitis regimen (Table 15) starts
Patients who have discontinued treatment early per protocol are to continue with study assessments. The last visit in the Early Discontinuation Induction Period is Week 16 and the last visit in the Early Discontinuation Maintenance Period is Week 52. Subsequent follow-up visits will also occur, as listed here:		
If the patient **did** discontinue study intervention early during Induction …	occurs after early discontinuation (ED) visit and approximately 4 weeks and ≥ 30 days [+ 7] after the last dose of study drug and this visit. The patient should then continue visits during the Induction Period up through and including Week 16.	occurs approximately every 13 weeks (± 14 days) from Week 16 for up to 12 months (ie, Weeks 29, 42, 55, 68) or until a new atopic dermatitis regimen (Table 15) starts
If the patient **did** discontinue study intervention early during Maintenance…	occurs after early discontinuation (ED) visit and approximately 4 weeks and ≥ 30 days [+7] after the last dose of study drug and this visit. The patients should then continue visits during the Maintenance Period up through and including Week 52.	occurs approximately every 13 weeks (± 14 days) from Week 52 (ie, Weeks 65, 78, 91, 104) or until a new atopic dermatitis regimen (Table 15) starts

	Blinding This study design includes Investigator and patient blinding (masking). Investigators will remain blinded to each patient's assigned study intervention throughout the course of the study. If a patient enrolls into the Escape Arm and receives open-label treatment, Investigators will remain blinded to the patient's study intervention assigned in the Induction Period and the Maintenance Period.
Key Inclusion Criteria:	Full inclusion criteria are provided in Section 4.1. **Informed consent and contraception requirements** • Provide written, informed consent to participate in the study and follow the study procedures, including compliance with the use of highly effective contraceptives. **Patient characteristics** • Male or female patients, at least 18 years of age, on the day of signing the informed consent form. Note: In some jurisdictions, the legal age of consent for study participation is greater than 18 years. For sites in such jurisdictions, the legal age of consent will be used as the lower limit of the age range for this criterion. **Disease-specific characteristics** • Present with a diagnosis of AD at least 12 months prior to screening (Visit 1), as defined by the American Academy of Dermatology "Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis" (Eichenfield, 2014). • Patients must meet the following AD severity criteria: a) EASI ≥ 16.0 at screening (Visit 1) and randomization (Visit 2). b) vIGA-AD score ≥ 3 at screening (Visit 1) and randomization (Visit 2). c) ≥ 10% of BSA involvement at screening (Visit 1) and randomization (Visit 2). • Are candidates for systemic therapy and have history, documented by a physician and/or the Investigator, of inadequate response to existing topical medications within 6 months preceding screening (Visit 1), or history of intolerance to topical therapy as defined by at least 1 of the following: a) Inability to achieve good disease control defined as mild disease or better (eg, vIGA-AD ≤ 2) after use of at least a medium potency TCS for at least 4 weeks, or for the maximum duration recommended by the product prescribing information, eg, 14 days for super potent TCS, whichever is shorter. Note: For the purpose of this criterion, a TCS may be used with or without TCI to address areas of disease. Note: Failing a nonbiologic systemic therapy intended to treat AD, eg, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or other small molecules, within 6 months before screening (Visit 1) will be considered a surrogate for inadequate response to existing topical medications. b) A history of clinically significant adverse reactions with the use of TCS, eg, skin atrophy, allergic reaction, or systemic effects that, in the opinion of the Investigator, outweigh the benefits of retreatment.

Key Exclusion Criteria:

Full exclusion criteria are provided in Section 4.2.

Skin conditions

- Are currently experiencing or have a history of concomitant skin conditions other than AD (eg, psoriasis or cutaneous lupus), that, in the opinion of the Investigator, would interfere with assessments or interpretation of the effect of study intervention on AD.
- Are currently experiencing a skin infection in the area affected by the patient's AD that requires treatment with, or is currently being treated with, topical antimicrobial therapy.

  Note: Patients who are not eligible (screen fail) due to this criterion should not be rescreened until at least 4 weeks after screen failure and at least 2 weeks after resolution of the infection.
- History of chronic idiopathic urticaria or urticaria from other causes within 4 weeks prior to randomization

Previous or current therapies

- Have a history of TCS use suggestive of a high risk for TCS withdrawal (eg, a history of prolonged or frequent use of moderate- to high-potency TCS, especially on the face [Hajar, 2015]), such that, in the opinion of the Investigator, the patient will be unable to withdraw and abstain from TCS for several weeks during the study.
- Have received any of the following treatments at any time before Visit 1:

  a) Aldesleukin

  b) Investigational IL-2 analog

  c) Oral Janus kinase (JAK) inhibitor for any indication, including, but not limited to, baricitinib, upadacitinib, abrocitinib, tofacitinib, and ruxolitinib, whether marketed or investigational

  d) Systemic immune-modulating biologic therapy (including, but not limited to, dupilumab, tralokinumab, lebrikizumab, nemolizumab, rocatinlimab, etc.) whether marketed or investigational
- Have received any of the following therapies during the specified time period ("washout") or are anticipated to require any of these therapies during the study:

Criterion	Therapy	Time period ("washout") before the first dose of study intervention[a]	Note
a.	Biologic agents, whether investigational or marketed, including, but not limited to: • dupilumab, tralokinumab, and other drugs in the same class targeting IL4/13/31 • omalizumab, and • other monoclonal antibodies	Any previous use	Not permitted

	b.	Oral JAK-inhibitors, whether investigational or marketed, including, but not limited to: • abrocitinib • baricitinib • upadacitinib	Any previous use	Not permitted
	c.	Corticosteroids that are • parenteral (administered via intra-articular, intramuscular, or IV route), or • rectally administered (enemas or suppositories)	4 weeks	Intranasal or inhaled or ophthalmic (ocular) steroids are allowed at any time.
	d.	Oral systemic corticosteroids	4 weeks	
	e.	Oral phosphodiesterase type 4 (PDE4) inhibitor	4 weeks	
	f.	Systemic immunomodulators, including, but not limited to: • cyclosporine • methotrexate • mycophenolate mofetil, or • azathioprine	4 weeks	
	g.	Other systemic therapy used to treat AD or symptoms of AD, whether approved/marketed or off-label use	4 weeks	
	h.	Any investigational small molecule	4 weeks or 5 half-lives (whichever is longer)	
	i.	Phototherapy, including • therapeutic phototherapy (psoralen plus ultraviolet A, ultraviolet B) • excimer laser, or • tanning beds	4 weeks	
	j.	Topical immune modulators, including TCIs (eg, tacrolimus, pimecrolimus) and topical JAK inhibitors (eg, ruxolitinib, delgocitinib)	1 week	
	k.	Topical PDE4 inhibitor (eg, crisaborole)	1 week	
	Criterion	**Therapy**	**Time period ("washout") before the first dose of study intervention[a]**	**Note**
	l.	Bleach bath		Patients regularly doing bleach baths may continue with a frequency of no more than twice per week during the study.

m.	TCS	1 week	Topical steroids are permitted as rescue therapy between Days 1 and 14 (inclusive) during the Induction Period and throughout the Maintenance Period per Section 5.8.1.
n.	Prescription moisturizers	1 week	

Abbreviations: AD = atopic dermatitis; IL-4/13/31 = interleukin 4/13/31; IV = intravenous; JAK = Janus kinase; PDE4 = phosphodiesterase type 4; TCI = topical calcineurin inhibitors; TCS = topical corticosteroid

a. The washout period in this table includes the day of the first dose of study intervention.

- Are unstable with respect to use of chronic treatments (prescription or over-the-counter) to improve sleep:

  a) Have started or restarted using a sleep medication during the 2 weeks before the day of the first dose of study intervention

  b) Have changed the dose of a sleep medication during the 2 weeks before the day of the first dose of study intervention, or

  c) Are likely to need to start or change the dose of sleep medication during this study, in the opinion of the Investigator.

  Note: Individuals on a stable dose of sleep medication at screening may be eligible to be enrolled if other study entry criteria are met, but such individuals should remain on the stable dose throughout the study unless, in the Investigator's opinion, the dose should be changed or stopped to address a safety concern.

Previous or current infections

- Have a current or recent acute, active infection. For at least 30 days prior to screening (Visit 1) and up to the Randomization Visit (Visit 2), patients must have no symptoms or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.

  Note: Patients who have an oral, upper respiratory, or vaginal candida infection and who are being treated only symptomatically and not requiring systemic anti-infectives may be considered for enrollment if other study eligibility criteria are met. Enrollment of patients with other uncomplicated local infections should be discussed with the Sponsor's designated Medical Monitor.

- Have had any of the following types of infection within 12 weeks prior to the Screening Visit (Visit 1) or develops any of these infections before the Randomization Visit (Visit 2):

  a) Serious (requiring hospitalization, or intravenous or equivalent oral antibiotic treatment, or both)

  b) Opportunistic (as defined in Winthrop, 2015)

  Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.

  c) Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)

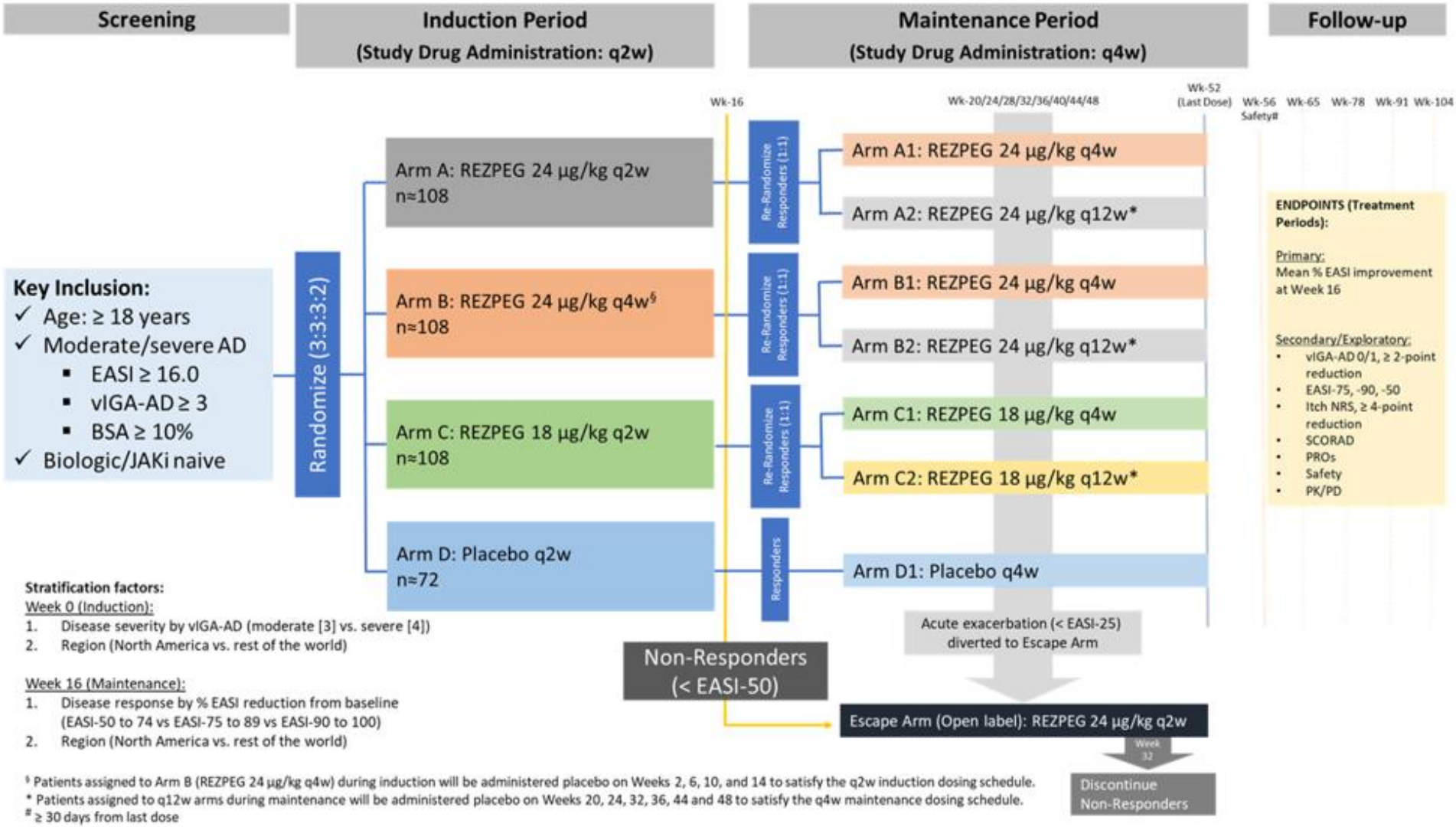
	d) Recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis). Note: Patients with only recurrent mild and uncomplicated oral herpes, or genital herpes, or both may be discussed with the Sponsor's designated Medical Monitor and considered for enrollment if other study eligibility criteria are met. **Diagnostic assessments** • Have any of the following specific abnormalities on screening laboratory tests: a) Serum creatinine, alanine transaminase (ALT), or aspartate transaminase (AST) > 2 × upper limit of normal (ULN) b) Alkaline phosphatase (ALP) ≥ 2 × ULN c) Total bilirubin level (TBL) ≥ 1.5 × ULN d) Hemoglobin < 10.0 g/dL e) Eosinophilia (absolute eosinophil count) > 1000 cells/µL f) Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine Equation) (FDA 2020; NKF 2021). Note: For repeat testing of screening laboratory tests, see Section 4.4.1. • Have other laboratory test results at screening (Visit 1) which are outside the normal reference range for the population or study site and, in the opinion of the Investigator, indicate unacceptable risk for the patient's safety in the study. **Other previous or current medical conditions** • Have a history of any of the following within 12 months before the Screening Visit (Visit 1): a) Myocardial infarction b) Unstable ischemic heart disease c) Cerebrovascular accident d) Stroke e) New York Heart Association Stage III or IV heart failure
Test Product, Dose, and Mode of Administration:	• Rezpegaldesleukin (NKTR-358; also known as LY3471851 or REZPEG) drug product will be provided as a 900 µg sterile solution in each vial for subcutaneous (SC) injection.
Comparator Product, Dose, and Mode of Administration:	• Placebo control will consist of sterile 0.9% sodium chloride saline solution.
Pharmacokinetic and Immunogenicity Evaluation:	• Blood samples will be collected for pharmacokinetic (PK) analyses as specified in the SoE (Section 1.2). Rezpegaldesleukin plasma concentration will be measured for each PK sample using validated methods. • Blood samples will be collected for quantification of antidrug antibodies (ADA) directed against rezpegaldesleukin and its components using validated methods. If appropriate, development of neutralizing antibodies (nAb) will also be assessed using a validated method. The proportion of patients with ADA and/or nAb will be calculated and the timing of appearance of ADA will be examined.

CCI	
Efficacy Evaluation:	The following will be completed and collected for primary, secondary, and exploratory endpoints: • The Investigator-reported Eczema Area and Severity Index (EASI) • Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) • Numerical Rating Scale for itching (Itch NRS) • SCORing Atopic Dermatitis Index (SCORAD) • Body Surface Area (BSA) involvement with respect to AD • Dermatology Life Quality Index (DLQI) • Patient-Oriented Eczema Measure (POEM) • Atopic Dermatitis Control Tool (ADCT)
CCI	
	• Atopic Dermatitis Sleep Scale (ADSS) • Numeric Rating Scale for skin pain (Skin Pain NRS)
Safety Evaluation:	Safety assessment will be performed by an ongoing review of the following: • Treatment-emergent adverse events (AEs), including treatment-related AEs, serious AEs (SAEs), and AEs leading to drug discontinuation • Evaluation of other safety assessments (see Section 9.1.10) • Clinical laboratory tests (see Appendix 1) • Electrocardiograms • Vital signs • Physical examination
Statistical Methods:	In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the number and percentage of patients. Two-sided statistical tests will be performed at a significance level of 0.05 if not specifically noted. The test results will be separately analyzed without adjustments for multiplicity. A description of analysis methods and detailed definitions for efficacy and safety endpoints will be provided in the statistical analysis plan (SAP). **Sample Size:** Approximately 396 patients will be randomized in a 3:3:3:2 ratio to receive either rezpegaldesleukin 18 µg/kg q2w, rezpegaldesleukin 24 µg/kg q2w, rezpegaldesleukin 24 µg/kg q4w, or placebo q2w during the Induction Period. The patients within each of the 3 rezpegaldesleukin arms who achieved EASI-50 at Week 16 and have adhered to the rescue medication rules will be rerandomized in a

	1:1 ratio to receive their last induction dosage (ie, 18 or 24 µg/kg or modified dose) either every 4 or 12 weeks during the Maintenance Period. The study of 72 patients in a placebo arm and 108 patients in a rezpegaldesleukin arm under the control of two-sided alpha level at 0.05 would provide approximately 98% power to detect an improvement of 26% in the percent change of EASI from baseline at Week 16 in the rezpegaldesleukin arm assuming 38% reduction of EASI in the placebo arm with a similar standard deviation as the rezpegaldesleukin arm (ie, standard deviation = 43%). **Analysis Populations:** The following populations are defined for analysis purposes: • Intent-To-Treat Population (ITT) • Per Protocol Population • Safety Population CCI • Pharmacokinetics Population **Efficacy:** For continuous efficacy endpoints including the primary endpoint, the mixed model for repeated measures (MMRM) will be used to estimate the treatment difference between each rezpegaldesleukin dosing regimen and placebo during the Induction Period. The MMRM will include baseline value, randomization stratification factors, treatment group, visit, and treatment-by-visit interaction as fixed factors. Visit index will be considered as the repeated factor. The least squares mean (LSMEAN) difference, standard error, p-value, and 95% confidence interval (CI) will be reported. The proportions of responders under different efficacy assessments and their 95% CIs will be provided for the binary endpoints. Both logistic regression and Cochran-Mantel-Haenszel (CMH) method will be applied to assess the association between a binary endpoint and the treatment arms. **Safety:** Overall safety and tolerability of rezpegaldesleukin will be measured by the incidence of Treatment Emergent Adverse Events (TEAEs) and SAEs summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) as well as by severity and relationship to the study treatment. Other safety parameters, including but not limited to, laboratory assessments, evaluation of other safety assessments (see Section 9.1.10), vital signs, and ECG will also be summarized as appropriate. Safety analyses will be performed in the Safety Population with descriptive statistics summarized by treatment arms.

1.1 Study Schematic

Figure 1: Study Schematic



Abbreviations: AD = atopic dermatitis; BSA = body surface area; EASI = Eczema Area and Severity Index; EASI-XX = patient's EASI is reduced by at least XX% relative to their baseline score; NRS = numerical rating scale; PK/PD = pharmacokinetic/pharmacodynamic; PRO = patient-reported outcome; q2w = once every 2 weeks; q4w = once every 4 weeks; q12w = once every 12 weeks; REZPEG = rezpegaldesleukin; SCORAD = SCORing Atopic Dermatitis Index; vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis; Wk = week
The schedule of study treatments administered is provided in Table 9, Table 11, and Table 13.

1.2 Schedule of Events

Table 1: Screening and Induction Treatment Periods Schedule of Events

Note: Screening procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance. On the days of study visits, emollients should not be applied until after the patient has undergone all study procedures and clinical evaluations. See Table 2 for patients proceeding to the Maintenance Period.

For patients who discontinue the study treatment for any reason, an ED from Study Drug visit will be conducted at the time of early discontinuation and patients will be asked to continue with all planned visits and assessments (except for study treatment administration) through Week 16; patients will also complete the follow-up visits (+ 4 weeks from last dose of study drug, Weeks 29, 42, 55, and 68).

The [ ] indicate visits and lab samples for a subset of patients. The Sponsor will notify sites once this sample collection is no longer required.

	Screening	**Treatment Period – Induction**													**UV**	**Early Discontinuation - During Induction (if applicable)**		
Week	—	**0**	**Phone Call**	**2**	**Phone Call**	**3**	**4**	**5**	**6**	**8**	**10**	**12**	**14**	**16**		**ED from Study Drug[aq]**	**+ 4-Week Safety Follow-Up Visit[aq]**	**Post-Treatment Follow-Up Visits**
Study Day	—	1	2-5[g]	15	16-19[g]	22	29	36	43	57	71	85	99	113	—	—	≥ 30 Days from last dose	W29, W42, W55, W68
Visit window (days)	35 to 15 before V2	—		±3		±3	±3[a]	±3	±3	±7	±7	±7	±7	±7	—	—	+ 7	± 14
Visit number	V1	V2		V3		[V3.5]	V4[a]	[V4.5]	V5	V6	V7	V8	V9	V10	UV	V800	V801	V802, V803, V804, V805
Informed consent[i]	X																	
Inclusion and exclusion criteria, review and confirm[j]	X[h]	X																

Table 1: Screening and Induction Treatment Periods Schedule of Events (Contd)

	Screening	Treatment Period – Induction													UV	Early Discontinuation - During Induction (if applicable)		
Week	—	0	Phone Call	2	Phone Call	3	4	5	6	8	10	12	14	16		ED from Study Drug[aq]	+ 4-Week Safety Follow-Up Visit[aq]	Post-Treatment Follow-Up Visits
Demographics[k]	X																	
Preexisting conditions and medical history[l]	X																	
Prespecified medical history (indication and history of interest)[m]	X																	
Prior treatments for indication[n]	X																	
Concomitant medications/ procedures[o]	X	X		X			X		X	X	X	X	X	X	X	X	X	
AEs / Other safety assessments (eg, ISRs)[p]	X	X		X			X		X	X	X	X	X	X	X	X	X	
Subsequent atopic dermatitis therapy[as]																	X	X

Table 1: Screening and Induction Treatment Periods Schedule of Events (Contd)

	Screening	Treatment Period – Induction												UV	Early Discontinuation - During Induction (if applicable)		
Week	—	0	Phone Call	2	Phone Call	3	4	5	6	8	10	12	14	16		ED from Study Drug[aq]	+ 4-Week Safety Follow-Up Visit[aq]	Post-Treatment Follow-Up Visits
Physical evaluation																		
Height (m) / BMI (kg/m^2)	X																	
Weight (kg)	X	X		X			X		X	X	X	X	X	X	X	X	X	
Physical examination[q]	X																	
Symptom-directed physical assessment[r]		X		Symptom directed physical exams should occur as needed										X	X	X	as needed	
Vital signs[s]	X	X		X			X		X	X	X	X	X	X	X	X	X	
12-lead ECG[t]	X													X	X	X	X	
Patient education - Provide additional education as needed.																		
Diary education	X													X			X	
Patient diary CCI																		
Diary disposition[u]	X	X													X	X	X	
Diary completion	Daily diary completion by patient: Itch NRS, NRS Skin Pain, and ADSS assessments.																	
Diary verification[v]		X		X			X		X	X	X	X	X	X	X[ar]	X	X	

Table 1: Screening and Induction Treatment Periods Schedule of Events (Contd)

	Screening	Treatment Period – Induction												UV	Early Discontinuation - During Induction (if applicable)		
Week	—	0	Phone Call	2	Phone Call	3	4	5	6	8	10	12	14	16		ED from Study Drug[aq]	+ 4-Week Safety Follow-Up Visit[aq]	Post-Treatment Follow-Up Visits
CCI																		
Patient-reported outcomes CCI																		
PHQ-9	X	X		X			X		X	X	X	X	X	X	X	X	X	
CCI																		
Clinician-administered assessments CCI																		
EASI	X	X		X			X		X	X	X	X	X	X	X[ar]	X	X	X
vIGA-AD	X[h]	X		X			X		X	X	X	X	X	X	X[ar]	X	X	X
SCORAD[y]	X	X		X			X		X	X	X	X	X	X	X[ar]	X	X	X

Table 1: Screening and Induction Treatment Periods Schedule of Events (Contd)

	Screening	Treatment Period – Induction												UV	Early Discontinuation - During Induction (if applicable)		
Week	—	0	Phone Call	2	Phone Call	3	4	5	6	8	10	12	14	16		ED from Study Drug[aq]	+ 4-Week Safety Follow-Up Visit[aq]	Post-Treatment Follow-Up Visits
Clinician-administered assessments CCI																		
C-SSRS[f]	X	X		X			X		X	X	X	X	X	X	X	X	X	
CCI																		
Laboratory tests and sample collections - Collect before dosing unless otherwise specified. See Appendix 1.																		
Hematology	X	X		X			X		X	X	X	X		X		X	X	
Clinical chemistry	X	X					X			X		X		X		X	X	
Lipid panel		X												X		X		
Urinalysis	X	X												X		X	X	
Serum pregnancy[ab]	X																	
Urine or serum pregnancy (local)[ac]		X					X			X		X		X		X		
FSH[ad]	X																	

Table 1: Screening and Induction Treatment Periods Schedule of Events (Contd)

	Screening	Treatment Period – Induction												UV	Early Discontinuation - During Induction (if applicable)		
Week	—	0	Phone Call	2	Phone Call	3	4	5	6	8	10	12	14	16		ED from Study Drug[aq]	+ 4-Week Safety Follow-Up Visit[aq]	Post-Treatment Follow-Up Visits
HbA1c[ae]	X													X		X		
TSH[ae]	X													X		X		
IgE		X								X				X		X	X	
CCI																		
TB test[ah]	X													X		X		
Viral screening tests (HIV, HCV, and HBV)[ai]	X																	
HBV DNA[aj]	X[d]									X				X		X		
HCV RNA[ak]	X[e]									X				X		X		
Pharmacokinetic (PK) samples[al]	CCI																	
Immunogenicity (ADA and nAb) samples[am]																		

Table 1: Screening and Induction Treatment Periods Schedule of Events (Contd)

	Screening	Treatment Period – Induction												UV	Early Discontinuation - During Induction (if applicable)		
Week	—	0	Phone Call	2	Phone Call	3	4	5	6	8	10	12	14	16		ED from Study Drug[aq]	+ 4-Week Safety Follow-Up Visit[aq]	Post-Treatment Follow-Up Visits
[redacted]																		
Randomization and dosing																		
Register visit with IRT	X	X		X			X		X	X	X	X	X	X		X		
Randomization via IRT		X																
Rerandomization via IRT														X[b]				
Dispense study drug via IRT		X		X			X		X	X	X	X	X	X[b]				

Table 1: Screening and Induction Treatment Periods Schedule of Events (Contd)

	Screening	Treatment Period – Induction												UV	Early Discontinuation - During Induction (if applicable)		
Week	—	0	Phone Call	2	Phone Call	3	4	5	6	8	10	12	14	16		ED from Study Drug[aq]	+ 4-Week Safety Follow-Up Visit[aq]	Post-Treatment Follow-Up Visits
Administer study drug[c, g, ap]		X[g]		X[g]			X		X	X	X	X	X	X[b]				
Post-treatment care guidance		X	X[g]	X	X[g]	X	X	X	X	X	X	X	X	X				

Abbreviations: CCI ADA = antidrug antibodies; CCI ADSS = Atopic Dermatitis Sleep Scale; AE = adverse event; anti-HBc = hepatitis B core antibody; BMI = body mass index; BSA = body surface area; C-SSRS = Columbia-Suicide Severity Rating Scale; CCI ; EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ED = early discontinuation; FSH = follicle stimulating hormone; CCI ; HbA1c = hemoglobin A1c; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; ICF = informed consent form; IgE = immunoglobulin E; IL = interleukin; IRT = interactive response technology; ISR = injection site reaction; CCI nAb = neutralizing antibodies; NRS = numerical rating scale; PD = pharmacodynamic(s); PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic(s); CCI RNA = ribonucleic acid; CCI ; SCORAD = SCORing Atopic Dermatitis Index; CCI ; TB = tuberculosis; TSH = thyroid stimulating hormone; UV = unscheduled visit; V = visit; CCI ; vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis; W = week; WOCBP = women of childbearing potential

a. Consult with Medical Monitor as necessary if patient cannot attend visit within specified window. V4 study assessments and drug administration should take precedence over Visits [3.5] and [4.5].

b. Shaded cells relate to the Maintenance Treatment Period and should occur after the completion of all Week 16 assessments.

c. A minimum of 9 days must elapse between each study drug administration (ie, subsequent dosing on or after 10 days).

d. If anti-HBc is positive or indeterminate at Screening, it will be followed by an HBV DNA test (Section 9.1.7).

e. If HCV antibody test is positive or indeterminate at Screening, it will be followed by an HCV RNA test (Section 9.1.8).

f. The "Baseline/Screening" version of the C-SSRS will be used at Screening to provide a pre-treatment assessment. On all subsequent visits, the "Since Last Visit" version will be used. For patients already enrolled at the time of implementation, the "Already Enrolled Subject" version will be used at their first visit following implementation and the "Since Last Visit" version will be used thereafter.

g. For study treatment visits at W0 and W2, site personnel must contact the patient (by telephone) once between Days 2 and 5 (inclusive) following treatment administration, to check on the general condition of the patient and provide reminders about post-treatment care guidance. In W4 and beyond, telephone follow-up is conducted as clinically indicated. Any identified AEs should be reported.

h. For patients with baseline vIGA-AD score of 4, the Screening window may be a minimum of 7 days if all other eligibility criteria has been met before V2.

i. The ICF must be signed before any protocol-specific tests or procedures are performed.

j. Inclusion and exclusion criteria must be confirmed before the patient is randomized to a study intervention and receives a first dose. Disease severity (EASI, BSA, vIGA-AD) must be re-confirmed at V2.

k. Includes year of birth, sex, ethnicity (where permissible), and race (Section 2.6.5).

l. All ongoing conditions and relevant past medical history should be collected.

m. Prespecified medical history includes, but is not limited to, conjunctivitis, CCI , allergies, CCI , depression, diabetes CCI , insomnia, and herpes infection, including herpes zoster.

n. Relevant prior therapies include, but are not limited to, biologics, eg, dupilumab. Includes all topical medications and emollients within 1 year from V1 and all systemic therapies within lifetime.

o. Data will be collected for all ongoing medications, including rescue medications and background emollients and procedures. If prohibited medications are initiated, refer to Section 5.8.3.

p. Events that occur after signing the ICF are considered AEs as defined in Section 9.2. CCI

q. The complete physical examination excludes pelvic, rectal, and breast examinations unless clinically indicated (Section 9.1.2).

r. Perform as shown in this schedule and as needed based on patient status and standard of care. May be performed by qualified personnel per local regulations.

s. Includes heart rate, blood pressure, respiratory rate, and body temperature. Measured after patient has been sitting at least 5 minutes (Section 9.1.1).

t. Local ECGs will be collected according to the instructions in Section 9.1.3.

u. Diary activated and if applicable dispensed at V1. Collect from Screen-Failure patients by V2.

v. Sites will verify completion of the diary at the specified visits.

