16.1.1 Protocol and Protocol Amendments

16.1.1.1 Clinical Study Protocol: ANB019-206 Original 2

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ANB019 in the Treatment of Subjects with Ichthyosis

Protocol Number: ANB019-206

Investigational New Drug (IND) Number: 136145

European Clinical Trials Database (EudraCT) Number: 2020-003476-41

Sponsor Name: AnaptysBio, Inc.

Sponsor Address: 10421 Pacific Center Court, Suite 200

San Diego, CA 92121, United States

Sponsor Medical Expert and Signatory: [redacted]

Original Protocol (Version 1.0)

30 October 2020

SPONSOR SIGNATURE PAGE

I confirm that I have read and approved this protocol in its entirety and will comply with the obligations as detailed in all applicable regulations and guidelines (eg, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] Good Clinical Practice [GCP] guidelines) and the protocol.

[redacted]

10/30/2020

Date (DD-MMM-YYYY)

AnaptysBio, Inc.

INVESTIGATOR'S AGREEMENT

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ANB019 in the Treatment of Subjects with Ichthyosis

PROTOCOL NO: ANB019-206

VERSION: Original Protocol (Version 1.0)

This protocol is a confidential communication of the Sponsor. I confirm that I have read this protocol; I understand it; and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

Instructions to the Investigator: Please SIGN and DATE (DD-MMM-YYYY) this signature page. PRINT your name, title, and the name of the study center in which the study will be conducted. Return the signed copy to the Sponsor or designee.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

DOCUMENT HISTORY

DOCUMENT HISTORY	
Document	**Date**
Original Protocol (Version 1.0)	30 October 2020

ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARCI	autosomal recessive congenital ichthyosis
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
BSA	body surface area
CDLQI	Children's Dermatology Life Quality Index
CFR	Code of Federal Regulations
CI	confidence interval
CK	creatine kinase
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus Disease 2019
CRO	contract research organization
CSR	Clinical Study Report
CV	coefficient of variation
cyIL-36R	cynomolgus monkey IL-36R
D	day
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
EC	Ethics Committee
ECG	electrocardiograms
eCRF	electronic case report form
EDC	electronic data capture
EOS	end of study
ET	early termination
EudraCT	European Clinical Trials Database
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GPP	generalized pustular psoriasis
H_0	null hypothesis
hCG	human chorionic gonadotropin
HHS	Health and Human Services
HIPAA	Health Information Portability and Accountability Act
hrs	hours
HRT	hormonal replacement therapy
hsCRP	human C-reactive protein
IA	interim analysis
IASI	Ichthyosis Area Severity Index
IASI50	improvement of 50% in Ichthyosis Area Severity Index
IASI75	improvement of 75% in Ichthyosis Area Severity Index
IASI-E	Ichthyosis Area Severity Index erythema
IASI-S	Ichthyosis Area Severity Index scaling

IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGA	Investigator Global Assessment
IgG4	immunoglobulin G4
IgE	immunoglobulin E
IL	Interleukin
IL-36R	interleukin 36 receptor
IL-36Ra	IL-36R antagonist
IND	Investigational New Drug
iQoL-32	Ichthyosis Quality of Life- 32 items
IRB	Institutional Review Board
ITT	intent-to-treat
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
IWRS	Interactive Web Response System
KD	dissociation constant
LMW	low molecular weight
LSM	least-squares means
mAb	monoclonal antibody
MAD	multiple ascending dose
MCH	mean cell hemoglobin
MCHC	mean cell hemoglobin concentration
MCV	mean cell volume
MedDRA	Medical Dictionary for Regulatory Activities
min	minute
MMRM	mixed effects model for repeated measures
NaCl	sodium chloride
NASA	Netherton Area and Severity Assessment
NOAEL	no observed adverse effect level
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drugs
PASI	Psoriasis Area and Severity Index
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PCV	packed cell volume
PD	pharmacodynamic
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PK	pharmacokinetic
PPP	palmoplantar pustulosis
PT	preferred term
QC	quality control
RBC	red blood cell
RNA	ribonucleic acid
RNA-seq	RNA sequencing
SAD	single ascending dose
SAE	serious adverse event
SAP	Statistical Analysis Plan

SAS	statistical analysis system
SC	subcutaneous/subcutaneously
SD	standard deviation
SoA	Schedule of Activities
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	terminal half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEWL	transepidermal water loss
Th-17	T-helper 17
TK	toxicokinetic
T_{max}	time to maximum observed concentration
TNF	tumor necrosis factor
ULN	upper limit of normal
W	week
WBC	white blood cell
WHO	world health organization
WOCBP	woman of childbearing potential

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the protocol, applicable ICH GCP guidelines, and applicable local laws and regulations. The