CCI

y. BSA assessment is completed with the SCORAD assessment.

CCI

ab. Only for WOCBP (Section 9.1.5).

ac. For WOCBP, a pregnancy test must be performed, with the result available **within 24 hours** prior to dosing (Section 9.1.5). Additional pregnancy tests should be performed at any time during the study if a menstrual period is missed, or there is clinical suspicion of pregnancy, or as required by local law or regulation.

ad. Optional; performed as needed to confirm postmenopausal status.

ae. See Table 27.

CCI

ah. TB testing is assessed via a central laboratory blood draw (Section 9.1.6).

ai. If HCV antibody test is positive or indeterminate, an HCV RNA test will be run by the testing laboratory (Section 9.1.8). Screening includes anti-HBc and HBsAg. If anti-HBc is positive or indeterminate, it will be followed by an HBV DNA test (Section 9.1.7).

aj. Only for patients who are anti-HBc positive or indeterminate at screening (Section 9.1.7).

ak. Only for patients who are anti-HCV positive or indeterminate at screening (Section 9.1.8).

al. On dosing visits, collect samples before dosing (Section 7.1.1). Visits [3.5] and [4.5], will no longer be necessary once collection of PD samples described in Section 7.2 is complete. Collect additional samples at specified times relative to onset of hypersensitivity events (Appendix 1).

CCI

ap. All study assessments and sample collections should be completed before a dose is administered at dosing visits. The dose of study drug administered at V10 is the first dose of the Maintenance Period and will be that to which the patient was rerandomized. See Table 9 for study treatment administration schedule.

aq. Patients who Early Discontinue from study drug during Induction should complete the ED visit, continue with all planned visits and assessments up through and including Week 16 (except for study treatment administration), complete the Safety Follow-Up Visit +4-weeks (≥ 30-days from last dose with a + 7 day window), and then continue to the Posttreatment Follow-Up Visits after Week 16 for up to 12 months (Weeks 29, 42, 55, and 68)

- If the timing of the ED from Study Drug Visit coincides with a study visit (eg, W6), then the ED Study Drug Visit replaces the study visit
- If the timing of the ED from Study Drug Visit coincides with the +4-week Safety Follow-Up Visit, then the ED Study Drug Visit replaces the +4-week Safety Follow-Up Visit.
- If the timing of the +4-week Safety Follow-Up Visit coincides with a study visit (eg, W12), then complete all the Safety Follow-Up Visit assessments at a minimum and any remaining study visit assessments CCI .

ar. These efficacy assessments are to be completed prior to initiating rescue therapy but are not required for other unscheduled visits.

as. If a new atopic dermatitis regimen is initiated during the posttreatment follow-up period, refer to Section 5.2.4.

Table 2: Maintenance Treatment Period Schedule of Events

Note: On the days of study visits, emollients should not be applied until after the patient has undergone all study procedures and clinical evaluations. For patients who discontinue the study treatment for any reason, an ED from Study Drug visit will be conducted at the time of early discontinuation and patients will be asked to continue with all planned visits and assessments (except for study treatment administration and Escape Arm visits) through Week 52; patients will also complete the follow-up visits (+ 4 weeks from last dose of study drug; Weeks 65, 78, 91, and 104). The [ ] indicate lab samples for a subset of patients. The Sponsor will notify sites once this sample collection is no longer required.

	Treatment Period – Maintenance									**Escape Arm**		**UV**	**ED from Study Drug[ae]**	**+ 4-Week Safety Follow-Up Visit[ae]**	**Post-Treatment Follow-Up Visits**
Week	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Additional Assessments to be Completed at First Escape Arm Visit if Not Week 16[a]**	**Additional Visits for Patients in the Escape Arm: Week 18, 22, 26, 30, 34, 38, 42, 46, 50**				
Study day	141	169	197	225	253	281	309	337	365	N/A	127; 155, 183, 211, 239, 267, 295, 323, 351	—	—	≥ 30 Days from last dose	W65,W78, W91,W104
Visit window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7		±7	—	—	+7	±14
Visit number	V11	V12	V13	V14	V15	V16	V17	V18	V19		VXX.5[b]	UV	V800	V801	V802, V803, V804, V805
Concomitant medications/ procedures[g]	X	X	X	X	X	X	X	X	X		X	X	X	X	
AEs / Other safety assessments (eg, ISRs)[h]	X	X	X	X	X	X	X	X	X		X	X	X	X	
Subsequent atopic dermatitis therapy[f]														X	X

Table 2: Maintenance Treatment Period Schedule of Events (Contd)

	Treatment Period – Maintenance									Escape Arm					
Week	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Additional Assessments to be Completed at First Escape Arm Visit if Not Week 16[a]**	**Additional Visits for Patients in the Escape Arm: Week 18, 22, 26, 30, 34, 38, 42, 46, 50**	**UV**	**ED from Study Drug[ae]**	**+ 4-Week Safety Follow-Up Visit[ae]**	**Post-Treatment Follow-Up Visits**
Physical evaluation															
Weight (kg)	X	X	X	X	X	X	X	X	X	X	X		X	X	
Symptom-directed physical assessment[i]	Symptom directed physical exams should occur as needed									X		X	X	As needed	
Vital signs[j]	X	X	X	X	X	X	X	X	X		X	X	X	X	
12-lead ECG[k]								X	X			X	X	X	
Patient education															
Diary education	Provide additional education as needed									X		X			
Patient diary [redacted]															
Diary completion	Daily diary completion by patient: Itch NRS, NRS Skin Pain, and ADSS assessments											X	X	X	
Diary verification[l]	X	X	X	X	X	X	X	X	X	X	X	X[ad]	X	X	

Table 2: Maintenance Treatment Period Schedule of Events (Contd)

	Treatment Period – Maintenance									Escape Arm					
Week	20	24	28	32	36	40	44	48	52	Additional Assessments to be Completed at First Escape Arm Visit if Not Week 16[a]	Additional Visits for Patients in the Escape Arm: Week 18, 22, 26, 30, 34, 38, 42, 46, 50	UV	ED from Study Drug[ae]	+ 4-Week Safety Follow-Up Visit[ae]	Post-Treatment Follow-Up Visits
CCI															
Patient-reported outcomes CCI															
PHQ-9	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CCI															
Clinician-administered assessments CCI															
EASI	X	X	X	X	X	X	X	X	X	X		X[ad]	X	X	X
vIGA-AD	X	X	X	X	X	X	X	X	X	X		X[ad]	X	X	X
SCORAD[o]	X	X	X	X	X	X	X	X	X	X		X[ad]	X	X	X

Table 2: Maintenance Treatment Period Schedule of Events (Contd)

	Treatment Period – Maintenance									Escape Arm					
Week	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Additional Assessments to be Completed at First Escape Arm Visit if Not Week 16[a]**	**Additional Visits for Patients in the Escape Arm: Week 18, 22, 26, 30, 34, 38, 42, 46, 50**	**UV**	**ED from Study Drug[ae]**	**+ 4-Week Safety Follow-Up Visit[ae]**	**Post-Treatment Follow-Up Visits**
Clinician-administered assessments CCI															
C-SSRS[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
CCI															
Laboratory tests and sample collections - Collect before dosing unless otherwise specified. See Appendix 1.															
Hematology	X	X	X	X	X	X	X	X	X	X			X	X	
Clinical chemistry	X	X	X	X	X	X	X	X	X	X			X	X	
TSH									X				X		
Lipid panel									X	X			X		
Urinalysis									X	X			X	X	
Urine or serum pregnancy (local)[r]	X	X	X	X	X	X	X	X	X				X		
HbA1c[s]									X				X		
TB test[t]									X				X		
HBV DNA[u]			X			X			X				X		
HCV RNA[v]			X			X			X				X		

Table 2: Maintenance Treatment Period Schedule of Events (Contd)

	Treatment Period – Maintenance									Escape Arm					
Week	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Additional Assessments to be Completed at First Escape Arm Visit if Not Week 16[a]**	**Additional Visits for Patients in the Escape Arm: Week 18, 22, 26, 30, 34, 38, 42, 46, 50**	**UV**	**ED from Study Drug[ae]**	**+ 4-Week Safety Follow-Up Visit[ae]**	**Post-Treatment Follow-Up Visits**
IgE									X	X			X	X	
CCI															
PK samples[y]															
Immunogenicity (ADA and nAb) samples[z]															
CCI															
Randomization and dosing															
Register visit with IRT	X	X	X	X	X	X	X	X	X		X		X		
Dispense study drug via IRT	X	X	X	X	X	X	X	X	X		X				

Table 2: Maintenance Treatment Period Schedule of Events (Contd)

	Treatment Period – Maintenance									Escape Arm		UV	ED from Study Drug[ae]	+ 4-Week Safety Follow-Up Visit[ae]	Post-Treatment Follow-Up Visits
Week	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**Additional Assessments to be Completed at First Escape Arm Visit if Not Week 16[a]**	**Additional Visits for Patients in the Escape Arm: Week 18, 22, 26, 30, 34, 38, 42, 46, 50**				
Administer study drug[c, ac]	X[e]	X[e]	X	X	X	X	X	X	X		X				
Post-treatment care guidance[e]	X	X	X	X	X	X	X	X	X	X[e]	X[e]				

Abbreviations: CCI ADSS = Atopic Dermatitis Sleep Scale; AE = adverse event; anti-HBc = hepatitis B core antibody; anti-HCV = antibodies to HCV; BSA = body surface area; C-SSRS = Columbia-Suicide Severity Rating Scale; CCI EASI = Eczema Area and Severity Index; ECG = electrocardiogram; ED = early discontinuation; CCI HbA1c = hemoglobin A1c; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; IgE = immunoglobulin E; IL = interleukin; IRT = interactive response technology; ISR = injection site reaction; CCI N/A = not applicable; CCI NRS = numerical rating scale; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic(s); CCI RNA = ribonucleic acid; CCI SCORAD = SCORing Atopic Dermatitis Index; CCI TB = tuberculosis; UV = unscheduled visit; TSH = thyroid stimulating hormone; V = visit; CCI vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis; W = week; WOCBP = women of childbearing potential

a. These additional assessments are only to be assessed if not already collected at that visit (ie, collected only at Visits XX.5).

b. Patients in the Escape Arm will follow the Maintenance Period schedule, with an additional study drug administration visit between each Maintenance Period study drug administration visit. These intervening visits are denoted as VXX.5. CCI

c. A minimum of 9 days must elapse between each study drug administration (ie, subsequent dosing on or after 10 days).

d. On all subsequent visits, the C-SSRS "Since Last Visit" version will be used. For patients already enrolled at the time of implementation, the "Already Enrolled Subject" version will be used at their first visit following implementation and the "Since Last Visit" version will be used thereafter.

e. For the first two Escape Arm study treatment visits (eg, at W16 and W18), site personnel must contact the patient (by telephone) once between Days 2 and 5 (inclusive) following the first two Escape Arm treatment administrations, to check on the general condition of the patient and provide reminders about post-treatment care guidance. Additional telephone follow-up is conducted as clinically indicated. Any identified AEs should be reported.

f. If a new atopic dermatitis regimen is initiated during the posttreatment follow-up period, refer to Section 5.2.4.

g. Data will be collected for all ongoing medications, including rescue medications and background emollients and procedures. If prohibited medications are initiated refer to Section 5.8.3.

h. Events that occur after signing the ICF are considered AEs as defined in Section 9.2. CCI

i. Perform as shown in this schedule and as needed based on patient status and standard of care. May be performed by qualified personnel per local regulations.

j. Includes heart rate, blood pressure, respiratory rate, and body temperature. Measured after patient has been sitting at least 5 minutes (Section 9.1.1).

k. Local ECGs will be collected according to the instructions in Section 9.1.3.

l. Sites will verify completion of the diary at the specified visits.

CCI

o. BSA assessment is completed with the SCORAD assessment.

CCI

r. For WOCBP, a local pregnancy test must be performed, with the result available **within 24 hours** prior to dosing (Section 9.1.5). Additional pregnancy tests should be performed at any time during the study if a menstrual period is missed, or there is clinical suspicion of pregnancy, or as required by local law or regulation.

s. See Table 27.

t. TB testing is assessed via a central laboratory blood draw (Section 9.1.6).

u. Only for patients with anti-HBc positive or indeterminate results at screening (Section 9.1.7).

v. Only for patients with anti-HCV positive or indeterminate results at screening (Section 9.1.8).

CCI

y. On dosing visits, collect samples before dosing (Section 7.1.1). Collect additional samples at specified times relative to onset of hypersensitivity events (Appendix 1).

CCI

ab. See Appendix 5. Samples will be taken from all patients.

ac. All study assessments and sample collections should be completed before a dose is administered at dosing visits. See Table 11 and Table 13 for study treatment administration schedule.

ad. These efficacy assessments are to be completed prior to initiating rescue therapy but are not required for other unscheduled visits.

ae. Patients who Early Discontinue from study drug during Maintenance should complete the ED visit, continue with all planned visits and assessments up through and including Week 52 (except for study treatment administration and Escape Arm visits), complete the Safety Follow-Up Visit +4-weeks (≥ 30-days from last dose with a + 7-day window), and then continue to the Posttreatment Follow-Up Visits after Week 52 for up to 12 months (Weeks 65, 78, 91, 104)

- If the timing of the ED from Study Drug Visit coincides with a study visit (eg, W40), then the ED Study Drug Visit replaces the study visit
- If the timing of the ED from Study Drug Visit coincides with the +4-week Safety Follow-Up Visit, then the ED Study Drug Visit replaces the +4-week Safety Follow-Up Visit
- If the timing of the +4-week Safety Follow-Up Visit coincides with a study visit (eg, W28), then complete all Safety Follow-Up assessments at a minimum and any remaining study visit assessments (eg, W28 [flow cytometry], HBV DNA, HCV RNA, and local pregnancy).

2.0 INTRODUCTION

2.1 Background

Atopic dermatitis (AD), also called atopic eczema, is a common noncontagious, chronic, relapsing, pruritic inflammatory skin disease. Clinically AD is characterized by severe pruritus and eczematous dermatitis and can be distinguished from other skin diseases by such factors as age of onset, distribution on the body, xerosis, lichenification, and atopy (Barrett, 2017; Bieber, 2021). AD may present with dry itchy skin and may be complicated by rashes that blister or weep. This may lead to an unrelenting itch scratch cycle (Frazier, 2020). Various factors have been implicated in the ongoing inflammation associated with AD, including genetics, environment, and pro-Th2 cytokines.

Patients with AD have a high burden of disease, and their quality of life is significantly affected (Galli, 2020). In the Global Burden of Disease Study 1990-2017, AD had the highest disease burden among skin diseases as measured by disability-adjusted life-years (Laughter, 2021). Because of pruritus and skin pain, patients with moderate-to-severe AD can experience severe and frequent disturbances of sleep, which can play a role in overall health (Silverberg, 2021a). In one study, AD was shown to have a greater negative effect on patient mental health than diabetes and hypertension (Kiebert, 2002). Symptoms of AD can impact a patient's self-esteem, social activities and relationships, and performance at work or school (Sibbald, 2017). The economic burden of AD can include increased sick leave, job changes, or job loss due to symptoms (Nørreslet, 2018).

Currently, there is no cure for AD. Common therapies for mild-to-moderate AD include avoidance of irritants; use of wet-wraps, soaking baths, and emollients; and use of topical corticosteroid (TCS) and topical calcineurin inhibitor (TCI). Topical medications provide some symptomatic relief for many patients, but do not always adequately control the disease. In patients with persistent moderate-to-severe disease, step-up options include phototherapy and systemic immunosuppressives, such as oral glucocorticosteroids, azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil (Simpson, 2017; Wollenberg, 2018; Bieber, 2021).

Recent advances in the understanding of the molecular pathogenesis of AD have led to the development and approval of more targeted therapies for AD (Worm, 2020). Some examples are listed in Table 3.

Table 3: Example Targeted Therapies for Atopic Dermatitis

Therapy	Description	Indication	Citation
Dupilumab	Human anti-IL-4R alpha monoclonal antibody that inhibits signaling for both IL-4 and IL-13	Moderate-to-severe AD	Boguniewicz, 2020 Dupixent package insert 2022 Dupixent summary of product characteristics
Tralokinumab	Human monoclonal antibody that binds to IL-13 and inhibits its interaction with IL-13Rα1 and IL-13Rα2	Moderate-to-severe AD	Adbry package insert 2021 Adtralza summary of product characteristics
Upadacitinib	Oral JAK1 inhibitor	Moderate-to-severe AD	Rinvoq package insert 2022 Rinvoq summary of product characteristics Guttman-Yassky, 2021
Abrocitinib	Oral JAK1 inhibitor	Moderate-to-severe AD	Cibinqo package insert 2022 Cibinqo summary of product characteristics Simpson, 2020a Silverberg, 2020
Ruxolitinib	Topical JAK1/2 inhibitor	Mild-to-moderate AD	Opzelura package insert 2022

Abbreviations: AD = atopic dermatitis; IL = interleukin; JAK = Janus kinase

Nevertheless, AD remains a major burden for patients and society. More efficacious and durable therapies with a favorable safety profile are needed.

2.2 Rezpegaldesleukin

Rezpegaldesleukin is a polyethylene glycosylated form of recombinant human interleukin-2, which has the same amino acid sequence as Proleukin® (aldesleukin), an approved drug indicated for metastatic renal cell carcinoma and melanoma (Proleukin PI, 2012; Fanton, 2022). Rezpegaldesleukin is a novel product with stable covalently attached polyethylene glycosylated moieties and, nonclinically, is differentiated from interleukin-2 in its biological activity and pharmacokinetic profile. Rezpegaldesleukin has shown the ability to effectively promote the expansion and activation of regulatory T-cells with relatively minimal effect on conventional T-cells, the latter of which consists of CD4+ and CD8+ cell subtypes, as well as natural killer (NK) cells.

In a Phase 1b study evaluating the safety, tolerability, pharmacodynamics, and pharmacokinetics of multiple subcutaneously administered doses of rezpegaldesleukin in adult patients with moderate-to-severe AD, robust and durable efficacy was demonstrated in the majority of patients (Schleicher, 2022).

Study 23-358-05 is a Phase 2b study to evaluate the efficacy and to describe the safety of rezpegaldesleukin in adult patients with moderate-to-severe AD. Results of this study will be used to guide the dose selection for future studies and to further characterize the benefit/risk profile of rezpegaldesleukin.

2.2.1 Rezpegaldesleukin Mechanism of Action

Rezpegaldesleukin (NKTR-358, formerly known as LY3471851) is a recombinant human interleukin 2 (rhIL-2) with stable covalently attached polyethylene glycol (PEG) moieties with the ability to promote the activation and expansion of regulatory T cells (Tregs) with minimal effect on conventional T cells (Tcons). CCI [redacted] Interleukin 2 (IL-2) has pleiotropic immunoregulatory functions and has a role in the control of the proliferation and survival of Treg cells, which are impaired in various autoimmune and inflammatory skin diseases, including AD (Nedoszytko, 2017; Abbas, 2018; Sharabi, 2018). As compared to rhIL-2, rezpegaldesleukin results in prolonged systemic exposure and provides preferential activation and proliferative expansion of Tregs.

Interleukin 2 (IL-2) is a pleiotropic cytokine which impacts both Tcon and Treg development by engaging the dimeric IL-2Rβγ or trimeric IL-2Rαβγ receptor on lymphocytes and inducing downstream signaling cascades. In response to infection or in an oncology setting, increased expression of IL-2 is essential for the generation of productive Tcon responses. However, at resting physiological levels, IL-2 is also required for the development of Tregs in the thymus, as well as their survival in the peripheral circulation. This apparent paradox is explained by the fact that compared with Tcons, Tregs are preferentially activated by IL-2 due to higher cell surface expression of the IL-2 receptor component CD25 (IL-2Rα) and enhanced downstream signaling associated with the trimeric IL-2Rαβγ receptor complex. Due to the difference in IL-2 receptor biology, Tregs are stimulated at much lower concentrations of IL-2 than Tcons. Consequently, IL-2 is an essential growth factor for Tregs, and impaired IL-2 production and dysfunction in Treg biology have been identified as key immunological defects leading to the breakdown of immune self-tolerance, a causative mechanism implicated in multiple autoimmune diseases.

Rezpegaldesleukin has covalently-bonded pegylation that provides an optimal pharmacokinetic (PK) and pharmacodynamic (PD) profile favoring Treg stimulation and expansion over Tcon. Following subcutaneous (SC) administration, rezpegaldesleukin achieves prolonged systemic exposure compared with native IL-2. In nonclinical pharmacology studies in mice and cynomolgus monkey, in vitro cellular assays utilizing cynomolgus monkey and human cells, and in Phase 1 and Phase 2 clinical trials, rezpegaldesleukin has demonstrated preferential stimulation of Treg relative to Tcon cell populations.

2.2.2 Clinical Experience with Rezpegaldesleukin

To date, rezpegaldesleukin has been evaluated in 9 studies involving human subjects (Table 4). Rezpegaldesleukin has not yet been approved for marketing in any country. CCI [redacted] In healthy volunteers, rezpegaldesleukin has been administered SC in single doses CCI [redacted] Multiple doses ranging from CCI [redacted] SC once every 2 weeks (q2w) or once every 4 weeks (q4w) have been administered to patients with a diagnosis of systemic lupus erythematosus (SLE), psoriasis, AD, and ulcerative colitis (UC). CCI [redacted]

Table 4: Rezpegaldesleukin Clinical Studies

Study Code	Study Title
16-358-01	Phase 1, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Single SC Dose of NKTR-358 in Healthy Volunteers
17-358-02	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Ascending Multiple-Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Subcutaneous NKTR-358 in Patients with Systemic Lupus Erythematosus
J1P-MC-KFAI	A Single Ascending Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of LY3471851 in Japanese and Caucasian Healthy Subjects
J1P-MC-KFAC	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous LY3471851 in Patients with Psoriasis
[redacted]	CCI [redacted]

Table 4: Rezpegaldesleukin Clinical Studies (Contd)

Study Code	Study Title	CCI
J1P-MC-KFAL	A Phase 1, Randomized, Single-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous LY3471851 in Healthy Participants	
J1P-MC-KFAD	A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Multiple-Dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Subcutaneous LY3471851 in Patients with Atopic Dermatitis	
J1P-MC-KFAJ	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study of LY3471851 (NKTR-358) in Adults with Systemic Lupus Erythematosus	
J1P-MC-KFAH	An Adaptive Phase 2, Randomized, Double Blind, Placebo Controlled Study of LY3471851 (NKTR-358) in Patients with Moderately to Severely Active Ulcerative Colitis	
J1P-MC-KFAN	A Phase 1, Randomized, Placebo-controlled, Participant- and Investigator-blind, Single-dose Study of the Pharmacokinetics of LY3471851 Following Subcutaneous Dosing of LY3471851 in Healthy Participants	

Abbreviations: LY3471851 = rezpegaldesleukin; NKTR-358 = rezpegaldesleukin; SC = subcutaneous

2.3 Rezpegaldesleukin Pharmacokinetics and Pharmacodynamics

2.3.1 Pharmacokinetics

As of the approval date of this protocol, 3 studies have been completed with the PK data reported. Following a single SC administration of rezpegaldesleukin in healthy volunteers (16-358-01) over the dose range of 0.3 to 28 µg/kg, maximum concentrations of 2 to 240 ng/mL were reached by 5 to 7 days postdose. Rezpegaldesleukin exhibited approximately dose-proportional PK over the investigated dose range, with a half-life ($t_{1/2}$) of approximately 8 to 11 days.

In the multiple ascending dose study 17-358-02, rezpegaldesleukin was given every 14 days with a total of 3 doses over the range of 3 to 24 µg/kg. Rezpegaldesleukin displayed approximately dose-proportional PK in patients with mild to moderate SLE. After administration, rezpegaldesleukin reached maximum plasma concentrations approximately 3 to 6 days postdose and declined with a mean terminal $t_{1/2}$ of approximately 10 to 13 days. The mean accumulation ratios (Dose 3/Dose 1) for area under the plasma concentration versus time curve (AUC) from time zero to 14 days ($AUC_{0\text{-}14\ day}$) postdose and maximum observed plasma concentration (C_{max}) ranged from approximately 1.5 to 2.5.

Study J1P-MC-KFAI (KFAI) was a single ascending dose study conducted in Japanese and Caucasian healthy subjects, in which rezpegaldesleukin was given as fixed doses CCI [redacted]

Please refer to the latest rezpegaldesleukin Investigator's Brochure for additional information and potential updates.

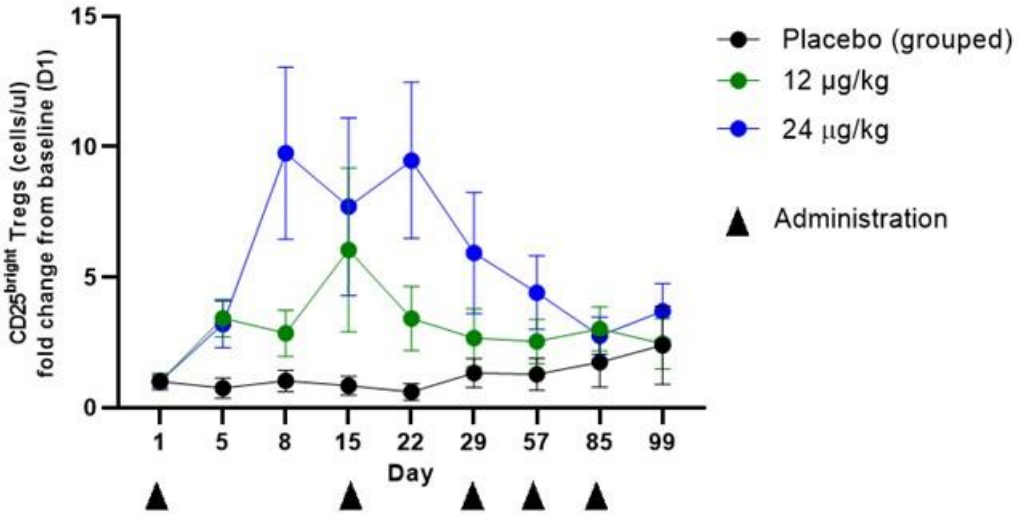
2.3.2 Pharmacodynamics

To assess the PD activity of rezpegaldesleukin, time-dependent changes of lymphocyte populations were characterized in peripheral whole blood using flow cytometry. At doses ≥ 3 µg/kg, rezpegaldesleukin led to a dose-dependent and sustained increase in the absolute numbers and percentages of total Tregs (CD4+FoxP3+CD25+ cells) and $CD25^{bright}$ Tregs (CD4+FoxP3+CD25++ cells) in both healthy volunteers (16-358-01) and patients with SLE (17-358-02). At the highest doses tested in both studies, there was a maximum 17-fold (16-358-01) and 12-fold (17-358-02) mean peak increase over baseline in the numbers of $CD25^{bright}$ Tregs, with levels peaking around Day 10 and remaining above baseline for 20 to 30 days following administration of the last dose. In the SLE population, the magnitude of the response appeared modestly attenuated in several patients with repeat dosing at 24 µg/kg, but the

mean CD25^{bright} Treg population remained above baseline levels through approximately Day 60. Rezpegaldesleukin led to a dose-dependent increase in the percentage of CD25^{bright} Tregs expressing Ki67 – a marker of proliferation and, therefore, of Treg activation – at doses ≥ 12 µg/kg in both studies. A maximum of 6-fold (16-358-01) and 5-fold (17-358-02) mean peak increases over baseline in Ki67+CD25^{bright} Tregs were observed (Fanton, 2022).

Similar effects on Tregs were observed in response to rezpegaldesleukin in patients with moderate-to-severe AD (Eli Lilly Study J1P-MC-KFAD [KFAD]) where there was a dose dependent increase in the percentage and absolute number of CD25^{bright} Tregs. In the 24 ug/kg dose level, there was a 9- to 10-fold increase in absolute numbers of Tregs relative to baseline after both the first and second administrations. Only trough levels of Tregs were measured at subsequent dose administrations (Figure 2).

Figure 2: Mean Fold Change in Absolute Number of CD25^{bright} Tregs in Study J1P-MC-KFAD

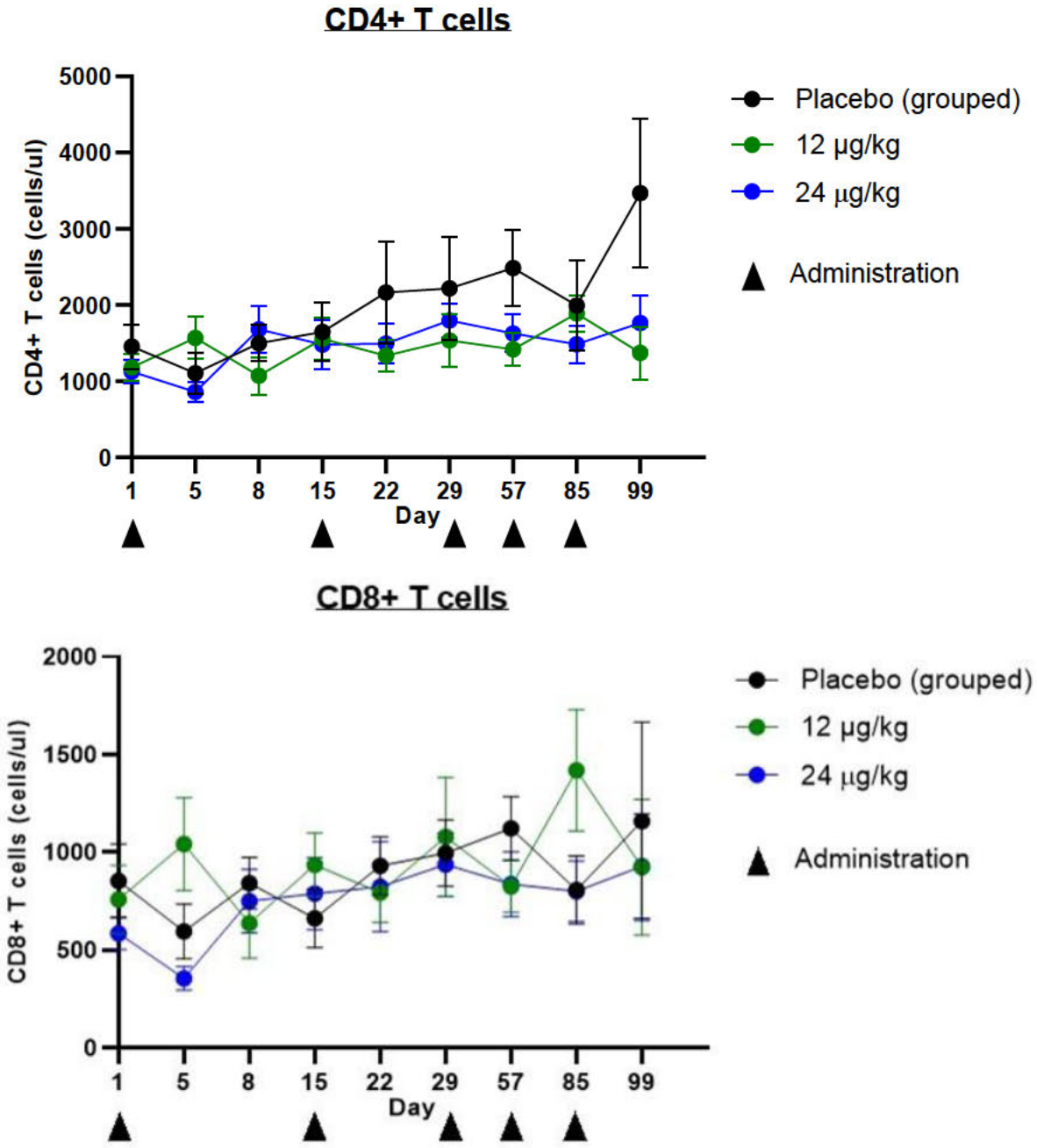


Abbreviations: D = day(s); Tregs = regulatory T cells

The absolute number and percentage of NK cells were variable across patients in Nektar Studies 16-358-01 and 17-358-02, and Study KFAD, with numbers appearing to increase with repeated dosing. In response to single and repeated dosing of rezpegaldesleukin (16-358-01, 17-358-02), an increase in percentages of circulating NK cells (as a percentage of CD45+ cells) was observed starting at the higher dose levels (Fanton, 2022). In Study KFAD, absolute number and percentages of circulating NK cells were relatively stable from baseline until Day 29 across all treatment groups. There was an observed increase in both rezpegaldesleukin cohorts (relative to placebo) in both the number and percentages of NK cells on Days 57 and 85, decreasing at Day 99.

No meaningful changes in the absolute numbers or percentages of Tcon cell populations (CD4+, CD8+) were observed for any of the dose levels tested in any of the studies described (Fanton, 2022; Figure 3).

Figure 3: Absolute Number of CD4+ & CD8+ T Cells in Study J1P-MC-KFAD



Please refer to the latest rezpegaldesleukin Investigator's Brochure for additional information and potential updates.

2.4 Rezpegaldesleukin Safety Profile

2.4.1 Evaluation of the Risks

The data from both nonclinical and clinical studies with rezpegaldesleukin suggest that it is safe and well tolerated at the doses to be administered in the present study. As of the approval date of this protocol, there were no important identified risks for rezpegaldesleukin based on safety data available from 592 subjects treated with rezpegaldesleukin including healthy volunteers and patients with a diagnosis of psoriasis, AD, SLE, or UC.

Please refer to the latest rezpegaldesleukin Investigator's Brochure for additional safety information and potential updates.

2.4.1.1 Injection Site Reactions

Localized injection site reactions (ISRs) have been frequently reported in rezpegaldesleukin-treated participants within the context of clinical research studies. These events have generally exhibited mild to moderate severity and have predominantly resolved on their own within a 2-week timeframe. The most commonly observed feature of ISR was erythema, followed by injection site pain, which was typically mild and resolved quickly. Other localized manifestations of ISRs included pruritus, swelling, induration, rash, and warmth at the injection site.

No case of anaphylaxis has been seen with rezpegaldesleukin to date.

2.4.1.2 Hepatic Enzyme Elevation

CCI

- The Investigator's Brochure (IB) and risk profile were updated to serve as guidance to the Investigators to carefully monitor hepatic enzymes as described in protocols.

2.4.1.3 Eosinophilia

During clinical trials, circulating eosinophilia without organ involvement has been observed in a few patients, CCI Historically, eosinophilia has been observed with IL-2 therapy (Cragun, 2005). CCI

CCI To mitigate this risk, study eligibility is being limited to patients with baseline absolute eosinophil count ≤ 1000 cells/µL and stopping rules are implemented for where organ involvement is noted with absolute eosinophil count > 2000 cells/µL or circulating eosinophil count (without evidence of organ involvement) is observed of > 5000 cells/µL.

2.4.2 Risk Mitigations

To reduce potential safety risks to patients enrolled in Study 23-358-05, patients will have appropriate predose safety assessments and postdose monitoring. The routine safety assessments include physical examinations, clinical safety laboratory tests (including hematology and chemistry, liver function tests), vital signs, electrocardiograms (ECGs), mental health questionnaires (Columbia-Suicide Severity Rating Scale [C-SSRS] and Patient Health Questionnaire-9 [PHQ-9]), and adverse events (AEs). The study design includes Posttreatment Study Visits for follow-up including 30-Day Safety Follow-Up Visit from last dose.

Investigators should monitor patients for symptoms and signs suggesting liver or biliary toxicity, including jaundice, scleral icterus, and pruritus, and should monitor patients' hepatic enzymes according to the protocol (Section 9.1.9; Appendix 4). In addition, Investigators should monitor patients for eosinophilia and adhere to the protocol specified stopping rules.

2.5 Clinical Studies

2.5.1 Summary of Safety from Rezpegaldesleukin Studies

Cumulatively as of March 15, 2024, 763 participants have been enrolled into the rezpegaldesleukin clinical program, of which 592 subjects from unblinded studies have received rezpegaldesleukin.

A total of 210 healthy volunteers and 382 patients (25 with psoriasis, 37 with AD, 253 with SLE, and 67 with UC) have received rezpegaldesleukin. Seventeen patients with AD have been randomized to receive either rezpegaldesleukin or placebo in ongoing Study 23-358-05. CCI [redacted]

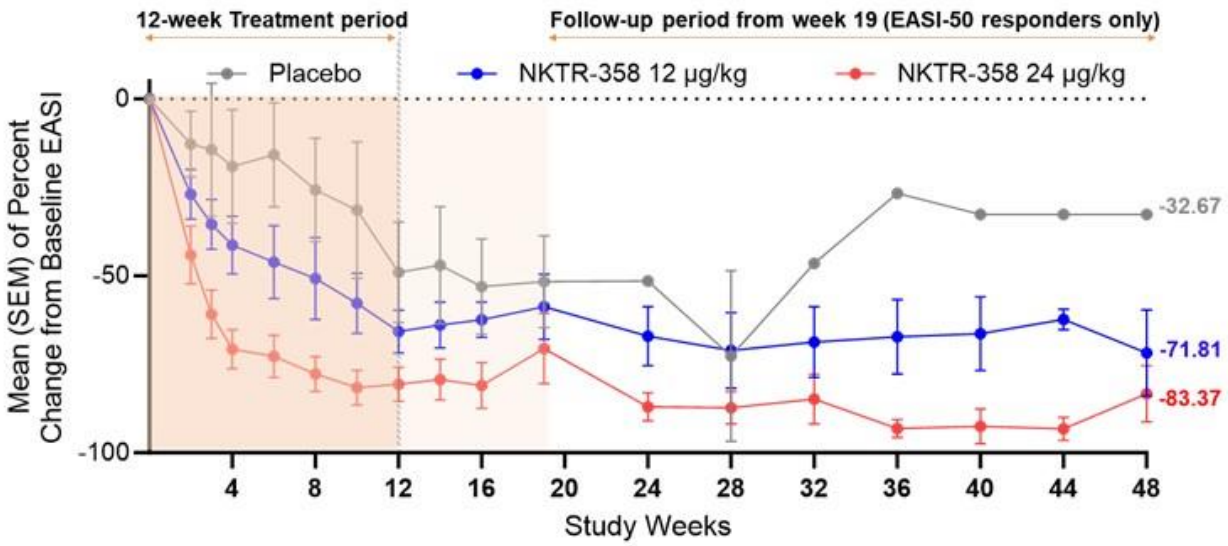
Please refer to the latest rezpegaldesleukin Investigator's Brochure for additional safety information and potential updates.

2.5.2 Study KFAD (Rezpegaldesleukin in Patients with AD)

Study KFAD was a Phase 1b, double-blind, randomized, placebo-controlled, multiple-dose study evaluating the safety, tolerability, and PK of rezpegaldesleukin in patients with moderate to severe AD. Overall, 48 patients were randomized and 44 patients were included in the adjusted intent-to-treat population, with patients having been randomized to placebo (10 patients), rezpegaldesleukin 10 µg/kg (1 patient), rezpegaldesleukin 12 µg/kg (16 patients), or rezpegaldesleukin 24 µg/kg (17 patients).

After 12 weeks of treatment, significant improvement in the least squares mean (LSMEAN) percent change (compared to baseline) in the Eczema Area and Severity Index (EASI) was observed in patients treated with rezpegaldesleukin 24 µg/kg versus placebo (83% vs 47%) (Figure 4).

Figure 4: Rezpegaldesleukin Significantly Improved EASI: Mean Percent Change in EASI Over Time



Abbreviations: EASI = Eczema Area and Severity Index; NKTR-358 = rezpegaldesleukin

In addition, compared to placebo, a higher proportion of patients treated with rezpegaldesleukin 24 µg/kg q2w achieved at least a 75% reduction in EASI relative to their baseline score (EASI-75) (41% vs 20%), and showed greater improvements in Validated Investigator Global Assessment for Atopic Dermatitis (vIGA-AD) score and itch numerical rating scale (NRS) after a 12-week induction period. Patients with an EASI-50 response at Week 19 were observed until Week 48 and demonstrated sustained improvements with rezpegaldesleukin 24 µg/kg versus placebo for EASI-75 (50% vs. 0%), vIGA-AD 0/1 (40% vs. 0%), and NRS Itch improvement of ≥ 4-point (55.6% vs. 0%). Absolute numbers of $CD25^{bright}$ Tregs increased up to 9- to 10-fold relative to baseline after both the first and second administrations in patients treated with rezpegaldesleukin at 24 µg/kg up to Week 12, ie, through the study treatment period.

No deaths, serious adverse events (SAEs), or severe AEs were reported among the patients receiving rezpegaldesleukin. CCI [redacted]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A total of 23 (67.6%) patients in the rezpegaldesleukin groups had at least 1 treatment emergent ISR. The majority of the reactions were mild to moderate and resolved within 14 days. No patient discontinued therapy due to an ISR in either the 12 µg/kg group or the 24 µg/kg group.

On balance, the efficacy signal in the KFAD study, particularly the sustained improvement in EASI-75, vIGA-AD (0,1), and itch ≥ 4-point improvement through the extended follow-up period to 48 weeks with rezpegaldesleukin 24 µg/kg, warrants further clinical development for patients with moderate to severe AD.

2.5.3 Summary of Benefits and Risks

To date, rezpegaldesleukin has been evaluated in over 590 subjects, including patients with AD, SLE, psoriasis, and UC (see Section 2.2). In these Phase 1b/2 studies, a potential efficacy signal (relative to placebo) has been detected in AD, SLE, and psoriasis. The Phase 1b study involving patients with moderate-to-severe AD has shown an 83% vs. 47% LSMEAN improvement in EASI score after 12 weeks of therapy at the 24 µg/kg dose level vs. placebo, respectively; the study also demonstrated durability of response, which extended through the 36-week off-treatment follow-up period among patients who were EASI-50 responders following the 12-week induction period (at Week 19). If confirmed in additional studies, the substantial improvement in AD severity, as assessed by the EASI, together with the long duration of response, indicates that rezpegaldesleukin could provide substantial benefit to patients with moderate-to-severe AD.

In the studies conducted to-date, no rezpegaldesleukin related deaths have been observed. Clinical safety data from completed and ongoing studies are reviewed on an ongoing basis to monitor data relevant to the nonclinical safety findings, including cytokine release syndrome (CRS) and the more severe events associated with high-dose IL-2 (Proleukin) such as capillary leak syndrome, autoimmune diseases, disseminated infections, cardiopulmonary disorders, or hematological toxicities.

In Study KFAL, ALT/AST elevations were observed in 50% of the healthy subjects who received high doses of rezpegaldesleukin CCI [redacted] and with careful hepatic monitoring (see Section 9.1.9).

The ability of rezpegaldesleukin to restore an adequate homeostatic capacity of the immune system has been demonstrated in nonclinical studies, suggesting it may have a beneficial therapeutic role in diseases where Treg dysfunction plays a central mechanistic role. Rezpegaldesleukin demonstrates Treg stimulation with almost absent effects on conventional T cells, including effector T cell subsets and NK cells. The sustained Treg induction combined with optimal PK and infrequent subcutaneous administration suggests that rezpegaldesleukin has the potential to be an effective treatment option for chronic autoimmune diseases, based on a potentially positive benefit-risk profile.

CCI [redacted]

2.6 Scientific Rationale for Study Design

2.6.1 The Primary Endpoint

Eczema Area and Severity Index is an acceptable instrument to measure the clinical signs of AD (Schmitt, 2013). As a validated measure, EASI has been used in clinical trials to assess the severity and extent of AD (Hanifin, 2001; Eichenfield, 2014; Hanifin, 2022). The mean percent change of EASI at the end of induction therapy (Week 16) relative to the baseline is applied as the primary measure of efficacy in this study.

2.6.2 Duration of Treatment Period and Posttreatment Follow-up

The duration of the Induction Period (16 weeks) and the primary endpoint at the end of induction therapy (ie, Week 16) is based on previous clinical trials of systemic therapies in AD (Simpson, 2016). The remaining duration of the study is intended to allow exploratory assessments of various rezpegaldesleukin maintenance dosing regimens. To reduce patient burden, topical rescue medication is permitted under certain circumstances (Section 5.8.1).

The Posttreatment Follow-up Period allows for continued monitoring of safety and response durability after the last dose. The duration of this period is considered sufficient to wash out rezpegaldesleukin based on the mean $t_{1/2}$, which has been estimated at between 8 to 13 days.

2.6.3 Appropriateness of Study Population

The study inclusion criteria will enable enrollment of patients who are representative of the general population with moderate-to-severe AD. The EASI $\geq$ 16.0, vIGA-AD score $\geq$ 3, and $\geq$ 10% of body surface area (BSA) involvement at baseline have been used as inclusion criteria in other studies of AD (Simpson, 2016) and were recommended by the Food and Drug Administration (FDA) for the Phase 1b study of rezpegaldesleukin in AD (Study KFAD).

2.6.4 Choice of Placebo Control, Number of Treatment Groups, and Escape Arm

A double-blinded, placebo-controlled design limits bias for the patient assessments and Investigator assessments and enables a clearer interpretation of the effects of the active study intervention.

The multiple dosing regimens enable an evaluation of safety and efficacy across several doses and frequencies, thereby providing information to guide the selection of dosing regimens for future studies.

The open-label, Escape Arm for nonresponders gives patients an opportunity to remain in the study and receive potential benefit from an active or more frequently administered dose. Further, nonresponder patients initially assigned to the 18-µg/kg arm will receive a higher dose level in the Escape Arm.

2.6.5 Rationale for Collection of Race and Ethnicity

In this study, collection of demographic information includes ethnicity (where permissible according to local regulations) and race. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. Such a need can be addressed only if all the relevant data are collected.

2.7 Justification for Dose

2.7.1 Dose Selection

The doses were selected based on evaluation of clinical safety, PK, PD, and where applicable, tolerability and efficacy data from:

- nonclinical toxicology studies,
- a single-ascending dose study in healthy volunteers (Nektar Study 16-358-01),
- a multiple-ascending dose study in patients with SLE (Nektar Study 17-358-02),
- a 12-week, Phase 1b, multiple dose study in patients with AD (Study KFAD),
- a 24-week, Phase 2, placebo-controlled, multiple dose study in patients with SLE (Eli Lilly Study J1P-MC-KFAJ [KFAJ]), and
- a 12-week, Phase 1b, multiple dose study in patients with psoriasis (Study KFAC).

2.7.2 Induction Dosing Regimens

The Induction Period will evaluate 3 rezpegaldesleukin dosing regimens versus placebo. Rezpegaldesleukin has altered binding dynamics to the IL-2 receptor subunits, favoring binding and signaling on Tregs. The rezpegaldesleukin dose will be 24 µg/kg q2w or q4w or 18 µg/kg q2w.

2.7.2.1 Arm A: High-Dose, High-Frequency Regimen: 24 µg/kg q2w

The 24 µg/kg dose was the highest dose tested in Study KFAD, in which 7 doses were given q2w, and in Nektar Study 17-358-02 in SLE patients, in which 3 doses were given q2w. In Study KFAJ in SLE patients, 12 doses of 1800 µg were given q2w (24 µg/kg for a 75 kg individual is 1800 µg). Detailed safety data from the Study KFAD at this dose level (ie, 24 µg/kg) are discussed in Section 2.5.

This dose was associated with pharmacological effects in Nektar Study 17-358-02 and Studies KFAD and KFAJ with increases in $CD25^{bright}$ Tregs and total Tregs observed at this dose. The mean maximum increase after the first dose in the absolute number of $CD25^{bright}$ Tregs in Nektar Study 17-358-02 was 12-fold relative to baseline (Fanton, 2022) and similar increases of approximately 10-fold relative to baseline were seen in the KFAD and KFAJ studies. In Study KFAD, a significant efficacy signal was detected at this dose level in patients with moderate-to-severe atopic dermatitis, as discussed in Section 2.5.2.

The predicted mean $AUC_{0\text{-}14\ day}$ exposure at 24 µg/kg is 4540 ng•day/mL (equivalent to 108,960 ng•h/mL), which is similar to the no-observed-adverse-effect-level (NOAEL) exposure in the 28-week, repeat-dose rat toxicity study (most sensitive species; 114,600 ng•h/mL; Study LS-2017-022) and below the 28-week, repeat-dose monkey toxicity study (308,000 ng•h/mL; Study LS-2017-023).

2.7.2.2 Arm B: High-Dose, Low-Frequency Regimen: 24 µg/kg q4w

A 12 µg/kg q2w dose showed lower efficacy than 24 µg/kg q2w in Study KFAD and was associated with pharmacological effects, albeit to a lesser degree compared with the 24 µg/kg dose in the multiple ascending dose study (Nektar Study 17-358-02).

The $t_{1/2}$ of rezpegaldesleukin is approximately 8 to 13 days and supports evaluation of a q4w dosing regimen. In addition, PK/PD modeling of data from the Phase 1 program suggests that 24 µg/kg q4w dosing may achieve a similar peripheral blood Treg PD response as the 24 µg/kg q2w regimen. Therefore, this less frequent dosing regimen will be evaluated to identify if there is a differential effect on the total PD response and how this relates to efficacy and tolerability.

2.7.2.3 Arm C: Low-Dose, High-Frequency Regimen: 18 µg/kg q2w

Though both the 12 µg/kg q2w and 24 µg/kg q2w regimens tested in the KFAD study demonstrated good efficacy and tolerability in patients with moderate-to-severe AD, the 24 µg/kg level showed relatively higher efficacy and the 12 µg/kg dose level demonstrated relatively better tolerability. The treatment effect remained more pronounced among the patients dosed at 24 µg/kg dose, even out to Week 48 without any additional therapy. However, 3 of the 17 patients enrolled at the 24 µg/kg dose level discontinued the study early due to a treatment-related AE, whereas only 1 of the 16 patients discontinued the study early due to a treatment-related AE at the 12 µg/kg dose level. Detailed safety data from the Study KFAD at this dose level (ie, 12 µg/kg) are discussed in Section 2.5.

The 18 µg/kg dose level, which represents a weight based mid-point between the 12 µg/kg and 24 µg/kg dose levels, will be evaluated to further optimize clinical efficacy and tolerability of rezpegaldesleukin, where the early clinical signal in this same indication is promising.

2.7.3 Maintenance Dosing Regimens

Four rezpegaldesleukin dosing regimens will be evaluated in the Maintenance Period of the study:

- 18 µg/kg q4w vs every 12 weeks (q12w) for patients assigned to the rezpegaldesleukin 18 µg/kg q2w regimen during induction and observed to have achieved at least an EASI-50 at the Week 16 Visit
- 24 µg/kg q4w vs q12w for patients assigned to the rezpegaldesleukin 24 µg/kg q2w or q4w regimen during induction and observed to have achieved at least an EASI-50 at the Week 16 Visit

Patients randomized in the Maintenance Period will be evaluated to determine whether the responses attained during induction can be sustained. Based on observations after dosing was completed in Study KFAD along with PK/PD modeling of the data in Study KFAD, it is anticipated that q12w dosing may result in response durability, albeit at a possibly lower extent in some patients. The less frequent dosing regimens in the Maintenance Period will also permit the evaluation of safety to determine if efficacy can be maintained with a potentially more favorable safety profile.

2.7.4 Dosing Duration Up to 52 Weeks

The available chronic toxicity studies, clinical safety, efficacy, and PD data from Phase 1 studies in healthy volunteers and patients support continued development over a longer time course in this study. The Phase 1 studies include data from a weight-based dose level given for 12 weeks approximating the highest dose to be used in this study (24 µg/kg). Further, the Phase 2 KFAJ study (in patients with SLE) evaluated flat-dosing of 900 to 1800 µg q2w for up to 24 weeks.

2.7.5 Weight-based Dosing

For this trial weight-based dosing will be used. Weight-based dosing is expected to minimize variability, ensure that each patient receives the target dose, and ensure a consistent safety profile with earlier studies. A number of prior studies with rezpegaldesleukin used weight-based dosing, including the single-ascending dose study (Nektar Study 16-358-01), multiple-ascending dose study (Nektar Study 17-358-02), and multiple dose studies (including KFAD, the Phase 1b study forming the basis for this Phase 2b study).

3.0 STUDY OBJECTIVES

Study objectives and endpoints are provided in Table 7. Additional details will be provided in the statistical analysis plan.

Table 7: Study Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To compare the efficacy of each dose regimen of rezpegaldesleukin versus placebo as measured by the percent change from baseline in EASI in the treatment of biologic-naive patients with moderate-to-severe AD.	Mean percent change in EASI from baseline at Week 16
Secondary Objectives	**Secondary Endpoints**
To compare the efficacy of rezpegaldesleukin versus placebo as measured by improvement in signs and/or symptoms in the treatment of biologic-naive patients with moderate-to-severe AD.	Proportion of patients from baseline at Week 16 achieving • vIGA-AD of 0 or 1 and at least a 2-point reduction. • EASI-75 • EASI-90 • EASI-50 • ≥ 4-point improvement from baseline in Itch NRS in the subset of patients with ≥ 4-point Itch NRS at baseline • SCORAD-75 • SCORAD-50 Mean percent change from baseline over the period between Week 0 and Week 16 in • EASI • SCORAD • BSA involvement In addition, all of the above efficacy assessments will be further evaluated at other time points during induction therapy, maintenance therapy, and follow-up.
In the subpopulation of patients with baseline EASI of at least 18.0, to compare the efficacy of rezpegaldesleukin versus placebo as measured by improvement in signs and/or symptoms in the treatment of biologic-naive patients with moderate-to-severe AD.	In the subpopulation of patients with baseline EASI of at least 18.0, proportion of patients from baseline at Week 16 achieving • **vIGA-AD of 0 or 1 and at least a** 2-point reduction. • EASI-75 • EASI-90 • EASI-50 • ⩾ 4-point improvement from baseline in Itch NRS in the subset of patients with ⩾ 4-point Itch NRS at baseline. • SCORAD-75 • SCORAD-50 Mean change/percent change from baseline over the period between Week 0 and Week 16 in • EASI • SCORAD • BSA involvement In addition, all of the above efficacy assessments will be further evaluated at other time points during induction therapy, maintenance therapy, and follow-up.

Table 7: Study Objectives and Endpoints (Contd)

Secondary Objectives	**Secondary Endpoints**
To characterize the PK of rezpegaldesleukin in patients with moderate-to-severe AD.	Rezpegaldesleukin plasma concentrations at various time points assessed throughout the study
To describe the observed safety of rezpegaldesleukin in patients with moderate-to-severe AD.	Incidence of • Serious adverse events • Treatment-emergent adverse events
Exploratory objectives and endpoints may include, but not be limited to, evaluations of the following at various study time points:	
Exploratory Objectives	**Exploratory Endpoints**
To evaluate signs and symptoms (including efficacy and patient-reported outcomes measures) at each time point collected in all patients.	Mean change/percent change as well as proportion of patients from baseline at Week 16 achieving • Improvement in DLQI • Improvement in POEM • Improvement in ADCT • Improvement in ADSS • Improvement in Skin Pain NRS CCI [redacted]

[redacted]
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Table 7: Study Objectives and Endpoints (Contd)

Abbreviations: CCI AD = atopic dermatitis; CCI ADCT = Atopic Dermatitis Control Tool; ADSS = Atopic Dermatitis Sleep Scale; BSA = body surface area; C-SSRS = Columbia-Suicide Severity Rating Scale; DLQI = Dermatology Life Quality Index; EASI = Eczema Area and Severity Index; EASI-50/75/90 = patient's EASI is reduced by at least 50%/75%/90% relative to their baseline score; CCI NRS = numerical rating scale; CCI CCI PK = pharmacokinetics; POEM = Patient-Oriented Eczema Measure; SALT = Severity of Alopecia Tool; SB = suicidal behavior; SCORAD = SCORing Atopic Dermatitis Index; SCORAD-50/75 = patient's SCORAD is reduced by at least 50%/75% relative to their baseline score; SI = suicidal ideation; CCI vIGA-AD = Validated Investigator Global Assessment for Atopic Dermatitis

4.0 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

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

Informed consent and contraception requirements

1) Provide written, informed consent to participate in the study and follow the study procedures, including compliance with the use of highly effective contraceptive methods for women of childbearing potential (WOCBP) or male patients with partners who are WOCBP.

Patient characteristics

2) Male or female patients, at least 18 years of age, on the day of signing the informed consent form.

   Note: In some jurisdictions, the legal age of consent for study participation is greater than 18 years. For sites in such jurisdictions, the legal age of consent will be used as the lower limit of the age range for this criterion.

Disease-specific characteristics

3) Present with a diagnosis of AD at least 12 months prior to screening (Visit 1), as defined by the American Academy of Dermatology "Guidelines of care for the management of atopic dermatitis: Section 1. Diagnosis and assessment of atopic dermatitis" (Eichenfield, 2014).
4) Patients must meet the AD severity criteria:
   a) EASI ≥ 16.0 at screening (Visit 1) and randomization (Visit 2).
   b) vIGA-AD score ≥ 3 at screening (Visit 1) and randomization (Visit 2).
   c) ≥ 10% of BSA involvement at screening (Visit 1) and randomization (Visit 2).
5) Are candidates for systemic therapy and have history, documented by a physician and/or the Investigator, of inadequate response to existing topical medications within 6 months preceding screening (Visit 1), or history of intolerance to topical therapy as defined by at least 1 of the following:
   a) Inability to achieve good disease control defined as mild disease or better (eg, vIGA-AD ≤ 2) after use of at least a medium potency TCS for at least 4 weeks, or for the maximum duration recommended by the product prescribing information, eg, 14 days for super potent TCS, whichever is shorter. Note: For the purpose of this criterion, a TCS may be used with or without TCI to address areas of disease.

      Note: Failing a nonbiologic systemic therapy intended to treat AD, eg, cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or other small molecules, within

6 months before screening (Visit 1) will be considered a surrogate for inadequate response to existing topical medications.

b) A history of clinically significant adverse reactions with the use of TCS, eg, skin atrophy, allergic reaction, or systemic effects that, in the opinion of the Investigator, outweigh the benefits of retreatment.

6) Have applied a stable dose of an emollient at least once daily for at least 1 week before the day of randomization (Visit 2) and agree to at least once daily use of an emollient continuously throughout the study.

7) Completed electronic diary entries for all protocol-required patient reported outcomes for a minimum of 4 of 7 days preceding randomization (Visit 2).

4.2 Exclusion Criteria

Patients will be excluded from the study if they meet any of the following criteria:

Skin conditions

1) Have a history of eczema herpeticum:
   a) Any episode within 12 months prior to randomization (Visit 2), or
   b) 2 or more episodes during lifetime
2) Are currently experiencing or have a history of concomitant skin conditions other than AD (eg, psoriasis or cutaneous lupus), that, in the opinion of the Investigator, would interfere with assessments or interpretation of the effect of study intervention on AD.
3) Are currently experiencing or have a history of erythrodermic, refractory, or unstable skin disease requiring frequent hospitalizations or intravenous (IV) treatment, and, in the opinion of the Investigator, could interfere with study participation.
4) Are currently experiencing a skin infection in the area affected by the patient's AD that requires treatment with, or is currently being treated with, topical antimicrobial therapy.

   Note: Patients who are not eligible (screen fail) due to this criterion should not be rescreened until at least 4 weeks after screen failure and at least 2 weeks after resolution of the infection.

5) History of chronic idiopathic urticaria at any time or urticaria from other causes within 4 weeks prior to randomization (Visit 2).
6) Are currently experiencing or have a history of unstable course of AD (ie, spontaneously improving or worsening) per Investigator's judgment (eg, greater than 25% improvement in EASI score between screening and randomization visit).

Previous or current therapies

7) Have a history of TCS use suggestive of a high risk for TCS withdrawal (eg, a history of prolonged or frequent use of moderate- to high-potency TCS, especially on the face [Hajar, 2015]), such that, in the opinion of the Investigator, the patient will be unable to withdraw and abstain from TCS for several weeks during the study.

8) Have received any of the following treatments at any time before Visit 1:

   a) Aldesleukin

   b) Investigational IL-2 analog

   c) Oral Janus kinase (JAK) inhibitor for any indication, including, but not limited to, baricitinib, upadacitinib, abrocitinib, tofacitinib, and ruxolitinib, whether marketed or investigational

   d) Systemic immune-modulating biologic therapy (including, but not limited to, dupilumab, tralokinumab, lebrikizumab, nemolizumab, rocatinlimab, etc.) whether marketed or investigational

9) Have received any of the following therapies during the specified time period ("washout") or are anticipated to require any of these therapies during the study:

Criterion	**Therapy**	**Time period ("washout") before the first dose of study intervention[a]**	**Note**
a.	Biologic agents, whether investigational or marketed, including, but not limited to: • dupilumab, tralokinumab, and other drugs in the same class targeting IL4/13/31 • omalizumab, and • other monoclonal antibodies	Any previous use	Not permitted
b.	Oral JAK-inhibitors, whether investigational or marketed, including, but not limited to: • abrocitinib • baricitinib • upadacitinib	Any previous use	Not permitted
c.	Corticosteroids that are • parenteral (administered via intra-articular, intramuscular, or IV route), or • rectally administered (enemas or suppositories)	4 weeks	Intranasal or inhaled or ophthalmic (ocular) steroids are allowed at any time.
d.	Oral systemic corticosteroids	4 weeks	
e.	Oral phosphodiesterase type 4 (PDE4) inhibitor	4 weeks	

Criterion	Therapy	Time period ("washout") before the first dose of study intervention[a]	Note
f.	Systemic immunomodulators, including, but not limited to: • cyclosporine • methotrexate • mycophenolate mofetil, or • azathioprine	4 weeks	
g.	Other systemic therapy used to treat AD or symptoms of AD, whether approved/marketed or off-label use	4 weeks	
h.	Any investigational small molecule	4 weeks or 5 half-lives (whichever is longer)	
i.	Phototherapy, including • therapeutic phototherapy (psoralen plus ultraviolet A, ultraviolet B) • excimer laser, or • tanning beds	4 weeks	
j.	Topical immune modulators, including TCIs (eg, tacrolimus, pimecrolimus) and topical JAK inhibitors (eg, ruxolitinib, delgocitinib)	1 week	
k.	Topical PDE4 inhibitor (eg, crisaborole)	1 week	
l.	Bleach bath		Patients regularly doing bleach baths may continue with a frequency of no more than twice per week during the study.
m.	TCS	1 week	Topical steroids are permitted as rescue therapy between Days 1 and 14 (inclusive) during the Induction Period and throughout the Maintenance Period, per Section 5.8.1.
n.	Prescription moisturizers	1 week	

Abbreviations: AD = atopic dermatitis; IL-4/13/31 = interleukin 4/13/31; IV = intravenous; JAK = Janus kinase; PDE4 = phosphodiesterase type 4; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid

a. The washout period in this table includes the day of the first dose of study intervention.

10) Have received any live vaccine (that is, live attenuated) within less than 12 weeks before randomization (Visit 2) or intend to receive a live vaccine during the study or within 12 weeks after receiving the last dose of study intervention.

    Note: The following are not considered live vaccines: ribonucleic acid (RNA) vaccines, vaccines with inactive viral elements, and/or nonreplicating viral vector vaccines.

11) Have received a Bacillus Calmette-Guerin (BCG) vaccination or treatment within less than 4 weeks before randomization (Visit 2) or intend to receive BCG vaccination or treatment during the study or within 12 weeks after receiving the last dose of study intervention.

12) Are unstable with respect to use of chronic treatments (prescription or over-the-counter) to improve sleep:

    a) Have started or restarted using a sleep medication during the 2 weeks before the day of the first dose of study intervention

    b) Have changed the dose of a sleep medication during the 2 weeks before the day of the first dose of study intervention, or

    c) Are likely to need to start or change the dose of sleep medication during this study, in the opinion of the Investigator

    Note: Individuals on a stable dose of sleep medication at screening may be eligible to be enrolled if other study entry criteria are met, but such individuals should remain on the stable dose throughout the study unless, in the Investigator's opinion, the dose should be changed or stopped to address a safety concern.

Previous or current infections

13) Have a current or recent acute, active infection. For at least 30 days prior to Screening (Visit 1) and up to the Randomization Visit (Visit 2), patients must have no symptoms or signs of confirmed or suspected infection, and must have completed any appropriate anti-infective treatment.

    Note: Patients who have an oral, upper respiratory, or vaginal candida infection and who are being treated only symptomatically and not requiring systemic anti-infectives may be considered for enrollment if other study eligibility criteria are met. Enrollment of patients with other uncomplicated local infections should be discussed with the Sponsor's designated Medical Monitor.

14) Have had any of the following types of infection within 12 weeks prior to the Screening Visit (Visit 1) or develops any of these infections before the Randomization Visit (Visit 2):

    a) Serious (requiring hospitalization, or IV or equivalent oral antibiotic treatment, or both)

    b) Opportunistic (as defined in Winthrop, 2015)

Note: Herpes zoster is considered active and ongoing until all vesicles are dry and crusted over.

c) Chronic (duration of symptoms, signs, and/or treatment of 6 weeks or longer)

d) Recurring (including, but not limited to, herpes simplex, herpes zoster, recurring cellulitis, chronic osteomyelitis)

Note: Patients with only recurrent mild and uncomplicated oral herpes, or genital herpes, or both may be discussed with the Sponsor's designated Medical Monitor and considered for enrollment if other study eligibility criteria are met.

15) Have active tuberculosis (TB) (See Section 9.1.6)

16) Have or have had latent tuberculosis infection that has not been treated with a complete course of appropriate therapy as defined by the World Health Organization (WHO) and the United States Centers for Disease Control (CDC), unless such treatment is underway (see Section 9.1.6.1)

Note: With a prior history of active or latent TB, even if having documented initiation or completion of a full course of anti-TB therapy, patient is only eligible for participation following a written approval by a TB specialist or an infectious diseases specialist.

17) Have a current infection with hepatitis B virus (HBV) (that is, positive for hepatitis B surface antigen [HBsAg] and/or polymerase chain reaction [PCR] positive for HBV deoxyribonucleic acid [DNA]) (see Section 9.1.7)

18) Have a current infection with hepatitis C virus (HCV) (that is, positive for HCV RNA) (see Section 9.1.8)

19) Have human immunodeficiency virus (HIV) infection

Diagnostic assessments

20) Have any of the following specific abnormalities on screening laboratory tests:

a) Serum creatinine, ALT, or AST > 2 × ULN

b) Alkaline phosphatase (ALP) ≥ 2 × ULN

c) Total bilirubin level (TBL) ≥ 1.5 × ULN

d) Hemoglobin < 10.0 g/dL

e) Eosinophilia (absolute eosinophil count) > 1000 cells/µL

f) Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] Creatinine Equation) (FDA 2020; NKF 2021)

Note: For repeat testing of screening laboratory tests, see Section 4.4.1.

21) Have other laboratory test results at screening (Visit 1) which are outside the normal reference range for the population or study site and, in the opinion of the Investigator, indicate unacceptable risk for the patient's safety in the study

22) Have screening ECG abnormalities that, in the opinion of the Investigator, are clinically significant and indicate an unacceptable risk for the patient's safety in the study

Other previous or current medical conditions

23) Have history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the patient to infection

24) Have a history of organ or bone marrow transplant or will require such a transplant during the study

25) Have any serious concomitant illness that:

a) Requires treatment with systemic corticosteroids, or

b) Requires active frequent monitoring (eg, unstable chronic asthma), or

c) Would otherwise interfere with study participation, in the opinion of the Investigator

26) Have history of any major surgery within 12 weeks before the Screening Visit (Visit 1) or will require major surgery during the study

27) Have experienced a thrombotic event within 24 weeks before randomization (Visit 2) or are on anticoagulants and in the opinion of the Investigator are not well controlled regarding management of hypercoagulable risk

28) Have a history of any of the following within 12 months before the Screening Visit (Visit 1):

a) Myocardial infarction

b) Unstable ischemic heart disease

c) Cerebrovascular accident

d) Stroke

e) New York Heart Association Stage III or IV heart failure

29) Have significant and uncontrolled disease, in the opinion of the Investigator, such as:

a) Cardiovascular disease, eg, uncontrolled hypertension, angina, or congestive heart failure

b) Endocrine disorder, eg, diabetes or thyroid dysfunction

c) Respiratory, hepatic, renal, gastrointestinal, hematologic, or neuropsychiatric disorder

Note: Neuropsychiatric disorders include, but are not limited to:

- History of severe depression within 6 months of Screening (Visit 1), or
- Patient Health Questionnaire-9 (PHQ-9) Score of ≥ 15 at Screening (Visit 1) or Randomization (Visit 2), or

- Psychiatric inpatient hospitalization (or partial hospitalization, sometimes referred to as a psychiatric day program) within the past year prior to screening;
- Changes in psychiatric medication or dosage within 8 weeks of Randomization (Visit 2).

Note: If the Investigator suspects a significant neuropsychiatric disorder, a mental health professional (ie, psychiatrist or clinical psychologist) should be consulted prior to randomizing the patient.

d) Are considered by the Investigator to be at significant risk for suicide based on the following criteria at Screening (Visit 1) or Randomization (Visit 2):

- Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia-Suicide Severity Rating Scale (C-SSRS), or
- Have answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS, and
- The ideation or behavior occurred within the past 6 months

Note: If the investigator suspects a significant risk for suicide, a mental health professional (ie, psychiatrist or clinical psychologist) should be consulted.

e) Any other serious or unstable illness that could constitute an unacceptable risk to the patient when taking an IMP or could interfere with the interpretation of study data

30) Have a diagnosis or history of malignant disease within 5 years prior to randomization (Visit 2), with the following exceptions:

a) Basal cell or squamous epithelial carcinomas of the skin that have been successfully treated with no evidence of metastatic disease for 3 years

b) Cervical carcinoma in situ that has been successfully treated, with no evidence of recurrence within the 3 years prior to randomization (Visit 2)

31) Have 1 or more of the following conditions suggesting a possibly greater risk of clinically significant hypersensitivity reactions:

a) Known allergy to rezpegaldesleukin, related compounds, or any components of the formulation, including PEG

b) History of drug hypersensitivity reactions that in the opinion of the Investigator may predispose the patient to a clinically significant hypersensitivity reaction to rezpegaldesleukin or its formula excipients

c) Clinically significant multiple or severe drug allergies

d) History of severe posttreatment hypersensitivity reactions, including, but not limited to, erythema multiforme major, linear immunoglobulin A (IgA) dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis

Previous or concurrent clinical trial participation

32) Have participated in a clinical study involving an IMP within the 30 days prior to Screening. If the previous IMP has a long half-life, at least 5 half-lives or 30 days (whichever is longer) should have passed before the Randomization Visit (Visit 2) of Study 23-358-05.

33) Are currently enrolled in any other clinical study involving an IMP or any other type of medical research judged not to be scientifically or medically compatible with this study

34) Was previously randomized in Study 23-358-05 or received rezpegaldesleukin in any other study

Other exclusions

35) Are pregnant or breastfeeding or are intending to become pregnant or to breastfeed at any time in the study

    Note: Individuals of childbearing potential must test negative for pregnancy as indicated by a negative serum pregnancy test at the Screening Visit (Visit 1) followed by a negative urine pregnancy test within 24 hours prior to the first exposure to study intervention.

36) Have evidence of current or a recent history (that is, within 6 months before Visit 1) of any substance use disorders, including but not limited to, cannabis use disorder, of any severity as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) (American Psychiatric Association [APA] 2013), in the opinion of the Investigator, excepting disorders of nicotine or caffeine use

    Note: Patients are to be excluded by this criterion if there is evidence (per Investigator or per patient's self-report) of use of marijuana, marijuana extract, or tetrahydrocannabinol (THC) containing products as self-medication for symptoms of AD or other conditions. See Section 5.8.3 for any prohibitions on the concomitant use of cannabidiol (CBD) products or medically prescribed marijuana, marijuana extract, or THC-containing products for the treatment of AD symptoms or other conditions during the study.

37) Have received blood products within 6 months prior to screening (Visit 1)

38) Have donated more than a single unit of blood within 4 weeks before randomization (Visit 2) or intend to donate blood during the study

39) Have insufficient venous access for the protocol-required blood sampling

40) Are investigative site personnel directly affiliated with this study or are their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

41) Are employees of Nektar Therapeutics or are employees of a third-party organization which is involved in the study and requires exclusion of their employees

42) Are unable or unwilling to make themselves available for the required number of study visits or unwilling to follow the restrictions and procedures of the study

43) Are, in the opinion of the Investigator, unsuitable for inclusion in the study

44) Have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

4.3 Lifestyle Considerations

Study patients should be instructed not to donate blood or blood products for 20 weeks following their last dose of study intervention.

Study patients must agree to the contraception and breastfeeding criteria detailed in Section 4.1, Section 4.2, and Appendix 3.

4.4 Screen Failures

A screen failure occurs when a patient who consents to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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 SAE.

4.4.1 Allowed Retesting of Screening Investigations

Repeating of screening investigations (without a requirement for screen failure and rescreening) is allowed at the discretion of the Investigator. These screening investigations may be retested 1 time at the discretion of the Investigator:

- Screening hematology and chemistry laboratory tests: These are allowed when results are outside the acceptable range for study entry but may be within the acceptable range upon retesting, due to test-retest variability.
- Retesting or confirmatory testing for TB:
  - One retest is allowed for patients with an “indeterminate” QuantiFERON®-TB Gold assay. Patients with 2 indeterminate QuantiFERON-TB Gold assays assays will be excluded. See Section 9.1.6.
  - The Investigator may discuss retesting with the Sponsor’s designated Medical Monitor if:
    - the Investigator suspects a false positive result in a patient with no increased risk of TB infection during lifetime, and
    - there is no evidence of prior or current TB on physical examination and/or on chest x-ray interpreted by radiologist and/or pulmonologist (Investigator assessment by history and physical examination, and with documented chest x-ray report).

- Repeating of other screening investigations should be discussed with the Sponsor's designated Medical Monitor prior to retesting.

4.4.2 Rescreening of Individuals Who Failed Screening

4.4.2.1 Informed Consent for Rescreenings

Each time an allowed rescreening is performed, the individual being rescreened must sign a new informed consent form (ICF).

4.4.2.2 Rescreening After Failure to Meet Study Entry Criteria

An individual who does not meet the study entry criteria may be rescreened 2 times if the reason for the screen failure has resolved and in consultation with the Sponsor's designated Medical Monitor in advance of the rescreening. The interval between the time of screen failure to the start of the rescreening should be at least 4 weeks, unless the Investigator and the Sponsor's designated Medical Monitor agree on a shorter interval.

4.4.2.3 Procedures Not Required to be Repeated During Rescreening

Protocol-required screening TB tests are not required to be repeated during rescreening if these procedures were performed within 90 days before the date of signing the rescreening ICF. However, these procedures can be repeated at the discretion of the Investigator if allowed by local regulations and guidelines.

4.4.2.4 Rescreening for Administrative Reasons

An individual may be rescreened 1 time for an administrative reason, including, but not limited to, falling out of the screening window due to scheduling conflicts. The Sponsor's designated Medical Monitor does not need to approve rescreening for an administrative reason. The rescreening can start immediately after the administrative reason has resolved.

5.0 INVESTIGATIONAL PLAN

5.1 Overall Study Design

This is a Phase 2b, multicenter, randomized, double-blinded, parallel-group, placebo-controlled, outpatient dose-ranging study to evaluate the efficacy and safety of multiple rezpegaldesleukin induction and maintenance dosing regimens in adult patients with AD. The study population includes biologic-naive patients with diagnosed AD which is moderate-to-severe as measured by EASI ≥ 16.0, vIGA-AD score ≥ 3, and ≥ 10% of BSA involvement at randomization.

The study schematic is provided in Figure 1.

5.2 Study Periods

This study includes 4 periods over a total study duration of approximately 106 to 109 weeks, inclusive of Screening:

- Screening: from 15 to 35 days prior to randomization at Week 0 (Visit 2)
- Treatment Period – Induction: from randomization at Week 0 (Visit 2) through assessments at Week 16 (Visit 10)
- Treatment Period – Maintenance: from dose administration at Week 16 through assessments at Week 52 (Visit 19), and
- Posttreatment Follow-up: 5 visits, the first occurring at Week 56 and the remaining visits occurring approximately every 3 months from last dose through Week 104 (±2 weeks)
    - Follow-Up Visit 1 should occur ≥ 30 (+7) days from the last dose of study drug or before a new atopic dermatitis regimen starts
    - Follow-Up Visits 2 through 5 occurs approximately every 13 weeks (±14 days) from the last dose of study drug or until a new atopic dermatitis regimen starts

5.2.1 Screening Period

The Screening Period begins with Visit 1, which occurs from 15 to 35 days before the Randomization Visit. For patients with severe AD (vIGA-AD score of 4) at Screening Visit 1, the screening window may be from 7 to 35 days before the Randomization Visit if all eligibility criteria have been met. Informed consent will be obtained at Visit 1 before any other study procedures are performed, and a patient identification number will be assigned. The Schedule of Events (SoE; Section 1.2) lists the screening procedures for Visit 1. Rescreening after screen failure may be allowed after discussion with the Medical Monitor (Section 4.4.2).

Eligible patients will be randomized to one of the induction dosing regimens listed in Table 8, using a 3:3:3:2 ratio.

Table 8: Dosing Regimens in the Induction Period

Induction Regimen	Approximate Number of Patients Planned
Rezpegaldesleukin 24 µg/kg q2w	108
Rezpegaldesleukin 24 µg/kg q4w	108
Rezpegaldesleukin 18 µg/kq q2w	108
Placebo q2w	72

Abbreviations: q2w = every 2 weeks; q4w = every 4 weeks

5.2.2 Treatment Period - Blinded Induction

Randomized patients will begin the double-blinded, placebo-controlled, 16-week induction period when the initial dose is administered at Visit 2 (Study Day 1).

The schedule of study treatments administered in the Induction Period is provided in Table 9.

Table 9: Study Treatments Administered in the Induction Period

Treatment Group	Study Week							
	0	2	4	6	8	10	12	14
Arm A: Rezpeg 24 µg/kg q2w	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg
Arm B: Rezpeg 24 µg/kg q4w	24 µg/kg	Placebo	24 µg/kg	Placebo	24 µg/kg	Placebo	24 µg/kg	Placebo
Arm C: Rezpeg 18 µg/kg q2w	18 µg/kg	18 µg/kg	18 µg/kg	18 µg/kg	18 µg/kg	18 µg/kg	18 µg/kg	18 µg/kg
Arm D: Placebo q2w	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Abbreviations: Rezpeg = rezpegaldesleukin; q2w = once every 2 weeks; q4w = once every 4 weeks
Refer to the pharmacy manual for additional information on weight-based dosing.

Between Days 1 and 14, patients experiencing intolerable AD symptoms may receive rescue treatment for AD, at the discretion of the Investigator. Additional guidance and restrictions in rescue treatment are provided in Section 5.8.

This study design includes Investigator and patient blinding (masking). Investigators will remain blinded to each patient's assigned study intervention throughout the course of the study. If a patient enrolls into the Escape Arm and receives open-label treatment, Investigators will remain blinded to the patient's study intervention assigned in the Induction Period and the Maintenance Period.

5.2.3 Treatment Period - Blinded Maintenance

The blinded 36-week maintenance treatment period begins with the dose administered at Week 16. Patients having at least an EASI-50 response at Week 16 will receive a maintenance dosing regimen, as listed in Table 10.

Table 10: Maintenance Dosing Regimen for Week 16 Responders (Achieved EASI-50)

Week 16 responders (ie, achieved EASI-50) who were originally randomized to this induction regimen…	**will receive this maintenance regimen:**
Arm A: Rezpegaldesleukin 24 µg/kg q2w	by rerandomization in 1:1 ratio: Arm A1: Rezpegaldesleukin 24 µg/kg q4w, or Arm A2: Rezpegaldesleukin 24 µg/kg q12w
Arm B: Rezpegaldesleukin 24 µg/kg q4w	by rerandomization in 1:1 ratio: Arm B1: Rezpegaldesleukin 24 µg/kg q4w, or Arm B2: Rezpegaldesleukin 24 µg/kg q12w
Arm C: Rezpegaldesleukin 18 µg/kg q2w	by rerandomization in 1:1 ratio: Arm C1: Rezpegaldesleukin 18 µg/kg q4w, or Arm C2: Rezpegaldesleukin 18 µg/kg q12w
Arm D: Placebo q2w	Arm D: Placebo q4w

Abbreviations: EASI-50 = patient's Eczema Area and Severity Index is reduced by at least 50% relative to their baseline score; q12w = every 12 weeks; q2w = every 2 weeks; q4w = every 4 weeks

Refer to the pharmacy manual for additional information on weight-based dosing.

Refer to Section 5.5 Dose Modification for patients with a reduced dose.

Patients assigned to q12w arms during maintenance will be administered placebo on Weeks 20, 24, 32, 36, 44, and 48 to satisfy the q4w maintenance dosing schedule.

The schedule of study treatments administered in the Maintenance Treatment Period is provided in Table 11.

Table 11: Study Treatments Administered in the Maintenance Period for Week 16 Responders (Achieved EASI-50)

Treatment Group	Study Week									
	16	20	24	28	32	36	40	44	48	52
Arms A1 and B1: Rezpeg CCI q4w	CCI									
Arms A2 and B2: Rezpeg CCI q12w										
Arm C1: Rezpeg CCI q4w										
Arm C2: Rezpeg CCI q12w										
Arm D1: Placebo q4w										

Abbreviations: EASI-50 = patient's Eczema Area and Severity Index is reduced by at least 50% relative to their baseline score; Rezpeg = rezpegaldesleukin; q12w = once every 12 weeks; q4w = once every 4 weeks

Refer to the pharmacy manual for additional information on weight-based dosing.

Refer to Section 5.5 Dose Modification for patients with a reduced dose.

Patients who have adhered to the rescue medication rules and who do not achieve EASI-50 at Week 16 may receive escape therapy. In addition, the Maintenance Period includes an Escape Arm for patients who, despite use of topical TCS, have an acute exacerbation (ie, drop to a score of less than EASI-25), suggesting the need for an active or more frequently administered dose. A patient will receive this Escape Arm therapy under the conditions listed in Table 12.

Table 12: Criteria for Escape Therapy

Begin Rezpegaldesleukin 24 µg/kg q2w as escape therapy…	**if the patient:**
At Week 16 following induction	has not achieved an EASI-50 response.
At Week 20, 24, 28, 32, 36, 40, 44, 48 or an unscheduled visit for patients on maintenance therapy	has dropped to less than an EASI-25 response and with Medical Monitor consultation.

Abbreviations: EASI = Eczema Area and Severity Index; EASI-25 = patient's EASI is reduced by at least 25% relative to their baseline score; EASI-50 = patient's EASI is reduced by at least 50% relative to their baseline score; q2w = every 2 weeks

The schedule of study treatments administered for patients receiving Escape Arm therapy is provided in Table 13.

Table 13: Study Treatments Administered in the Maintenance Period for Patients in the Escape Arm

Treatment Group	Study Weeks																		
	16	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**32**	**34**	**36**	**38**	**40**	**42**	**44**	**46**	**48**	**50**	**52**
Rezpeg q2w	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg	24 µg/kg

Abbreviations: Rezpeg = rezpegaldesleukin; q2w = once every 2 weeks

Refer to the pharmacy manual for additional information.

Refer to Section 5.5 Dose Modification for patients with a reduced dose.

A patient assigned to the Escape Arm will continue receiving escape therapy through the last dosing visit of the study (Week 52) unless the patient is discontinued from study therapy per protocol. Additionally, any patient on the Escape Arm that does not achieve an EASI-50 at any point through Week 32 assessment will discontinue from study therapy. Patients in the Escape Arm will follow the Maintenance Period schedule, with an additional study drug administration visit between each Maintenance Period study drug administration visit to increase the frequency of study drug administration to q2w.

In the Maintenance and Posttreatment Follow-up Period, intermittent use of topical rescue medication is permitted (not required) for patients who demonstrate need based on clinical judgment.

Section 1.2 provides the study assessments to be performed during the treatment period. If scheduled visits or assessments coincide with a weekend or holiday, schedule at the next feasible date. Please contact the Medical Monitor to discuss any concerns about study visits or assessments that may fall out of the protocol-specified window because of unforeseen delays or other patient-specific circumstances. All out of window visits and procedures will incur a protocol deviation.

5.2.4 Posttreatment Follow-up Period

For patients who have completed treatment per protocol, the last visit in the Maintenance Period is Week 52. Five subsequent follow-up visits will also occur, as listed in Table 14.

For patients who discontinue study intervention, the Posttreatment Follow-Up visits will occur as listed in Table 14 and SoE Table 1 or Table 2 based on whether the discontinuation occurred during the Induction Period or the Maintenance Period, respectively.

Table 14: Schedule for Follow-up Visits

Condition	First Posttreatment Safety follow-up visit (+4-Weeks and ≥ 30 Days [+ 7])	Posttreatment follow-up visits every three months (q3m)
If the patient **did not** discontinue study intervention early…	occurs approximately 4 weeks and ≥ 30 days [+ 7] after the last dose of study drug (ie, Week 56) or before a new atopic dermatitis regimen (Table 15) starts	occurs approximately every 13 weeks (± 14 days) from the last dose of study drug (ie, Weeks 65, 78, 91, 104) or until a new atopic dermatitis regimen (Table 15) starts
Patients who have discontinued treatment early per protocol are to continue with study assessments. The last visit in the Early Discontinuation Induction Period is Week 16 and the last visit in the Early Discontinuation Maintenance Period is Week 52. Subsequent follow-up visits will also occur, as listed here:		
If the patient **did** discontinue study intervention early during Induction…	occurs after the early discontinuation (ED) visit and occurs approximately 4 weeks and ≥ 30 days [+ 7] after the last dose of study drug and this visit. The patient should then continue visits during the Induction Period up through and including Week 16.	occurs approximately every 13 weeks (± 14 days) from Week 16 for up to 12 months (ie, Weeks 29, 42, 55, 68) or until a new atopic dermatitis regimen (Table 15) starts
If the patient **did** discontinue study intervention early during Maintenance…	occurs after early discontinuation (ED) visit and occurs approximately 4 weeks and ≥ 30 days [+ 7] after the last dose of study drug and this visit. The patient should then continue visits during the Maintenance Period up through and including Week 52.	occurs approximately every 13 weeks (± 14 days) from Week 52 (ie, Weeks 65, 78, 91, 104) or until a new atopic dermatitis regimen (Table 15) starts

Abbreviations: ED = early discontinuation; q3m = once every 3 months

5.3 Randomization Stratification

The randomization stratification factors are as follows:

- At Visit 2 (Week 0 Day 1) for the Induction Period
  - Disease severity measured by vIGA-AD (vIGA-AD score of 3 [moderate] vs 4 [severe])
  - Region (North America vs rest of world)
- At Visit 10 (Week 16 Day 1) for the Maintenance Period
  - Disease response measured by % EASI reduction from baseline (EASI-50 to EASI-74 vs EASI-75 to EASI-89 vs EASI-90 to EASI-100)
  - Region (North America vs rest of world)

5.4 Treatment Compliance

Patients will receive study drug at the study site directly from the Investigator or designee, under medical supervision. The date and time of each study drug dose administered in the clinic will be recorded in the source documents and recorded in the case report form (CRF). The dose of study drug and study patient identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering study drug.

5.5 Dose Modification

The dosing regimens used in this study are described in Sections 5.2 and 6.1. No modifications to these protocol-specific regimens (dose or frequency) are permitted, except for reasons of immediate patient safety. The Investigator, in consultation with the Sponsor's Medical Monitor, may reduce the dose of the study drug for the following reasons:

- Intolerable and persistent ISR
- Eosinophilia without organ involvement and absolute eosinophil count > 3000 cells/µL with a repeat measurement to confirm the count
- Any toxicity experienced by the patient and deemed by the Investigator to be a tolerability concern that would preclude the patient from continuing treatment at the assigned dose

The dose of the study drug may be modified one time during the study. Once reduced, the dose may not be subsequently increased throughout the remainder of the study Patients requiring dose modification remain eligible for maintenance therapy and/or escape therapy based on Week 16 response assessment criteria at their reduced rezpegaldesleukin dose.

5.6 Continued Access to Study Intervention After the End of the Study

Continued access to the investigational medicinal product will not be provided for patients in this clinical trial.

5.7 Treatment of Overdose

An overdose of rezpegaldesleukin is considered to be any dose greater than the highest dose of rezpegaldesleukin planned for use in this study. The treatment for suspected overdose with rezpegaldesleukin is supportive care.

In the event of an overdose, the Investigator should:

- Contact the Medical Monitor immediately.
- Evaluate the patient to determine, in consultation with the Medical Monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the patient for any AEs/SAEs and laboratory abnormalities as medically appropriate for at least 12 weeks.

5.8 Prior and Concomitant Therapy

Prior Therapy

Relevant prior therapies, as defined in the SoE (Section 1.2), are to be assessed and recorded according to the instructions of the CRF.

Concomitant Therapy

Any vaccine, therapy, or medication, including over-the-counter medicines, prescription medicines, vitamins, and herbal supplements, that the patient receives during the study must be identified and at a minimum assessed and recorded at the visits specified in the SoE, along with:

- reason for their use
- dates of administration, including start and end dates, and
- dosage information for concomitant therapy of special interest, including rescue medication.

The Sponsor's designated Medical Monitor should be contacted if there are any questions regarding concomitant therapy.

5.8.1 Rescue Medication

Rescue medication refers to the use of concomitant medication for treatment of AD. Concomitant medications used for indications other than AD are not considered rescue medications.

5.8.1.1 Rescue Medication During Induction Period

Rescue medications for AD are not permitted after Day 14.

Between Days 1 and 14, patients experiencing intolerable AD symptoms may use rescue treatment for AD, at the discretion of the Investigator, with the following restrictions:

- Up to 5 days of consecutive use of TCS or TCI is permitted.
- Only a mid-potency TCS (eg, triamcinolone acetonide ointment 0.1%) or a low-potency TCS (hydrocortisone 1% cream) or TCI (for use on sensitive skin areas, eg, face) is to be used by the patient.
- High potency TCSs (eg, fluocinonide, clobetasol) are not allowed.
- All patients who adhere to the rescue medication stipulations during the Induction Period, and who complete the study through Week 16 will be eligible to proceed to the Maintenance Treatment Period. Failure to comply with the topical rescue medication stipulations will render a patient ineligible to participate in the Maintenance Treatment and/or Escape Arm; these patients should complete Posttreatment Follow-up Visits per the SoE, respectively.

- Systemic rescue treatments (eg, oral corticosteroids, phototherapy, cyclosporin) are prohibited. If systemic rescue therapy is used, study drug must be discontinued. The patient should continue trial participation by attending all study visits through Week 16. In addition, these patients should complete Posttreatment Follow-up Visits per the SoE, respectively. Patients who required systemic rescue medication are not eligible to participate in the Maintenance Treatment and/or Escape Arm component of the study.

5.8.1.2 Rescue Medication During Maintenance and Posttreatment Follow-up Periods

In the Maintenance and Posttreatment Follow-up Periods, intermittent use of topical rescue medication is permitted (not required) for patients who demonstrate need based on clinical judgment.

5.8.1.3 Assessments Prior to Initiation of Rescue Medication

Investigators should make every attempt to conduct efficacy and safety assessments immediately before administering any rescue medication. An unscheduled visit can be used for this purpose if necessary. This is to allow adequate assessment of skin dryness at the visit.

5.8.1.4 Documentation of Rescue Medication

Rescue medication must be recorded as stated in Section 5.8.

5.8.1.5 Discontinuation Due to Inadequate Control with Rescue Medication

Patients receiving topical rescue medication will continue to receive the assigned study interventions. Patients who receive systemic rescue medication will be discontinued from study intervention and should continue with study assessment per the SoE.

5.8.2 Permitted Concomitant Therapy

5.8.2.1 Permitted Concomitant Therapies for AD

Concomitant therapies for AD during the study are permitted only as described here:

- Daily use of emollients is required as background therapy, as described in Section 6.1.3.
- Topical rescue medication is permitted but not required between Days 1 and 14 (inclusive) of the Induction Period and throughout the Maintenance Period, as described in Section 5.8.1.
- Use of topical and oral nonsedating antihistamines is permitted.

5.8.2.2 Permitted Concomitant Therapies for Other Conditions

Concomitant therapies for conditions other than AD are generally allowed unless described as prohibited in Section 5.8.3. Here is guidance for some of the permitted concomitant therapies:

- Intranasal or inhaled steroids: Use of intranasal or inhaled steroids is allowed at any time for patients with such conditions as asthma and allergic rhinitis.
- Stable dose of sleep medications: Individuals on a stable dose of sleep medication at screening should remain on this stable dose throughout the study unless, in the Investigator's opinion, the dose should be changed or stopped to address a safety concern.
- Use of topical medication(s) is permitted on non-AD affected area(s), as clinically indicated per the product label or prescribed by a medical provider and without additional limitations on time window of usage.
- Use of prophylactic medication(s) is permitted as clinically indicated for tolerability concerns (eg, ISRs) and/or other conditions (eg, COVID).

5.8.3 Prohibited Concomitant Therapy

Medications and treatments prohibited before screening or randomization are noted in the study exclusion criteria (Section 4.2).

Table 15 lists medications and treatments prohibited throughout the study, that is, from randomization until the last Posttreatment Follow-up Visit.

Table 15: Medications and Treatments Prohibited from Randomization through the Last Posttreatment Follow-up Visit

Prohibited Concomitant Therapy	Notes
Biologics: immunomodulating monoclonal antibodies, including, but not limited to, dupilumab, tralokinumab, and omalizumab	
Oral JAK-inhibitors, whether investigational or marketed, including, but not limited to, abrocitinib, baricitinib, upadacitinib	
Systemic corticosteroids, including, but not limited to, oral or parenteral corticosteroids (intra-articular, intramuscular, IV, or rectally administered)	Note: Intranasal or inhaled or ophthalmic (ocular) steroid use is allowed at any time (Section 5.8.2).
Topical treatments: TCS, topical immunomodulators, including, but not limited to, TCIs (tacrolimus, pimecrolimus), topical phosphodiesterase type 4 (PDE4) inhibitors (eg, crisaborole), and topical JAK inhibitors (eg, ruxolitinib and delgocitinib)	Some are permitted as rescue medication, as described in Sections 5.8.1 and 5.8.2, or for non-AD related conditions described in Section 5.8.2.2. Topical JAK inhibitors are not allowed as rescue medication.
Systemic immunomodulators, including, but not limited to, oral JAK inhibitors (eg, baricitinib, upadacitinib, abrocitinib, tofacitinib, ruxolitinib), oral phosphodiesterase type 4 (PDE4) inhibitors, cyclosporine, methotrexate, mycophenolate mofetil, and azathioprine; IL-2 derivatives including but not limited to, aldesleukin, other IL-2 muteins; other immunomodulators marketed or in development for inflammatory diseases	
Phototherapy, including therapeutic phototherapy (psoralen plus ultraviolet A, ultraviolet B), excimer laser, and tanning beds	
Any investigational therapy that is not rezpegaldesleukin	
CBD products and any of the following substances if medically prescribed for the treatment of symptoms of AD: marijuana, marijuana extract, and THCs-containing products	
Allergen immunotherapy	
Sedating antihistamines	Unless part of patient's stable sleep regimen prior to randomization.
Live vaccines or BCG vaccination	The following are not considered live vaccines: RNA vaccines, vaccines with inactive viral elements, and/or nonreplicating viral vector vaccines. Live vaccines and BCG vaccination are prohibited during the study and within 12 weeks after the last dose of study intervention.

Abbreviations: AD = atopic dermatitis; BCG = Bacillus Calmette-Guerin; CBD = cannabidiol; IL = interleukin; IV = intravenous; JAK = Janus kinase; PDE4 = phosphodiesterase type 4; RNA = ribonucleic acid; TCI = topical calcineurin inhibitor; TCS = topical corticosteroid; THC = tetrahydrocannabinol

5.9 Discontinuation of Study Intervention and Patient Discontinuation/Withdrawal

This section describes reasons for a patient's:

- temporary or permanent discontinuation of study intervention (Section 5.9.1), or
- discontinuation (withdrawal) from the study (Section 5.9.2).

5.9.1 Discontinuation of Study Intervention

5.9.1.1 Temporary Discontinuation of Study Intervention

A patient may need to have study drug temporarily interrupted (withheld) during the study. Except in cases of emergency, the Investigator should consult the Sponsor's designated Medical Monitor:

- before temporarily interrupting study drug for reasons not specified in this protocol, and
- before resuming interrupted study drug, unless otherwise specified in this protocol.

Table 16 lists criteria for temporary interruption (withholding) of study drug and, for each criterion, describes conditions for resumption of study drug.

Table 16: Criteria for Temporary Interruption (Withholding) and Resumption of Study Drug

Temporarily interrupt study drug if the patient...	Conditions for resuming study drug
has an AE or abnormal laboratory value which, in the opinion of the Investigator, may have an unclear relationship to study drug.	when the Investigator and the Sponsor's designed Medical Monitor agree that resumption of study drug is appropriate for the patient
has neutropenia – absolute neutrophil count (ANC) 500-999/µL or 0.5 to 0.99 GI/L.	ANC $\geq 1.0 \times 10^3$/µL or $\geq$ 1.0 GI/L
has hepatic events or liver test abnormalities as described in Section 5.9.1.1.1.	as described in Section 5.9.1.1.1
has a serious infection, as defined in Section 4.2.	after resolution of all acute clinical signs and symptoms, and after completion of all appropriate anti-infective treatment.
has a change in mental health, as defined in Section 5.9.1.1.2.	after the documented evaluation by a mental health professional and the opinion of the Investigator
has been diagnosed with latent TB, or is found to be positive or indeterminate in the TB testing, as defined in Section 5.9.1.1.3.	after approval by a TB specialist or an infectious diseases specialist is obtained in writing

Abbreviations: AE = adverse event; ANC = absolute neutrophil count; TB = tuberculosis

5.9.1.1.1 Elevated Liver Test Results

Interrupting Study Drug Based on Liver Test Elevations in Patients with Normal or Near-normal Baseline Liver Tests

In study patients with normal or near normal baseline liver tests (ALT, AST, ALP < 1.5 × ULN), the study drug should be interrupted and close hepatic monitoring initiated (see Section 9.1.9) if 1 or more of the conditions in Table 17 occur.

Table 17: Conditions to Interrupt Study Drug Based on Liver Test Elevations in Patients with Normal or Near-normal Baseline Liver Tests

Elevation	Exception
ALT or AST > 8 × ULN	
ALT or AST > 5 × ULN for more than 2 weeks	
ALT or AST > 3 × ULN and either TBL > 2 × ULN or INR > 1.5	For patients with Gilbert's syndrome: If baseline direct bilirubin is > 0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL > 2 × ULN.
ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	
ALP > 3 × ULN, when the source of increased ALP is the liver	
ALP > 2.5 × ULN and TBL > 2 × ULN	For patients with Gilbert's syndrome: If baseline direct bilirubin is > 0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL > 2 × ULN.
ALP > 2.5 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	
Source: FDA 2009 and other consensus guidelines, with minor modifications	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; TBL = total bilirubin level; ULN = upper limit of normal

Interrupting Study Drug Based on Elevated Liver Tests in Patients with Abnormal Baseline Liver Tests

In study patients with abnormal baseline liver tests (ALT, AST, ALP ≥ 1.5 × ULN), the study drug should be interrupted if 1 or more of the conditions in Table 18 occur. The international normalized ratio (INR) assessment is required when the AST or ALT is > 3 × ULN.

Table 18: Conditions to Interrupt Study Drug Based on Elevated Liver Tests in Patients with Abnormal Baseline Liver Tests

Elevation	Exception
ALT or AST > 4 × baseline	
ALT or AST > 3 × baseline for more than 2 weeks	
ALT or AST > 2 × baseline and either TBL > 2 × ULN or INR > 1.5	For patients with Gilbert's syndrome: If baseline direct bilirubin is > 0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL > 2 × ULN.
ALT or AST > 2 × baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	
ALP > 2.5 × baseline, when the source of increased ALP is the liver	
ALP > 2 × baseline and TBL > 2 × ULN	For patients with Gilbert's syndrome: If baseline direct bilirubin is > 0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL > 2 × ULN.
ALP > 2 × baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, or rash	
Source: FDA 2009 and other consensus guidelines, with minor modifications	

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; INR = international normalized ratio; TBL = total bilirubin level; ULN = upper limit of normal

Resuming study drug after elevated liver tests

Resumption of the study drug can be considered only in consultation with the Sponsor-designated Medical Monitor and only if the liver test results return to baseline or near baseline values and if a self-limited non-drug etiology is identified. Otherwise, the study drug should be discontinued (Section 5.9.1).

5.9.1.1.2 Changes in Mental Health

The study treatment should at least be temporarily discontinued, and consideration should be given to referring the patient to a mental health provider (ie, psychiatrist or clinical psychologist) when the patient:

- Reports new onset suicidal ideation (eg, on the C-SSRS, answers "yes" to Questions 1, 2, or 3 after previous "no" answers);
- Develops new onset moderate depression (eg, a PHQ-9 score of 10 to 19 and with an associated 5-point increase from Baseline [Visit 2]); and/or
- Raises Investigator concern (see Section 9.1.10.5).

For any patient resuming study intervention following a change in mental health, the Investigator, in consultation with the Medical Monitor, shall document the rationale for continued patient participation, which must be supported by an evaluation by a mental health professional (ie, psychiatrist or clinical psychologist) prior to the next study drug administration.

5.9.1.1.3 Tuberculosis (TB) Testing

Periodic TB testing will be performed at defined time points during the study. If during the study the patient is diagnosed with latent TB or is found positive or indeterminate for TB testing, the study treatment must be discontinued until approval by a TB specialist or an infectious disease specialist is obtained in writing.

5.9.1.2 Permanent Discontinuation of Study Intervention

When necessary, a patient may be permanently discontinued from study intervention. If so, the patient will discontinue the study intervention (treatment), thereby discontinuing the treatment period, and will remain in the study to complete procedures for the following:

- an Early Discontinuation (ED) Visit, and Posttreatment Follow-up Visits, as shown in the SoE.
- If a patient permanently stops treatment during the Induction Period, they should complete study assessments up to and including Week 16. Thereafter, they should complete the Posttreatment Follow-Up Visits per the SoE.
- If a patient permanently stops treatment during the Maintenance Period, they should complete regularly scheduled visits per the SoE through the end of the Maintenance Period. Thereafter, they should complete the Posttreatment Follow-Up Visits per the SoE.
    - If a patient permanently stops treatment during the Escape Arm, they should complete study assessments per the Maintenance Period SoE.

Possible reasons for permanent discontinuation of study drug include, but are not limited to, the reasons listed here:

Patient decision: The patient asks to stop receiving study drug.

Pregnancy: The patient becomes pregnant (Sections 9.1.5 and 9.2.2).

Hypersensitivity: The Investigator, after consultation with the Sponsor's designated Medical Monitor, determines that a systemic hypersensitivity reaction has occurred and is related to study drug administration; in this case, the patient should be permanently discontinued from study drug.

Malignancy: The patient develops a malignancy (except for successfully treated basal or squamous cell skin carcinoma).

Changes in mental health: See Section 5.9.1.1.2. If dose resumption is not supported based on the evaluation by a mental health professional (ie, psychiatrist or clinical psychologist), the patient will be permanently discontinued from study treatment.

In addition, treatment should be permanently discontinued if a patient:

- answered "yes" to either Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS, or
- answered "yes" to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS, or
- answered "yes" to any of the suicide-related behaviors (Actual attempt, Interrupted attempt, Aborted attempt, Preparatory act or behavior) on the "Suicidal Behavior" portion of the C-SSRS, or
- Develops severe depression (eg, a PHQ-9 score of 20 to 27 and with an associated change of a 5-point increase from Baseline [Visit 2]), or
- Raises Investigator concern (see Section 9.1.10.5).

HIV or acquired immunodeficiency syndrome (AIDS): The patient develops HIV infection or AIDS.

Active TB or untreated latent tuberculosis infection (LTBI): The patient develops active TB or has untreated LTBI (Section 9.1.6).

HBV: The patient tests positive for HBV DNA (Section 9.1.7).

Note: The HBV DNA result is to be confirmed if initial positive test result is positive but below the level of quantification (Section 5.9.1.1). Prior to discontinuation of any immunomodulatory and/or immunosuppressive therapy, including study drug, the patient is to be referred to,

evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study drug relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the Investigator, and aligned with medical guidelines and standard of care.

HCV: The patient tests positive for HCV RNA (Section 9.1.8).

Opportunistic Infection: The patient has an opportunistic infection as defined in Winthrop, 2015.

Clinically significant ECG finding: Discontinuation of study drug may occur after consultation with the Sponsor's Medical Monitor (see Section 9.1.3).

Cytokine Release Syndrome (CRS):

In consultation with the Sponsor's designated Medical Monitor, a patient will be permanently discontinued from study drug if the patient has an AE deemed possibly or probably due to CRS and assessed as higher than mild in severity, based on:

- the details and severity of clinical signs and symptoms,
- the time course of symptom onset relative to study drug administration, and if possible,
- a cytokine panel from a blood sample obtained at the time of the event.

Hypereosinophilia: The patient develops hypereosinophilia.

In consultation with the Sponsor's Medical Monitor, patients will be permanently discontinued from study drug if they have:

- Absolute eosinophil counts > 2000 cells/µL and signs and/or symptoms of target organ involvement that are not consistent with AD or with the patient's AD and medical history.

  Such patients will undergo appropriate medical evaluation, which should take into account the patient's known AD and past medical history according to the patient's history and medical records, including previous imaging, biopsies, and laboratory findings. Evaluation of target organ involvement will involve additional diagnostic tests as appropriate, including laboratory tests, imaging (eg, echocardiogram, chest x-ray, computed tomography [CT] scan), and biopsies. New onset cardiac, pulmonary, and skin findings in the setting of peripheral eosinophilia will be considered as target organ involvement, unless attributable to other causes.
- Asymptomatic patients with an absolute eosinophil count > 5000 cells/µL should have a repeat measurement to confirm the count. If the count is confirmed, the patient will be permanently discontinued from study drug and undergo appropriate medical evaluation.

Liver test abnormality: Section 5.9.1.1 describes temporary interruption of study drug based on liver test abnormalities. If, after temporary interruption of study drug, liver test results fail to return to baseline or near baseline and a self-limited nondrug etiology is not identified, study drug is to be permanently discontinued.

Abnormal laboratory values: The patient has any of the following results on 2 consecutive samples taken at least 48 hours, but no more than 1 week, apart:

- Hemoglobin < 8.0 g/dL
- Neutropenia: absolute neutrophil count (ANC) < 0.5 × 10^3/µL or < 0.5 GI/L
- Lymphopenia: lymphocyte count < 0.5 × 10^3/ µL or < 0.5 GI/L
- Thrombocytopenia: platelets < 50.0 × 10^3/µL or < 50.0 GI/L
- eGFR < 30 mL/min/1.73 m^2 (CKD-EPI Creatinine Equation [2021]) (FDA 2020; NKF 2021).

Other AEs or changes in laboratory values: The patient has an AE, an SAE, or a clinically significant change in a laboratory value that, in the opinion of the Investigator, merits the permanent discontinuation of study drug and appropriate measures being taken.

Inadequate response to Escape Arm medication in patients who have been receiving Escape Arm medication: Any patient on the Escape Arm that does not achieve an EASI-50 at any point through Week 34 assessment will discontinue from study therapy.

Inadequate response to rescue medication in patients who have been receiving rescue medication: If the Investigator determines that rescue medication (Section 5.8.1) is inadequate to control the patient's AD symptoms, and the patient needs systemic treatment with an AD therapy which is prohibited by the protocol (Section 5.8.3), the patient will be discontinued from study treatment. In such cases, the patient is to be discontinued from the study drug before starting the protocol-prohibited AD therapy.

Patient received systemic rescue medication: If a patient received systemic medication to control AD symptoms, the patient will be discontinued from study treatment (Section 5.8.1).

Noncompliance: If the Investigator determines the patient is not compliant with study drug administration or other study procedures.

Unblinding: If an unblinding event occurs, the patient may be discontinued from study treatment; refer to Section 6.4.

Note: The presence or absence of an ISR will not be considered an unblinding event; patients with an ISR may remain in the study and continue to receive study drug, and this will not be considered a protocol deviation.

5.9.2 Patient Discontinuation/Withdrawal from the Study

Discontinuation (withdrawal) from the study is expected to be uncommon.

A patient may withdraw from the study in these circumstances:

- At any time at the patient's own request for any reason or without providing any reason
- At the request of the patient's designee
- At the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons
- If enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

Data Collection and Follow-up for Patients who Discontinue the Study Intervention

At the time of discontinuing from the study intervention, if possible, the patient will complete procedures for an ED visit, ED Induction or ED Maintenance assessments, and Posttreatment Follow-up, as shown in the SoE.

Withdrawal of Consent for Disclosure

If the patient withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a patient withdraws from the study, the patient may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records and communicate the request to the Sponsor.

5.9.3 Lost to Follow-up

A patient will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

5.10 End of Study

The study will be considered complete when the last patient's last visit has been conducted and the data is mature for analysis. In the event of early termination of the study, patients will have a final safety follow-up visit as shown in the SoE.

End of study is defined as the date of the last visit or last scheduled procedure shown in the SoE for the last patient in the trial globally or Sponsor decision to terminate the study, whichever comes first.

6.0 INVESTIGATIONAL PRODUCT(S)/STUDY DRUGS

Investigational medicinal product is defined as any investigational intervention, marketed product, placebo, or medical device intended to be administered to, or used by, a study patient according to the study protocol.

6.1 Study Treatment(s) Administered

This study involves placebo and rezpegaldesleukin administered according to the SoE (Section 1.2).

Table 9, Table 11, and Table 13 provide the study treatments that will be administered in the study.

6.1.1 Rezpegaldesleukin

Rezpegaldesleukin is the International Nonproprietary Name for LY3471851 or NKTR-358.

Rezpegaldesleukin drug product will be provided as a CCI sterile solution in each vial for SC injection. The drug product will be supplied in cartons. Cartons will contain the appropriate quantity specific to the planned dispensing schedule. The rezpegaldesleukin drug product will be prepared according to the guidance in the Pharmacy Manual.

6.1.2 Placebo

The placebo dosing solution is 0.9% Sodium Chloride for Injection (United States Pharmacopeia). The placebo will be prepared according to the guidance in the Pharmacy Manual.

6.1.3 Background Therapy

At least 1 emollient is to be used once daily throughout the study as background therapy. Moisturizers with additives such as antipruritics or antiseptics, are not permitted. Background therapies should be used according to their local product labeling.

On the days of study visits, emollients should not be applied until after the patient has undergone all study procedures and clinical evaluations. This is to allow adequate assessment of skin dryness at the visit.

Emollient therapy must be recorded as stated in Section 5.8.

Table 19 describes background therapy that will be used as shown.

Table 19: Background Therapy

Study Treatment Name	Background therapy: emollient without additives such as antipruritics or antiseptics, as described in Section 6.1.3
Dose Levels	Per local approved label, if applicable
Frequency of Administration	Once daily, not to exceed local approved label, if applicable
Route of Administration	Topical
Authorized as Defined by EU Clinical Trial Regulation	Not authorized[a]

Abbreviations: EU = European Union

a. This medicinal product is not authorized in accordance with Directive 2001/83/EC and Regulation (EC) No 726/2004 of the European Parliament and of the Council. However, emollients are authorized according to EU Regulation 1223/2009 and are being used according to their authorization.

6.1.4 Anatomical Site of Injections

The abdomen is the preferred anatomical site for injections of all study interventions. When multiple injections are required, each injection should be administered as a SC injection in a separate quadrant of the abdomen (1 syringe per quadrant). Rotate quadrants at subsequent dosing visits.

There may be situations when the abdomen is not the preferred location, eg, because of presence of an ISR or because of patient's preference. In such situations, injections can be given in the upper arm or thigh, with 1 injection per location, rotating locations at each dosing visit.

Do not administer an injection into the area affected with AD. Do not administer an injection into an ongoing ISR from a prior injection or into any skin that is tender, damaged, bruised, or scarred.

6.1.5 Monitoring after Dose Administration

All patients should remain under observation for at least 30 minutes after the first study treatment administration and at least 15 minutes after subsequent administrations, or longer, as per Investigator's clinical judgment.

6.1.6 Drug Packaging and Labeling

Rezpegaldesleukin and placebo will be supplied by the Sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.1.7 Drug Preparation, Handling, Storage, and Accountability

The Pharmacy Manual provides instructions for the preparation, handling, and storage of study interventions, and describes site responsibility and accountability for the administered products.

Investigators and authorized site personnel should consult the information provided in the Pharmacy Manual and on the labels for specific preparation, handling, storage, and administration information, including warnings, precautions, contraindications, adverse reactions, and dose modifications.

The study drug(s) must be prepared according to the Pharmacy Manual.

When prepared for dosing according to the detailed instructions provided by the Sponsor, it will not be possible to distinguish rezpegaldesleukin from placebo.

See Section 6.4 for measures to be taken for maintaining blinding as appropriate for patients, Investigators, or other site personnel performing assessments.

6.1.8 Drug Shipment

For all countries, the Sponsor will supply rezpegaldesleukin. The placebo will be provided from a central source or from a commercially available supply. Refer to the Pharmacy Manual for additional details for ordering drug supply.

6.2 Study Drug Accountability and Reconciliation

Rezpegaldesleukin and placebo are considered Investigational Medicinal Product.

Study drug supplies must be kept in an appropriate, secure, locked area and stored in accordance with the conditions specified in the Pharmacy Manual and on the labels. Depending on local health authority guidelines, ancillary supplies (eg, syringe and needles) may be obtained through commercial supply, the site pharmacy, or through a central depository.

The Investigator, pharmacist, or designee must maintain an accurate record of dispensing the study drug supplies in a Drug Accountability Log, a copy of which must be given to Nektar Therapeutics or its designee.

The Drug Accountability Log may record specifics to study drug dispensation such as:

- Records of product delivery, inventory, temperature monitoring, destruction, and return as per Sponsor’s instructions.
- Doses prepared, time prepared, doses dispensed.
- Doses and/or vials destroyed.

The Drug Accountability Log will be reviewed by the monitor during site visits and at the completion of the study.

Please refer to the Pharmacy Manual for details.

6.3 Assignment to Study Intervention

An interactive response technology (IRT) will be employed to manage patient randomization and drug supply.

Each patient will be assigned a unique patient number after signing the ICF. Patient numbers will be used on all patients' study information. Patient numbers will not be reassigned.

The randomization ratios are described in Sections 5.2.1 and 5.2.3.

Randomization stratification factors are listed in Section 5.3.

6.4 Blinding/Unblinding

The patients, Investigators, site staff and all individuals involved in performing assessments will remain blinded to each patient's assigned study intervention throughout the course of the study except for the Escape Arm.

The designated Sponsor study team will be unblinded at the primary database lock (as described in Section 10.5). Subsequent unblinded analyses for the Maintenance Period may also be conducted by the Sponsor study team prior to the final database lock of the study (see Section 10.5 for details).

Guidance for maintaining the study blind is described in a Site Blinding Plan document. The unblinding event types are briefly summarized as follows:

- **Emergency Unblinding**. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a patient's intervention assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, it is the responsibility of the Investigator to promptly document the decision and rationale and notify the Sponsor as soon as possible. Emergency unblinding should be an exceedingly rare instance given the historical tolerability profile of rezpegaldesleukin and since there are no specific antidotes available for rezpegaldesleukin. Instead, patients with study related AEs will generally require general medical management.

  If, because of emergency unblinding, a patient's study treatment assignment is unblinded to the patient or to blinded site personnel who are performing assessments, including the Investigator, the Investigator may continue the patient with subsequent study therapy in consultation with the unblinded Medical Monitor (Section 5.9.1.2), at the same dose of study drug as prior unblinding.

- **Unplanned Accidental Unblinding.** When any patient or blinded site personnel receive information inadvertently revealing the treatment assignment to one or more patients before planned unblinding or unplanned unblinding for safety reasons, the person will be required to not disseminate the treatment information and appropriate measures will be taken to maintain the study blind and data integrity. The patient may continue the study treatment after the Investigator consults with the Sponsor's designated unblinded Medical Monitor.

Note: The presence or absence of an ISR will not be considered an unblinding event; patients with an ISR may remain in the study and continue to receive study drug, and this will not be considered a protocol deviation.

7.0 STUDY ASSESSMENTS AND PROCEDURES

7.1 Pharmacokinetics

7.1.1 Collection Visits and Times

At the visits and times specified in the SoE (Section 1.2), venous blood samples will be collected to determine the plasma concentrations of rezpegaldesleukin. The actual date and time (24-hour clock time) of dosing and sample collection must be recorded accurately on the appropriate forms.

Visits [3.5] and [4.5], and collection of PK samples at these visits, will no longer be necessary once collection of PD samples from patients described in Section 7.2 is complete. The Sponsor will notify sites once this visit collection is no longer required based on the samples received. Applicable documents and supplies will be updated as required to reflect the change.

7.1.2 Handling and Analysis of Samples

Instructions for the collection and handling of blood samples will be provided by the Sponsor. Samples will be analyzed at a laboratory approved by the Sponsor. Concentrations of rezpegaldesleukin will be assayed using a validated PK assay. Analyses of samples collected from patients while receiving placebo in the Induction Period are not planned.

7.1.3 Additional and Unused Samples

A maximum of 3 additional samples may be collected at additional time points during the study if warranted and agreed upon between both the Investigator and Sponsor. CCI [redacted]

In the case of systemic hypersensitivity reactions, additional blood samples will be obtained for PK analyses (Appendix 1).

7.1.4 Pharmacokinetic Sample Blinding

Drug concentration information that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

7.1.5 Sample Retention

The purpose of retention and the maximum duration of retention for long-term storage of samples are described in Section 7.5.

7.2 Pharmacodynamics

CCI [redacted] PD biomarker samples will be collected for a minimum of 100 to approximately 140 patients in North America and the European Union. The Sponsor will notify sites once this sample collection is no longer required based on the samples received. Applicable documents and supplies will be updated as required to reflect the change.

7.2.1 Collection Visits and Times

At the visits and times specified in the SoE (Section 1.2), blood samples will be collected for the exploratory analysis of PD biomarkers.

7.2.2 Pharmacodynamic Sample Blinding

PD sample results that may unblind the study will not be reported to investigative sites or to personnel who are blinded to study data.

7.3.1 Collection Visits and Times

The samples for nonpharmacogenetic biomarker research will be collected at the visits and times specified in the SoE (Section 1.2), where local regulations allow.

Visits [3.5] and [4.5], and collection of samples CCI [redacted] will no longer be necessary once collection of PD samples from patients described in Section 7.2 is complete. The Sponsor will notify sites once this visit collection is no longer required based on the samples received. Applicable documents and supplies will be updated as required to reflect the change.

7.3.2 Sample Use

Samples may be used for research on the:

- drug target
- disease process
- variable response to treatment with rezpegaldesleukin
- pathways associated with AD
- mechanism of action of rezpegaldesleukin, and/or
- research methods in validating diagnostic tools or assays related to AD or to rezpegaldesleukin.

7.3.3 Sample Confidentiality

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigative site personnel.

7.3.4 Sample Retention

Samples will be retained at a facility selected by the Sponsor or its designee. Samples will be retained while research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified in Section 7.5.

7.4 Immunogenicity Assessments

7.4.2 Handling and Analysis of Samples

Instructions for the collection and handling of blood samples will be provided by the Sponsor.

CCI

7.5 Sample Collection and Storage

This protocol will include residual sample storage for additional research. Residual samples from all PK, immunogenicity, CCI [redacted] collections from all time points will be retained.

- **For All United States (US) sites**: Additional research participation is required for all investigational sites in the US. If the institutional review board (IRB) and investigative site agree to the mandatory additional research retention and/or collection, then the study patient must agree to the mandatory additional research collection as a requirement for participation in the study.
- **For non-US Sites**: Additional research is optional for all study patients, except where retention and/or collection is prohibited by local laws or regulations, ethics committees, or institutional requirements.

Samples will be retained at a facility selected by the Sponsor or its designee. Samples will be retained while research on the study indication, study intervention, or the class of study intervention continues, but no longer than the maximum retention time specified below:

- Up to 2 years for all PK samples
- Up to 15 years for CCI [redacted] immunogenicity samples

The retention period begins after the last patient's last visit. Any samples remaining after the retention period will be destroyed.

Further details of sample collection and processing will be provided to the site in the Laboratory Manual.

8.0 ASSESSMENT OF EFFICACY

Every reasonable effort should be made for the same Investigator to assess the patient throughout the duration of the study.

8.1 Primary Efficacy Assessment

8.1.1 Eczema Area and Severity Index

The EASI will be collected for the primary and secondary efficacy assessments per the SoE. This index is an Investigator-reported, 20-item scale that evaluates 2 dimensions of AD in patients:

- extent of disease at 4 body regions (head/neck, trunk, upper and lower extremities), and
- 4 clinical signs (erythema, induration/papulation, excoriation, and lichenification).

The clinical signs are assessed for severity on a scale of 0 (absent) to 3 (severe).

The scores are added up for each of the 4 body regions. The assigned percentages of BSA for each section of the body are:

- 10% for head/neck
- 20% for upper extremities
- 30% for trunk, and
- 40% for lower extremities.

In addition, an area score of 0 to 6 is assigned for each body region, depending on the percentage of AD-affected skin in that area:

- 0 (none)
- 1 (1% to 9%)
- 2 (10% to 29%)
- 3 (30% to 49%)
- 4 (50% to 69%)
- 5 (70% to 89%), or
- 6 (90% to 100%).

Each of the body area scores is multiplied by the area affected. The final EASI is the sum of the 4 regional scores with ranges from 0 to 72 points, with the highest score indicating worse severity of AD (Hanifin, 2001; Hanifin, 2022). The recall period of this scale is present time.

8.2 Secondary Efficacy Assessment

8.2.1 vIGA-AD

The vIGA-AD® measures the Investigator's global assessment of the patient's overall severity of their AD, based on a single-item, numerical, 5-point scale from 0 (clear skin) to 4 (severe disease) (Simpson, 2020b). The score is based on an overall assessment of the degree of erythema, papulation or induration, oozing or crusting, and lichenification. The recall period of this assessment is present time.

8.2.2 Itch Numerical Rating Scale

The Itch NRS is a patient-reported, single item, 11-point scale anchored at 0 and 10, with 0 representing "no itch" and 10 representing "worst itch imaginable" in adults. Overall severity of a patient's itching is indicated by selecting the number that best describes the worst level of itching in the past 24 hours (Yosipovitch, 2017; Yosipovitch, 2019).

8.2.3 SCORing Atopic Dermatitis Index

The SCORing Atopic Dermatitis Index (SCORAD) (European Task Force on AD, 1993; Oranje, 2007) is a mathematically derived composite scoring index that combines extent, severity and subjective symptoms of atopic dermatitis. To measure the extent of AD, the rule of nines is applied on a front/back drawing of the patient's inflammatory lesions. The extent can be graded from 0 to 100. The intensity part of the SCORAD index consists of six items: erythema, edema/papulation, excoriations, lichenification, oozing/crusts, and dryness. Each item can be graded on a scale of 0 to 3. The subjective items include daily pruritus and sleeplessness. Each subjective item is scored on a scale of 0 to 10 and the maximum subjective score is 20. All items should be filled out in the SCORAD evaluation form. The SCORAD index formula is: A/5 + 7B/2 + C. In this formula A is defined as the extent (0 to 100), B is defined as the intensity (0 to 18) and C is defined as the subjective symptoms (0 to 20). The maximum SCORAD score is 103.

8.3 Other Efficacy, Patient-Reported Outcomes, and Quality of Life Assessments

8.3.1 Body Surface Area

The BSA assessment estimates the extent of disease or skin involvement with respect to AD and is expressed as a percentage of total body surface. BSA value is extracted from Part A of the SCORAD.

8.3.2 Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) is a patient-reported, 10-item, quality of life (QoL) questionnaire in those ≥ 16 years of age that covers 6 domains (symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment). The recall period of this scale is over the "last week." Response categories include "not at all," "a little," "a lot," and "very much," with corresponding scores of 0, 1, 2, and 3, respectively, and unanswered (or "not relevant") responses scored as 0.

Scores range from 0 to 30 with higher scores indicating greater impairment of QoL. A DLQI total score of 0 to 1 is considered as having no effect on a patient's health-related quality of life (HRQoL) (Hongbo, 2005), and a 4-point change from baseline is considered as the minimal clinically important difference threshold (Khilji, 2002; Basra, 2015).

8.3.3 Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) is a simple, patient-reported, 7-item scale that assesses disease severity in adults. Patients respond to questions about the frequency of 7 symptoms (itching, sleep disturbance, bleeding, weeping or oozing, cracking, flaking, and dryness or roughness) over the past week. Response categories include "No days," "1-2 days," "3-4 days," "5-6 days," and "Every day" with corresponding scores of 0, 1, 2, 3, and 4, respectively. Scores range from 0 to 28, with higher total scores indicating greater disease severity (Charman, 2004).

8.3.4 Atopic Dermatitis Control Tool

The Atopic Dermatitis Control Tool (ADCT) is a patient-reported, simple, brief tool for adults and adolescents, which evaluates 6 symptoms and effects associated with AD over the past week:

- overall severity of symptoms
- days with intense episodes of itching
- intensity of bother
- problem with sleep
- impact on daily activities, and
- impact on mood or emotions.

Each of the 6 ADCT items has a score range from 0 (no problem) to 4 (worst), rating the severity of each concept. The total score ranges from 0 to 24, which is the summation of the responses to all the items. A score of ≥ 7 points was derived as the threshold to identify patients "not in control." The threshold for meaningful within-person change was estimated to be 5 points (Simpson, 2019; Pariser, 2020).


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8.3.8 Atopic Dermatitis Sleep Scale

The Atopic Dermatitis Sleep Scale (ADSS) is a patient-reported, 3-item questionnaire in adults developed to assess the impact of itch on sleep, including difficulty falling asleep, frequency of waking, and difficulty getting back to sleep last night. Patients rate their difficulty falling asleep and difficulty getting back to sleep, Items 1 and 3, respectively, using a 5-point Likert-type scale. Response options include "Not at all," "A little bit," "Somewhat," "Quite a bit," and "Very difficult," with corresponding scores of 0, 1, 2, 3, and 4, respectively. Patients report their frequency of waking last night, Item 2, by selecting the number of times they woke up each night, ranging from 0 to 29 times. The ADSS is designed to be completed each day with respondents thinking about sleep "last night." Each item is scored individually (Silverberg, 2021b).

8.3.9 Skin Pain Numerical Rating Scale

Skin Pain NRS is a patient-reported, 11-point scale anchored at 0 and 10, with 0 representing "no pain" and 10 representing "worst pain imaginable." Overall severity of a patient's skin pain is indicated by selecting the number that best describes the worst level of skin pain in the past 24 hours (Newton, 2019; Silverberg, 2021b).

9.0 ASSESSMENT OF SAFETY

9.1 Safety Assessments

Visits and Order of Safety Assessments

Safety assessments occur at visits specified in the SoE (Section 1.2). If multiple safety assessments are scheduled for the same visit, the preferred order of completion is:

1. ECGs and vital signs
2. other safety assessments, including physical examinations and nonleading (spontaneous) AE collection, and finally,
3. sample collections for clinical laboratory testing and for PK, immunogenicity, biomarkers, and other sample testing specified in the SoE.

Data Collection and Reporting

The AE data collection and reporting requirements are described in Section 10.4 and Appendix 2.

Safety Monitoring

The Principal Investigator will monitor the safety data throughout the study. Immediate safety concerns should be discussed with the Sponsor's Medical Monitor immediately upon occurrence or awareness to determine if the patient should continue or discontinue the study intervention.

The Sponsor's Medical Monitor or designee will monitor the safety data, including AEs, SAEs, discontinuations, vital signs, and clinical laboratory results in a blinded manner on an ongoing basis. In addition, a functionally independent safety physician and/or clinical research scientist will regularly review SAE reports in real time and across studies and review applicable clinical safety and epidemiological publications from the literature. CCI [redacted] In cases when routine monitoring by the study team uncovers a safety issue that needs to be addressed by unblinding at the individual or group level, additional analyses of the safety data will be performed by the Sponsor's DSC.

Appropriateness of Safety Assessments

The safety assessments used in this study are routine elements of clinical health assessment and Phase 2b drug development.

9.1.1 Vital Signs

Vital sign measurements will be recorded according to the Schedule of Events (Section 1.2). Additional vital signs may be measured during study visits if warranted, as determined by the Investigator.

Vital signs should be measured after the patient has been sitting for at least 5 minutes.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If the patient feels unable to stand, sitting or supine vital signs will be recorded.

9.1.2 Physical Examinations

Physical examinations should be conducted according to the Schedule of Events (Section 1.2). Symptom-directed physical assessments may also be conducted at other visits, as determined by the Investigator, if a patient presents with complaints or as needed based on patient status and standard of care.

9.1.2.1 Complete Physical Examination

The complete physical examination should include the following regions and body systems:

- general appearance
- skin
- head, ears, eyes, nose, throat
- lymph nodes
- cardiovascular
- respiratory
- abdominal
- genitourinary (only as clinically indicated)
- extremities
- neurologic

Pelvic, rectal, and breast examinations are not required unless clinically indicated.

9.1.2.2 Symptom-directed Physical Assessments

After screening, physical assessments should include a symptom-directed evaluation, as well as evaluation of eyes, heart, lungs, abdomen, and visual evaluation of the skin (other than area covered by clothing or other material).

9.1.2.3 Height and Weight

Height and weight will also be measured and recorded as specified in the SoE (Section 1.2).

9.1.3 Electrocardiograms

All patients will have 12-lead ECG done during Screening as specified in the Schedule of Events (Section 1.2). The ECGs should be collected at least 30 minutes before collecting blood samples for laboratory testing, including PK samples. Patients should be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

ECGs may be obtained at additional visits at the Investigator's discretion. Collection of additional ECGs at any particular time point is allowed to ensure high quality records.

ECGs will be interpreted by a qualified physician (the Investigator or a qualified designee such as cardiologist) as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets the study entry criteria and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes from baseline in QT/corrected QT interval by Fridericia's formula [QTcF] interval from baseline) after enrollment, the Investigator or qualified designee, in conjunction with the Sponsor's Medical Monitor, will determine whether the patient can continue on the study intervention and if any change in patient management is needed (Section 5.9.1).

The review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

9.1.4 Clinical Laboratory Tests

Clinical laboratory tests will be conducted according to the Schedule of Events (Section 1.2). A list of the clinical laboratory analytes to be tested is provided in Appendix 1.

Samples for laboratory testing will be obtained in the event of a systemic hypersensitivity reaction, as described in Appendix 1. Additional tests may be performed at any time during the study as deemed necessary by the Investigator or as required by local regulations.

All protocol-required laboratory assessments, as defined in Appendix 1, must be conducted in accordance with the SoE, standard collection requirements, and the laboratory manual.

If laboratory values from nonprotocol-specified laboratory assessments performed at an Investigator-designated local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then report the information as an AE.

9.1.4.1 Reviewing and Recording Test Results

The Investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.

9.1.4.2 Repeat Testing After Clinically Significant Abnormal Finding

All laboratory tests with abnormal values considered clinically significant during participation in the study or within 8 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

9.1.5 Pregnancy Testing

Serum or urine pregnancy tests will be performed on WOCBP according to the Schedule of Events (Section 1.2), and as defined in Appendix 3.

9.1.5.1 Pregnancy Testing Visits and Times

Serum pregnancy testing will be performed centrally at screening.

Urine pregnancy testing will be performed locally at other time points specified in the SoE (Section 1.2). If the specified visit includes administration of study intervention, the pregnancy test must be "negative" within 24 hours before the study intervention is administered.

If a urine pregnancy test is not available, a local serum pregnancy test is an acceptable alternative.

If the urine pregnancy test is inconclusive at any visit, an additional serum pregnancy test should be performed.

9.1.5.2 Pregnancy Testing at Any Time During the Study

Additional pregnancy testing may be performed at any time in the study, at the discretion of the Investigator, if the patient's menstrual period is missed or there is clinical suspicion of pregnancy, or as required by local law or regulation.

9.1.5.3 Discontinuation of Patients who are Pregnant

Patients who are pregnant will be permanently discontinued from the study intervention (Section 5.9.1).

9.1.5.4 Optional FSH testing

The patient's follicle stimulating hormone (FSH) level can be measured centrally at the discretion of the Investigator at screening. The FSH level can also be measured locally after screening at the discretion of the Investigator. The purpose of this optional FSH testing is to assist the Investigator in determining whether a patient can be considered "postmenopausal" for the purposes of pregnancy testing and contraception requirements (Appendix 3).

9.1.6 Tuberculosis Testing

During screening, all patients will have a blood test for TB via the central laboratory QuantiFERON® TB Gold test. Patients who have a positive blood test must be evaluated for active TB. Patients determined to have active TB are excluded. If patients have a history of latent TB infection, they must meet Exclusion Criterion 15 to be eligible for randomization.

Additional TB testing is to be performed according to the SoE.

9.1.6.1 Diagnosed LTBI

Patients diagnosed with LTBI are excluded (Section 4.2) unless they are candidates for LTBI treatment, are treated for LTBI, and the following criteria are met:

- The patient must be evaluated (and obtain written approval for study participation) by a TB specialist or an infectious disease specialist.
- After receiving at least 4 weeks of appropriate LTBI therapy (as per WHO or the United States CDC guidelines), there is no evidence of hepatotoxicity (ALT/AST must remain $\leq 2 \times$ ULN) or other treatment intolerance. In this case, the patient may be rescreened (Section 4.4.2) and is not excluded due to LTBI.
- The patient must continue and complete appropriate LTBI therapy in order to remain eligible to continue to receive study intervention (Section 5.9.1).
- If during the study the patient is found to have latent TB, or is found to have a positive or indeterminate TB result, the study treatment must be temporarily held until approved by a TB specialist or an infectious disease specialist in writing.

9.1.7 Hepatitis B Testing

As specified in the SoE (Section 1.2), initial testing for HBV infection includes hepatitis B core antibody (anti-HBc) and hepatitis B surface antigen (HBsAg).

- If HBsAg is positive, the patient is excluded.
- If HBsAg is negative and anti-HBc is negative, the patient is not excluded.
- If anti-HBc is positive or indeterminate, further testing for HBV DNA is required at screening and at defined timepoints.
  - If the screening HBV DNA is positive, the patient is excluded (see Section 4.2).
  - If the screening HBV DNA is negative, the patient is not excluded.
- On treatment, HBV DNA testing will be performed per SoE.
  - If the HBV DNA is positive during treatment, the study treatment must be discontinued.

9.1.8 Hepatitis C Testing

As specified in the SoE (Section 1.2), initial testing for HCV infection includes testing for antibodies to HCV (anti-HCV).

- If anti-HCV is positive or indeterminate, a test for circulating HCV RNA is required at screening and at defined timepoints.
  - If the screening HCV RNA test is positive, the patient is excluded (see Section 4.2).
  - If the screening HCV RNA test is negative, the patient is not excluded.
- On treatment, the HCV RNA testing will be performed per SoE.
  - If the HCV RNA is positive during treatment, the study treatment must be discontinued.

Patients who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion) are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

If HCV RNA is detected during the study, the study intervention will be discontinued, as described in Section 5.9.1, and the patient should receive appropriate follow-up medical care.

9.1.9 Hepatic Safety Testing and Monitoring

9.1.9.1 Close Hepatic Monitoring

Laboratory tests (Appendix 4), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of the conditions in Table 20 occur.

Table 20: Conditions Triggering Additional Hepatic Laboratory Tests

If a patient with baseline results of...	develops the following elevations:
ALT or AST < 1.5 × ULN	ALT or AST ≥ 3 × ULN
ALP < 1.5 × ULN	ALP ≥ 2 × ULN
TBL < 1.5 × ULN	TBL ≥ 2 × ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥ 1.5 × ULN	ALT or AST ≥ 2 × baseline
ALP ≥ 1.5 × ULN	ALP ≥ 2 × baseline
TBL ≥ 1.5 × ULN	TBL ≥ 1.5 × baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; TBL = total bilirubin; ULN = upper limit of normal

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the Investigator in consultation with the Sponsor-designated Medical Monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (eg, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the patient's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the patient's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

9.1.9.2 Comprehensive Hepatic Evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in Table 21 occur.

Table 21: Laboratory Assessments Triggering a Hepatic Evaluation

If a patient with baseline results of...	develops the following elevations:
ALT or AST < 1.5 × ULN	ALT or AST ≥ 3 × ULN with hepatic signs/symptoms[a], or ALT or AST ≥ 5 × ULN
ALP < 1.5 × ULN	ALP ≥ 3 × ULN
TBL < 1.5 × ULN	TBL ≥ 2 × ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥ 1.5 × ULN	ALT or AST ≥ 2 × baseline with hepatic signs/symptoms[a], or ALT or AST ≥ 3 × baseline
ALP ≥ 1.5 × ULN	ALP ≥ 2 × baseline
TBL ≥ 1.5 × ULN	TBL ≥ 2 × baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; TBL = total bilirubin; ULN = upper limit of normal

a. Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, or rash.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time and international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (eg, ultrasound or CT scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Sponsor's designated Medical Monitor, including tests for hepatitis D virus, cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol. Based on the circumstances and the Investigator's assessment of the patient's clinical condition, the Investigator should consider referring the patient for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

9.1.9.3 Additional Hepatic Data Collection in Patients Who Have Abnormal Liver Tests During the Study

Additional hepatic safety data collection in hepatic safety CRFs should be performed for study patients who meet 1 or more of the following conditions:

- Elevation of serum ALT to ≥ 5 × ULN on 2 or more consecutive blood tests (if baseline ALT < 1.5 × ULN)
- In patients with baseline ALT ≥ 1.5 × ULN, the threshold is ALT ≥ 3 × baseline on 2 or more consecutive tests.
- Elevation of serum AST to ≥ 5 × ULN on 2 or more consecutive blood tests (if baseline AST < 1.5 × ULN)
- In patients with baseline AST ≥ 1.5 × ULN, the threshold is AST ≥ 3 × baseline on 2 or more consecutive tests.
- Elevated TBL to ≥ 2 × ULN on 2 or more consecutive tests (if baseline TBL < 1.5 × ULN) (except for cases of known Gilbert's syndrome)
- In patients with baseline TBL ≥ 1.5 × ULN , the threshold should be TBL ≥ 2 × baseline on 2 or more consecutive tests.
- Elevation of serum ALP to ≥ 2 × ULN on 2 or more consecutive blood tests (if baseline ALP < 1.5 × ULN)
- In patients with baseline ALP ≥ 1.5 × ULN, the threshold is ALP ≥ 2 × baseline on 2 or more consecutive blood tests.
- Hepatic event considered to be an SAE
- Discontinuation of study drug due to a hepatic event (Section 5.9.1)

  Note: The interval between the 2 consecutive blood tests should be at least 2 days.


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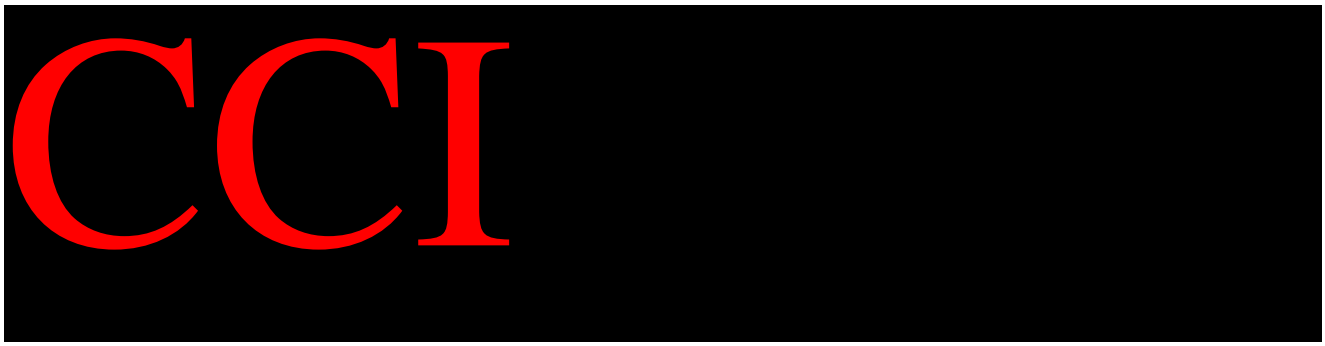

9.2 Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 2:

- AEs
- SAEs, and
- Product complaints (PCs).

These events will be reported by the patient (or, when appropriate, by a caregiver or surrogate, or the patient's legally authorized representative). Additionally, these events may come to the attention of study personnel during study visits and interviews of a study patient presenting for medical care, or upon review by a study monitor.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study intervention or the study (see Section 5.9).

Care will be taken not to introduce bias when detecting events. Open-ended and nonleading verbal questioning of the patient is the preferred method to inquire about event occurrences.

After the initial report, the Investigator is required to proactively follow each patient at subsequent visits or contacts. All AEs and SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 5.9.3). For PCs, the Investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality, or both. Further information on follow-up procedures is provided in Appendix 2.

9.2.1 Timing and Mechanism for Collecting Events

The timing, deadlines, and mechanism for collecting AEs, SAEs, pregnancy, and PCs are provided in Table 24.

Table 24: Timing, Deadlines, and Mechanism for Collecting Events

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Non-Serious Adverse Event					
AE	After randomization	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – after informed consent and prior to randomization and start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form and SAE eCRF (if randomized)	N/A
SAE and SAE updates – after randomization and start of study intervention	After randomization and start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE paper form and SAE eCRF	SAE paper form
SAE[a] – after patient's study participation has ended **and** the Investigator becomes aware	After patient's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female patients and female partners of male patients	After the start of study intervention	12 weeks after the last dose	Within 24 hours (see Section 9.2.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	PC form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	PC form	N/A
Updated PC information	_	_	As soon as possible upon site awareness	Originally completed PC form with all changes signed and dated by the Investigator	N/A
PC (if Investigator becomes aware)	Participation in study has ended	N/A	Promptly	PC form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event

a. These SAEs should not be reported unless the Investigator deems them to be possibly related to study treatment or study participation.

9.2.2 Collection of Pregnancy Information

Male patients with partners who become pregnant

The Investigator will attempt to collect pregnancy information on any male patient's female partner who becomes pregnant while the male patient is in this study. This applies only to male patients who receive study intervention.

After learning of a pregnancy in the female partner of a study patient, the Investigator will:

- obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the Sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

Female patients who become pregnant

The Investigator will collect pregnancy information on any female patient who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a patient's pregnancy.

The patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the patient and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at < 20 weeks gestational age) or still birth (occurring at ≥ 20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 9.2.1. While the Investigator is not obligated to actively seek this information in former study patients, the Investigator may learn of an SAE through spontaneous reporting.

Any female patient who becomes pregnant while participating in the study will permanently discontinue study intervention (Section 5.9.1). When study treatment is discontinued, the patient will be asked to continue with all planned visits and assessments as shown in the SoE (except for study treatment administration). The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

10.0 STATISTICAL PLAN

A summary of the statistical analysis plan for the primary and secondary objectives is provided in this section. It describes a brief guidance for the general considerations. More description about analysis methods and detailed definitions for efficacy and safety endpoints will be provided in the statistical analysis plan (SAP).

10.1 Statistical Hypotheses and Estimands

For the primary endpoint, the null hypotheses with respect to mean percent change from baseline in EASI at Week 16 (%EASI@W16) are that:

- the treatment effect of rezpegaldesleukin 24 μg/kg q2w is not different from the effect of placebo q2w
- the treatment effect of rezpegaldesleukin 24 μg/kg q4w is not different from the effect of placebo q2w
- the treatment effect of rezpegaldesleukin 18 μg/kg q2w is not different from the effect of placebo q2w

For the secondary endpoints related to the efficacy assessment, the null hypotheses are that there is no difference in the treatment effect between each of the rezpegaldesleukin arms and placebo with respect to:

- proportion of patients achieving vIGA-AD of 0 or 1 and at least a 2-point reduction at Week 16 (vIGA-AD01@W16)
- proportion of patients achieving EASI-75 at Week 16 (EASI-75@W16)
- proportion of patients achieving EASI-90 at Week 16 (EASI-90@W16)
- proportion of patients achieving EASI-50 at Week 16 (EASI-50@W16)
- proportion of patients achieving ≥ 4-point improvement from baseline in Itch NRS at Week 16 in the subset of patients with ≥ 4-point Itch NRS at baseline (ItchNRS4+@W16)
- proportion of patients achieving at least a 75% reduction in SCORAD relative to their baseline score (SCORAD-75) at Week 16 (SCORAD-75@W16)
- proportion of patients achieving at least a 50% reduction in SCORAD relative to their baseline score (SCORAD-50) at Week 16 (SCORAD-50@W16)
- Mean percent change from baseline in SCORAD at Week 16 (%SCORAD@W16)
- Mean percent change from baseline in BSA involvement at Week 16 (%BSA@W16)


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10.2 Analysis Populations

The planned analysis populations are provided in Table 25.

Table 25: Analysis Populations

Population	Description
Intent-To-Treat (ITT) Population	All patients who are randomized to treatment.
Per Protocol Population	All patients who complete the study without important protocol deviations.
Safety Population	All patients who are randomized to treatment and receive at least 1 dose of study intervention.
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Pharmacokinetics Population	All patients who are randomized to treatment, receive at least 1 dose of rezpegaldesleukin and have available and applicable PK data.
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Abbreviations: AA = alopecia areata; PK = pharmacokinetics

Additional analysis sets will be defined in the statistical analysis plan to support exploratory analyses.

10.3 Sample Size Determination

Approximately 396 patients will be randomized in a 3:3:3:2 ratio at Week 0 Day 1 (Visit 2 in SoE; Table 1) to receive either rezpegaldesleukin 24 µg/kg q2w, rezpegaldesleukin 24 µg/kg q4w, rezpegaldesleukin 18 µg/kg q2w, or placebo q2w in the Induction Period. The patients within each of the 3 rezpegaldesleukin arms who achieve EASI-50 at Week 16 and have adhered to the rescue medication rules will be rerandomized in a 1:1 ratio to receive their last Induction Period dosage (ie, 18 or 24 µg/kg or modified dose) either every 4 or 12 weeks during the Maintenance Period.

The study of 72 patients in a placebo arm and 108 patients in each rezpegaldesleukin arm under the control of two-sided alpha level at 0.05 would provide approximately 98% power to detect an improvement of 26% in the percent change of EASI from baseline at Week 16 in the

rezpegaldesleukin arm assuming 38% reduction of EASI in the placebo arm with a similar standard deviation as the rezpegaldesleukin arm (ie, standard deviation [SD] = 43%). The assumptions on the placebo arm and SD are estimated from dupilumab and lebrikizumab trials (Simpson, 2016; Thaci, 2016; Blauvelt, 2017; Guttman-Yassky, 2020; Silverberg, 2023; Simpson, 2023).

10.4 Statistical Analyses

10.4.1 General Considerations

In general, continuous data will be summarized by descriptive statistics, including number of patients, mean, standard deviation, median, minimum, and maximum. Categorical data will be summarized by the frequency counts and percentage. Two-sided statistical tests will be performed at a significance level of 0.05 if not specifically noted. For the data collected during the Induction Period, comparisons between each rezpegaldesleukin arm and placebo will be conducted with respect to the Investigator- and/or patient- reported efficacy endpoints. The test results will be separately analyzed without adjustments for multiplicity.

Two Study Periods: At the end of the Induction Period, the patients within each of the 3 rezpegaldesleukin arms who achieved EASI-50 at Week 16 and have adhered to the rescue medication rules will be rerandomized in a 1:1 ratio to receive their last induction dosage (ie, 18 or 24 µg/kg or modified dose) either every 4 or 12 weeks during Maintenance Period. In the placebo arm, patients who achieved EASI-50 will continue with placebo q4w.

Escape Arm: All patients from the Induction Period who have adhered to the rescue medication rules and who do not achieve EASI-50 at Week 16 may receive escape therapy. In addition, the Maintenance Period includes an Escape Arm for patients who, despite use of topical TCS, have an acute exacerbation (ie, drop to a score of less than EASI-25), suggesting the need for an active or more frequently administered dose. The escape therapy is rezpegaldesleukin 24 µg/kg q2w. The conditions for patients to receive this escape therapy are listed in Table 12.

Definition of Baseline: The latest efficacy/safety assessments provided prior to the first dose (ie, the Week 0 administration of study drug) will be referred to as the baseline measurements, and the latest samples collected prior to the first dose will be considered as the baseline samples. If a patient does not receive the study intervention, the last available measurement on or prior to randomization date will be applied as the baseline value.

If the analyses are only focusing on the Maintenance Period, the latest available value before the first dose of study intervention during the Maintenance Period will be applied as the baseline value, eg, the prior-dose measurements at Week 16 (Visit 10) in most cases.

If the analyses are only focusing on the Posttreatment Follow-up Period, the latest non-missing measurements on or prior to entering the Posttreatment Follow-up Period will be applied as the baseline value, eg, Week 52 (Visit 19) or ED Visit.

Changes of Methods: This protocol provides general guidance for the data analysis methods. If any changes are needed and only if the changes affect the principal feature, an amendment of the protocol may be required. Otherwise, the justification for the changes to the data analysis methods should be described in the related documents such as clinical study report (CSR). Based on the availability and applicability, the data collected for the exploratory objectives will be analyzed as deemed appropriate.

10.4.2 Primary Endpoint Analysis

The primary objective is to compare the efficacy of each dosing regimen of rezpegaldesleukin versus placebo as measured by the percent change from baseline in EASI, in treatment of biologic-naive patients with moderate-to-severe AD. Correspondingly, the primary endpoint is the mean percent change from baseline at Week 16 in EASI. The primary endpoint analysis will use mixed models for repeated measures (MMRM) to estimate the treatment difference between each rezpegaldesleukin dosing regimen and placebo during the Induction Period. The MMRM model will include baseline value, randomization stratification factors, treatment group, visit and treatment-by-visit interaction as fixed factors. Visit index will be considered as the repeated factor. The LSMEAN difference, standard error, p-value, and 95% confidence interval (CI) will be reported. Sensitivity analyses and additional analyses for supportive estimands will be detailed in the SAP. Details for handling missing data are provided in Section 10.4.5.

10.4.3 Secondary and Exploratory Efficacy Endpoints Analysis

The secondary objectives and corresponding endpoints are provided in Section 3.0. For continuous variables, the same analysis method as the primary endpoint will be used. For binary variables, logistic regression with treatment group, baseline value and randomization stratification factors as covariates will be used to produce estimates of odds ratio, p-value and 95% CI. The Cochran-Mantel-Haenszel (CMH) test p-value adjusted by stratification factors will also be provided. Additionally, the estimates and 95% CIs associated with the treatment response rate and treatment difference will be reported.

Integrated statistics, such as average across selected period or AUC over selected period, may be explored to assess the overall improvement for continuous efficacy variables over time.

For efficacy analyses on the maintenance regimens, descriptive statistics over the Maintenance Period will be mainly provided, including but not limited to, frequencies and percentages for categorical outcomes, and means and standard deviations for continuous outcomes. CCI [redacted]

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10.4.4 Safety Analyses

Safety assessment will be performed by an ongoing review of the following methods:

- Treatment-emergent AEs, including treatment-related AEs, SAEs, and AEs leading to drug discontinuation

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- Clinical laboratory tests (see Appendix 1)
- ECGs
- Vital signs
- Physical examination

Incidence rates (ie, numbers and percentages of patients) will be provided for categorical safety measures. Mean change with standard deviation by visit will be calculated for continuous safety measures, such as vital signs, laboratory results, and ECGs, etc. Duration of study drug Induction Period and duration of Maintenance Period for each patient will be summarized by treatment arms.

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC), preferred term (PT), severity, and relationship to the study intervention by treatment arms.

A TEAE is defined as:

- Any AE that occurs after study intervention initiation
- An AE that was present at Visit 2 prior to the first dose of study intervention but worsened after study intervention initiation
- An AE that was present and resolved prior to the first dose of study intervention but reappeared after study intervention initiation
- Any treatment-related AE

The study period for the safety analysis will include the Induction Period, the Maintenance Period, and the Follow-up Period. For events that are specific to a subgroup such as sex, only the subgroup of patients will be applied to the denominator for the proportion or percentage. TEAEs (all, by maximum severity), SAEs including deaths, and AEs that lead to treatment discontinuation will be summarized and analyzed by MedDRA SOC and PT.

The treatment-related adverse events (TRAEs) are the events that are indicated by the Investigator on the CRF to be related to treatment.

Overall safety and tolerability of rezpegaldesleukin will be summarized by the incidence of TEAEs, TRAEs, SAEs, abnormal vital signs, abnormal ECGs, laboratory abnormalities, deaths, and other safety measurements if available and applicable. Safety analyses will be performed in the Safety Population with descriptive statistics summarized by treatment arms. Analysis about adverse events, including preexisting conditions, will be listed by patient, visit, SOC, PT, treatment arm, severity, and relationship to the treatment.

10.4.5 Handling of Missing and Spurious Data

To carefully address the primary estimand and avoid unnecessary bias, the methods for handling missing values are planned as follows:

a) Patients who receive any rescue medication outside specifications per the protocol version they are enrolled under or who discontinue treatment early prior to Week 16 due to lack of efficacy are considered treatment failures. The Baseline Observation Carry Forward (BOCF) method for continuous endpoints and Non-Responder Imputation (NRI) for binary endpoints will be applied for subsequent visits through Week 16.
b) For patients who discontinue study treatment prior to Week 16 due to reasons other than lack of efficacy, the efficacy values for subsequent visits through Week 16 will be set to missing. The Multiple Imputation (MI) method will be applied to fill in the missing data through Week 16.
c) For remaining missing efficacy outcomes, the MI method will be applied under the assumption of Missing at Random (MAR).

For MI, three steps are involved as follows:

- Step 1: Using the PROC MI procedure in SAS under the arbitrary pattern of missing data with Fully Conditional Specification regression method (FCS REG) for continuous outcomes, the number of replicated complete datasets of the imputation process will be set as 50 (NIMPUTE=50). The imputations will be conducted within each treatment group independently to avoid the influence in the estimates between treatment conditions. For integer outcomes, standard rounding rules will be used for the imputed values. For example, an imputed vIGA-AD score of 2.4 would be rounded down to 2, and 2.5 would be rounded up to 3. Binary outcomes, such as 0 (=No) and 1 (=Yes), are considered as integers in the MI process. The random seeds for each treatment condition and efficacy endpoint are listed in Table 26.
- Step 2: For the continuous endpoints, such as change or percent change from baseline, PROC MIXED will be used to perform the MMRM analysis within each of the complete datasets. For the binary endpoints, the values will be derived directly based on the corresponding continuous outcome after MI.
- Step 3: The results in Step 2 will be combined across the multiple complete datasets using PROC MIANALYZE procedure to obtain the integrative estimates.

10.4.6 Other Analyses

10.4.6.1 Patient Disposition

Patient disposition will be summarized in tables including, but not limited to, the numbers and percentages of patients in Intent-To-Treat (ITT) population who complete the study or discontinue, both overall and by reason for discontinuation.


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10.5 Interim Analyses

When all patients have completed Week 16 or ED Visit, the primary database lock for this study will be triggered. This interim database lock will be considered as the primary database lock for the study because data for the primary objective and those for the secondary objectives related to the Induction Period are mature at this time. Study endpoints associated with the Induction Period will be assessed. CCI The final database lock for the study will occur when 100% of all patients complete all study required end of treatment/ED and follow up visits.

Details for the planned interim analyses will be described in the SAP.

11.0 STUDY OR STUDY SITE TERMINATION

The Sponsor has the right to suspend or terminate the study. Sponsor reasons for suspension or termination of the study may include, but are not limited to, the following:

- Study is terminated due to safety concerns (ie, the benefit-risk balance is unacceptable).
- Lack of efficacy or not meeting the study objectives.
- Development of rezpegaldesleukin is terminated.
- Other business decisions.

If an Investigator suspends or terminates their study site, the Investigator will promptly (if possible, within 24 hours) inform the Sponsor and the IRB/independent ethics committee (IEC) and provide them with a detailed written explanation. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports, summaries, and other documentation as required by health authorities, IRB/IEC, and other regulatory requirements.

12.0 QUALITY CONTROL AND QUALITY ASSURANCE

The Sponsor will implement and maintain quality control and quality assurance procedures with written standard operating procedures to ensure that the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements.

12.1 Changes to the Protocol

The Investigator may not deviate from the protocol without a formal protocol amendment having been established and approved by an appropriate IRB/IEC and the regulatory agency, as required by regulations, except when necessary to eliminate immediate hazards to the patient or when the change(s) involve only logistical or administrative aspects of the study. Any deviation may result in the patient having to be withdrawn from the study and rendering that patient nonevaluable. All protocol deviations and the reasons for such deviations are to be documented and reported to the Sponsor promptly.

12.2 Monitoring

In accordance with Code of Federal Regulations 21 CFR 312.56, International Council for Harmonisation (ICH) GCP, and local regulations, the clinical monitor will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times during and after completion of the study. As required by 21 CFR 312 Subpart D (Responsibilities of Sponsors and Investigators), ICH GCP, and local regulations, the monitoring visits provide the Sponsor with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of eCRFs; ensure that all protocol requirements, applicable FDA, ICH GCP, local regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records that are required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by the Sponsor. The Investigational New Drug (IND) Application regulations and ICH GCP guidelines also require the Investigator to allow authorized representatives of the Sponsor, IRB/IEC, FDA, and other relevant regulatory authorities direct access to study source records, and to inspect and make copies of the same records. The names and identities of the patients need not be divulged to the Sponsor; however, the records must nevertheless be available to be inspected for review. This can be accomplished by blacking out the patient's name and replacing the name with the patient's study identification number. If these requirements are in conflict with local regulatory restrictions or institutional requirements, the Investigator must inform the Sponsor of these restrictions before initiation of the study.

12.3 Direct Access to Source Data/Documents for Audits and Inspections

The Sponsor or designees may conduct auditing activities of a clinical site at any time during or after completion of the study. The Investigator will be informed of such activities.

Representatives of the FDA or other regulatory agencies, including IRB/IEC representatives, may also conduct an inspection or perform an audit of the study. The Investigator(s)/institution(s) will permit trial-related audits, IRB/IEC review, and regulatory inspection(s) by providing direct access to source data/documents and study records. If informed of such an inspection, the Investigator shall notify the Sponsor immediately. The Investigator will ensure that the inspectors and auditors have access to the clinical supplies, study site facilities, and laboratory, and that all data (including original source documentation) and all study files are available, if requested.

13.0 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted to be consistent with the principles that have their origin in Declaration of Helsinki and in accordance with FDA regulations (21 CFR § 11, 50, 54, 56, and 312), with ICH GCP, European Union Clinical Trials Regulation (536/2014), as well as with any applicable regulatory authority, federal, state and/or local laws and regulations.

13.1 IRB/IEC Approval

Before enrollment of patients into the study, as required by FDA regulations (21 CFR § 56), ICH GCP, applicable regulatory authority requirements, and local regulations, the current protocol, Investigator's Brochure, and ICF will be reviewed and approved by the applicable regulatory authority and/or competent IRB/IEC. A letter documenting the IRB/IEC approval must be received by the Sponsor before the initiation of the study at a clinical site. Amendments to the protocol will be subject to the same requirements as the original protocol in accordance with Section 12.1.

The Investigator, Sponsor, or their designees will submit a progress report at least once yearly to the IRB/IEC, more frequently if required by the IRB/IEC. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB/IEC per the IRB/IEC requirements, and in compliance with FDA regulations, applicable regulatory authority requirements, and ICH GCP.

The Investigator, the Sponsor, or their designees shall promptly notify the IRB/IEC of any SAEs, suspected unexpected serious adverse reactions (SUSARs), or any other information that may affect the safe use of the study drug(s) during the study, per the IRB/IEC local requirements, and in compliance with FDA regulations, regulatory authority regulations, and ICH GCP.

13.2 Written Informed Consent

A freely and voluntarily written documentation of informed consent must be obtained from each patient before entering the study. The content and approval of the ICF must meet requirements of regulations and ICH GCP. Patients will be informed of all aspects of the study that are relevant to the patient's decision to participate, and the ICF must be presented to each patient in the language in which the patient is fluent.

Informed consent will be obtained from and documented for each patient prior to the conduct of any protocol-specific procedures. Signed and dated ICFs will be retained by the Investigator with the study records. Each patient will be given a copy of the signed and dated ICF.

Any pregnancy that occurs in a study patient or the female partner of a male study patient should be reported to the Sponsor or designee. Only if a pregnant patient or partner has signed an informed consent form for disclosure information will the Sponsor or designee be able to collect any pregnancy surveillance information. Information on this pregnancy will be collected on the Pregnancy Surveillance Form (see Section 9.2.2).

14.0 DATA HANDLING AND RECORD KEEPING

14.1 Data Collection Instruments and Source Documents

14.1.1 Study Records

During the study, the Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail). The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports. The Investigator/institution should, at a minimum, maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by the applicable regulatory requirement(s). The Investigator/institution should take measures to prevent accidental or premature destruction of these documents.

14.1.2 Data Collection Instruments

Data collection instruments (DCIs) (eg, eCRFs, electronic clinical outcomes assessments [eCOA], and paper forms) will be used in this study. These instruments are used to transmit the information collected during the performance of this study to the Sponsor or Sponsor's designee and regulatory authorities.

The Investigator must review the DCIs for completeness and accuracy and must approve all data, including any changes made. Furthermore, the Investigator retains full responsibility for the appropriateness and accuracy of all data collected in the DCIs.

14.2 Retention of Essential Documents

The Essential Documents contained in the clinical trial master files shall be retained for 25 years or per local and regional regulations and guidelines, whichever is longer. These documents should be retained for a longer period, however, if required by an agreement with the Sponsor. At all times, the retention must meet applicable data protection laws. It is the responsibility of the Sponsor to inform the Investigator/institution in writing as to when these documents no longer need to be retained.

The Investigator shall archive the clinical trial master file securely and in a way that ensures that it is readily available and accessible, upon request, to the regulatory authorities. Sites must inform the Sponsor in writing if documents will be disposed of per Institutional Policy.

The Investigator will contact the Sponsor before transferring or destroying any study records. The Investigator will also promptly notify the Sponsor in writing in the event of accidental loss or destruction of any study records.

14.3 Confidentiality

Patient confidentiality will be maintained per legal and regulatory requirements and ICH GCP. To comply with GCP guidelines and requirements, patient records will be reviewed during monitoring visits and audits conducted by the Sponsor, Sponsor's representatives, or health authorities. During these activities, every reasonable effort will be made to keep medical information, including patient identifying information, as confidential as possible as required by law.

Study data given to, and used by, Nektar are protected by the use of a patient identification number. The assignment of unique patient identification number to each patient by IRT system enables de-identification.

Demographic identifiers that will be collected as part of Study Data include year of birth, age, sex, race, and ethnicity provided this is permitted under applicable laws. Exact date of birth and patient name/initials are not collected.

The study site is not to attach the names or other directly identifying information of the patients to any Study Data or biological samples that will be transferred to Nektar. Only pseudonymized / key-coded Study Data and biological samples will be transferred to Nektar, and only the study site will be able to connect the patient identification number to a patient’s personal data.

14.4 Security Measures

Sites will employ both technical and organizational measures (such as, but not limited to, controlling access to personal patient data to only those with a need to know such data, data encryption, data anonymization and pseudonymization, and so forth) to ensure patient and patient data privacy. Sites will adhere to a “privacy by design” and “privacy by default” approach in collecting, storing, and processing personal patient data.

In the event of a breach of the security measures used by the Site to ensure patient and patient data privacy, the Site will immediately notify the Sponsor.


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15.0 PUBLICATION PLAN

All data are the property of the Sponsor. Any formal presentation or publication of data from this study will be considered for joint publication by the Sponsor personnel and Investigator(s).

Any publications or abstracts arising from this study must adhere to the publication requirements set forth in the clinical trial agreement governing participation in the study. Study data shared by Nektar will not contain patient identifiable information.

The Investigator may be required to sign the clinical study report if it is to be used in a registration submission to the health authorities of some countries.

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APPENDIX 1: CLINICAL LABORATORY TESTS

CLINICAL LABORATORY TESTS

Laboratory tests performed in this study are provided in Table 27.

Use of central or local laboratories

Clinical laboratory tests will be performed by a central laboratory or by a local laboratory as detailed in the tables in this appendix.

If laboratory tests are performed to obtain results with an intent to resume administration of study intervention after a temporary interruption, the samples should be assayed centrally.

In circumstances where the Sponsor approves local laboratory testing in lieu of the central laboratory testing specified in the tables, the local laboratory must be qualified in accordance with applicable local regulations.

Laboratory tests for inclusion/exclusion of potential study patients

Protocol-specific requirements for the inclusion or exclusion of patients are specified in Section 4.0 of the protocol.

Pregnancy testing

Pregnancy testing is described in the SoE (Section 1.2), in Section 9.1.5, and in the tables below.

Allowance for additional laboratory testing

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Investigator responsibilities

Investigators must document their review of the laboratory safety results.

Provision of laboratory test results

Laboratory test results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Table 27: Laboratory Tests Performed in This Study

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology[1]</th><th>Chemistry[1]</th><th>TB Testing</th></tr>
<tr>
<td>• Hemoglobin (Hgb)
• Hematocrit (HCT)
• Erythrocytes count (red blood cells)
• Mean cell volume
• Mean cell hemoglobin
• Mean cell hemoglobin concentration
• Absolute neutrophil count (ANC), segmented and bands
• Platelet count
• White blood cell (WBC) count
• Differential, percent, and absolute count of:
  ○ Neutrophils, segmented
  ○ Neutrophils, bands (report if detected)
  ○ Lymphocytes
  ○ Monocytes
  ○ Eosinophils
  ○ Basophils
• Cell morphology (RBC and WBC)</td>
<td>• Sodium
• Potassium
• Chloride
• Bicarbonate
• Total bilirubin
• Direct bilirubin
• Alkaline phosphatase (ALP)
• Alanine transaminase (ALT)
• Aspartate transaminase (AST)
• Gamma-glutamyl transferase (GGT)
• Blood urea nitrogen (BUN) or serum urea
• Creatinine[2]
• Creatine kinase (CK)
• Uric acid
• Total protein (TP)
• Albumin
• Calcium
• Phosphorus
• Glucose (non-fasting)</td>
<td>• QuantiFERON®-TB Gold[1]
HIV and Hepatitis Serology[1]
• Human immunodeficiency virus (HIV) antibody[6]
• HCV antibody
• HCV RNA; Performed only for patients who test positive for hepatitis C antibody.
• Hepatitis B core antibody (anti-HBc)
• Hepatitis B surface antigen (HBsAg)
• Hepatitis B virus (HBV) DNA; For patients who are anti-HBc positive at screening.</td>
</tr>
<tr><th>Lipid Panel[1]</th><th>Additional Labs</th><th rowspan="2"></th></tr>
<tr>
<td>• High-density lipoprotein (HDL)
• Low-density lipoprotein (LDL), if triglycerides > 400 mg/dL, LDL will be assayed
• Cholesterol
• Triglycerides</td>
<td>• Serum pregnancy[1,3]
• Urine pregnancy, evaluated locally[3]
• Follicle-stimulating hormone (FSH)[1]
• Hemoglobin A1c[4]
• Thyroid Stimulating Hormone (TSH)[5]</td>
</tr>
<tr><th colspan="3">Urinalysis[1]</th></tr>
<tr>
<td colspan="2">• Specific gravity
• pH
• Protein
• Glucose
• Ketones
• Bilirubin</td>
<td>• Urobilinogen
• Blood
• Nitrite
• Leukocyte esterase
• Microscopic examination of sediment if abnormalities were detected on urinalysis</td>
</tr>
</table>

1 Assayed by designated laboratory (note: the LDL is calculated using the Friedewald Equation).
2 Estimated glomerular filtration rate (eGFR) will be calculated when serum creatinine is measured and is generated by the designated laboratory via Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation.
3 For women of childbearing potential only (Section 9.1.5).
4 Collected at Screening, Week 16, and End of Treatment.
5 Collected at Screening, Week 16, and Week 52.
6 Only the confirmatory results will be provided.

The following assessments will be assayed by the designated laboratory, and results will not be provided to the investigative sites:

- Immunoglobulins: Immunoglobulin E

- Pharmacokinetic samples: rezpegaldesleukin concentration
- Immunogenicity samples

Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of Collecting Samples after a Systemic Hypersensitivity Event

The samples listed in this appendix are not collected for acute study patient management. The Sponsor will use the laboratory test results from these samples to characterize hypersensitivity events across the clinical development program.

When to Collect Samples after a Systemic Hypersensitivity Event Occurs

Collect the samples listed in Table 28 if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the patient has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess postevent return-to-baseline values.

Table 28: Timing and Laboratory Tests to be Obtained Following a Systemic Hypersensitivity Event

Timing	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. • Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase
	complements (C3, C3a, and C5a)
	cytokine panel cytokine panel CCI [redacted]
Collect only if not already collected on the same day as the event. • Note: If collecting, collect up to 12 hours after the start of the event.	CCI [redacted]
	rezpegaldesleukin concentration

Abbreviations: CCI [redacted] C = complement; IFN-γ = interferon gamma; IL = interleukin;

a. All samples for hypersensitivity testing will be assayed by the designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What Information to Record

Record the date and time when the samples are collected.

Allowed Additional Testing for Patient Management

The Investigator may perform additional tests locally, if clinically indicated, for acute study patient management.

APPENDIX 2: ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Definition of AE

AE Definition
An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae. Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting diseases or conditions present or detected at the start of the study that do not worsen.

Definition of SAE

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

a. Results in death

b. Is life-threatening

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

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the patient has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

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

Definition of Product Complaints

Product Complaint
A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs: • Deficiencies in labeling information, and • Use errors for device or drug-device combination products due to ergonomic design elements of the product. PCs related to study interventions used in clinical trials are collected in order to ensure the safety of patients, monitor quality, and to facilitate process and product improvements. Investigators will instruct patients to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed. An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording
When an AE/SAE/PC occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event. The Investigator will then record all relevant AE/SAE/PC information in the patient's medical records, in accordance with the Investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form. Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE. It is **not** acceptable for the Investigator to send photocopies of the patient's medical records to the Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs. There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before submission to the Sponsor or designee. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories: • **Mild:** A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. • **Moderate:** A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research patient. • **Severe:** A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The Investigator will use clinical judgment to determine the relationship.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The Investigator will also consult the IB in their assessment.

For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings, including histopathology.

Reporting of SAEs

SAE Reporting via Paper Form

For SAEs, follow the SAE reporting and completion guidelines. SAEs will be reported to Nektar Therapeutics Drug Safety immediately without undue delay, under no circumstances later than 24 hours following knowledge of the event. Facsimile or email transmission of the SAE paper form is the primary method to transmit this information.

Regulatory Reporting Requirements

SAE Regulatory Reporting
Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention under clinical investigation are met. The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and Investigators. An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. Consistent with the European Union Clinical Trials Regulation (536/2014), the Sponsor has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs. Upon an Investigator's report of an SAE, the Sponsor will evaluate the data, including confirmation of relatedness and assessment of expectedness. The Sponsor will submit any qualifying reports to the Eudravigilance database within the required time frame. Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and will be forwarded to Investigators as necessary.

APPENDIX 3: WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF HIGHLY-EFFECTIVE CONTRACEPTION

DEFINITIONS

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Women in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

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

- Postmenopausal female
  - A postmenopausal state is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause.

CONTRACEPTION GUIDANCE FOR FEMALE PATIENTS OF CHILDBEARING POTENTIAL

One of the highly effective methods of contraception listed below is required during study duration and until the end of relevant systemic exposure, defined as CCI the last dose of study drug (Note: local laws and regulations may require use of alternative and/or additional contraception methods).

Highly Effective Contraceptive Methods That Are User Dependent *Failure rate of < 1% per year when used consistently and correctly.*[a]
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b] • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • oral • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Hormonal methods of contraception including vaginal ring, injectables, implants and intrauterine hormone-releasing system (IUS)[c] • Intrauterine device (IUD)[c] • Bilateral tubal occlusion
• Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
• Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the patient.* • It is not necessary to use any other method of contraception when complete abstinence is elected. • WOCBP patients who choose complete abstinence must continue to have pregnancy tests, as specified in Section 1.2. • Acceptable alternate methods of highly effective contraception must be discussed in the event that the WOCBP patient chooses to forego complete abstinence

NOTES:
a. Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for patients participating in clinical studies. b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. Hormonal contraception is permissible only when there is sufficient evidence that the IMP and other study medications will not alter hormonal exposures such that contraception would be ineffective or result in increased exposures that could be potentially hazardous. In this case, alternative methods of contraception should be utilized. c. Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.
Unacceptable Methods of Contraception[a]
• Male or female condom with or without spermicide. Male and female condoms cannot be used simultaneously • Diaphragm with spermicide • Cervical cap with spermicide • Vaginal Sponge with spermicide • Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mechanism of action • Periodic abstinence (calendar, symptothermal, postovulation methods) • Withdrawal (coitus interruptus). • Spermicide only • Lactation amenorrhea method (LAM)

a. Local laws and regulations may require use of alternative and/or additional contraception methods.

CONTRACEPTION GUIDANCE FOR MALE PATIENTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male patients with female partners of childbearing potential are eligible to participate if they agree to the following during the treatment and until the end of relevant systemic exposure.

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator.
- Male patients are required to use a condom for study duration and until end of relevant systemic exposure defined CCI following the last dose of study drug.
- Female partners of males participating in the study to consider use of highly effective methods of contraception until the end of relevant systemic exposure, CCI following the last dose of study drug.
- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration during the treatment and CCI following the last dose of study drug.
- Refrain from donating sperm for the duration of the study treatment and CCI following the last dose of study drug.

COLLECTION OF PREGNANCY INFORMATION

Guidance for collection of Pregnancy Information is provided in Sections 9.2.2 and 13.2.

APPENDIX 4: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

Hepatic Evaluation Testing

See Section 9.1.9 for guidance on appropriate test selection.

The designated central laboratory should complete the analysis of all selected testing except for testing listed in the Investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available. Laboratory tests assayed by the designated central laboratory are provided in Table 29.

In circumstances where required in accordance with local regulations, local laboratory testing may be performed in lieu of designated central laboratory testing (Table 30).

Local testing may be performed *in addition to central testing* when necessary for immediate patient management.

The local laboratory must be qualified in accordance with applicable local regulations.

Table 29: Laboratory Tests Assayed by Designated Central Laboratory

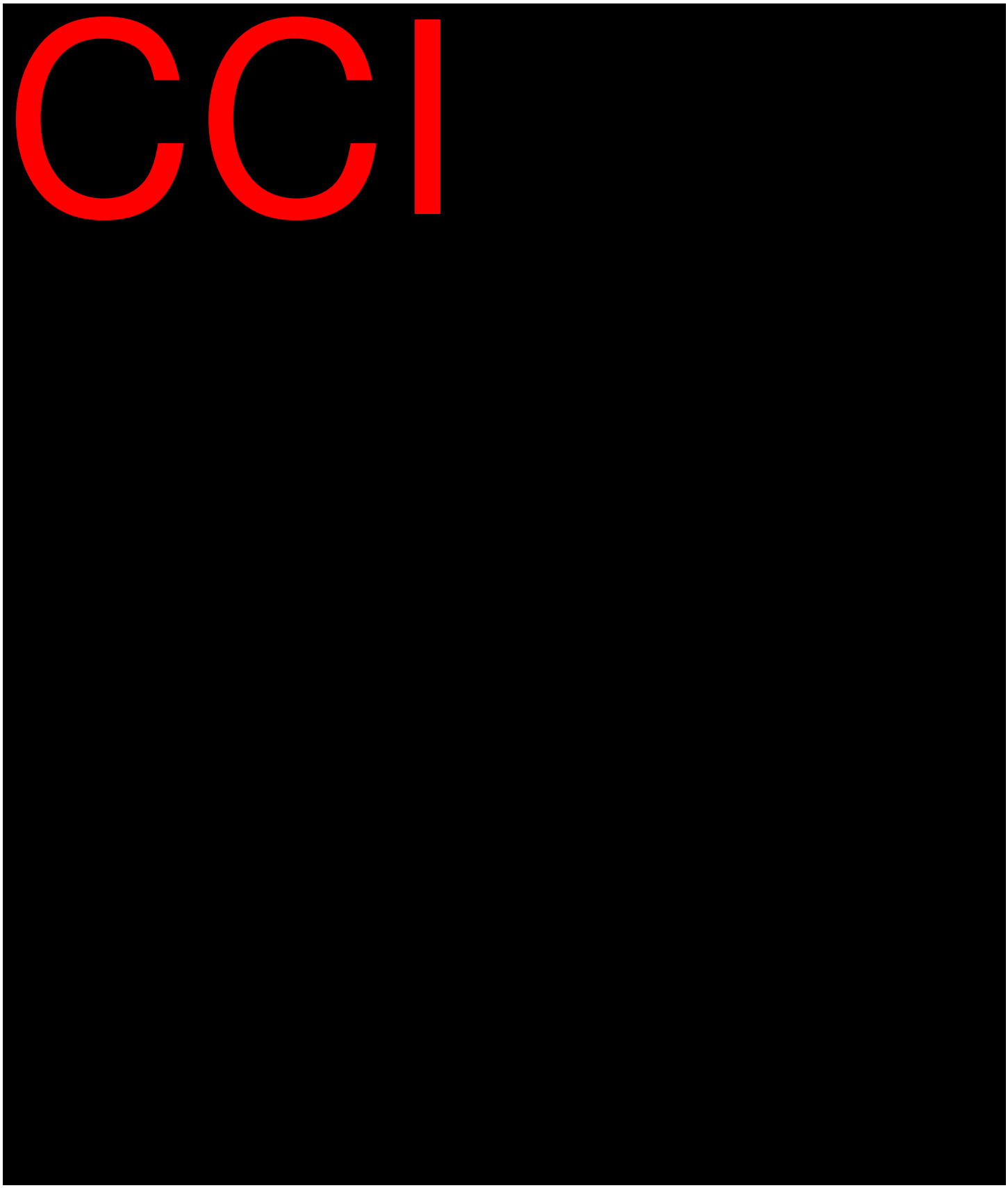
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[a]
Basophils	**Hepatis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV Total antibody where available
Total bilirubin	Hepatitis Delta antibody where available
Direct bilirubin	**Hepatitis E virus (HEV) testing:**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine transaminase (ALT)	HEV IgM antibody
Aspartate transaminase (AST)	HEV RNA[a]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)**
Hepatic Coagulation Panel	
Prothrombin time, international normalized ratio (INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	

a. Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

Table 30: Laboratory Tests Assayed ONLY by Investigator-designated Local Laboratory

Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[a]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[a]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology**
Ethyl glucuronide (EtG)	Culture:
Epstein-Barr virus (EBV) testing:	Blood
EBV DNA [a]	Urine
EBV antibody	

a. Reflex/confirmation dependent on regulatory requirements, testing availability, or both.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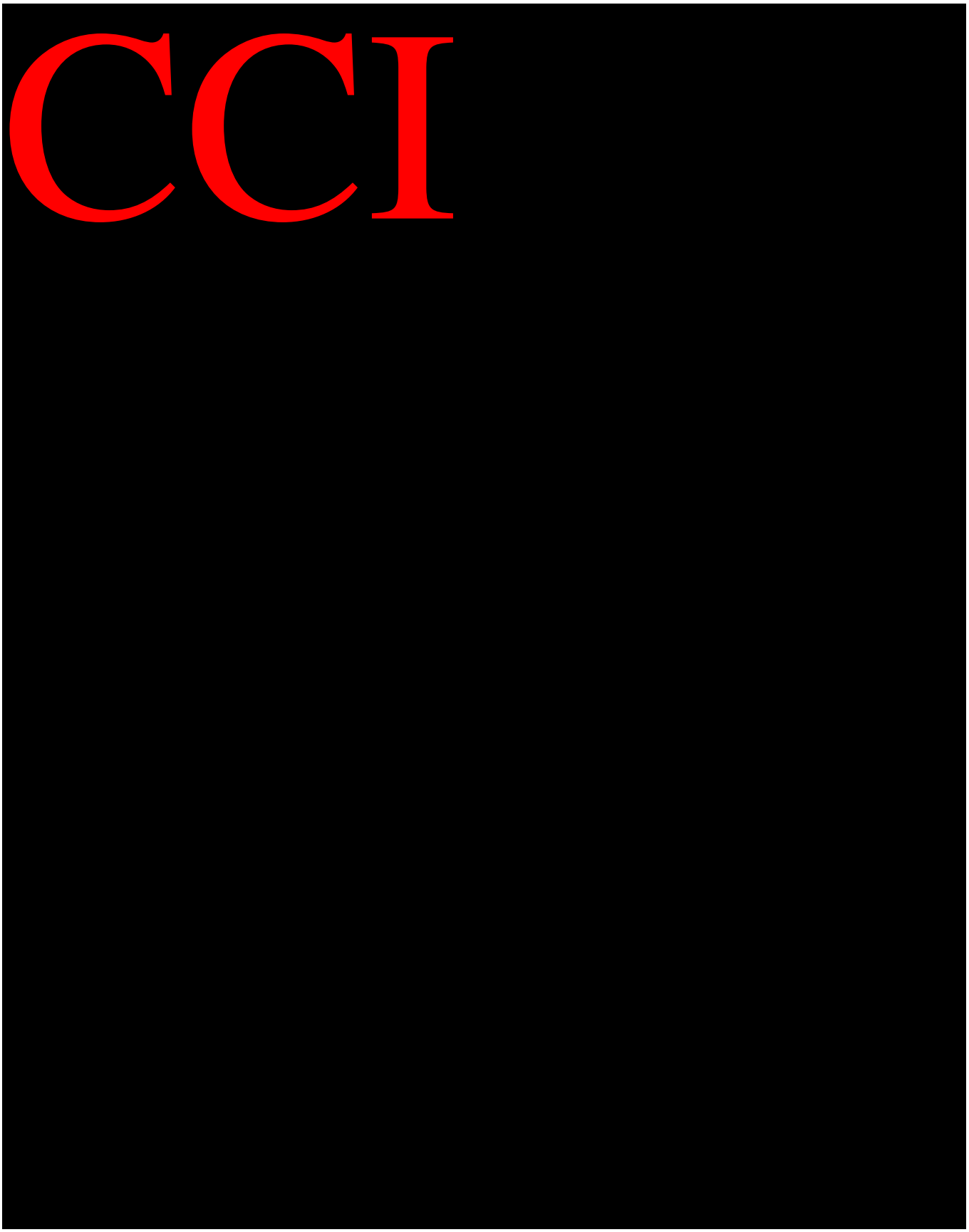
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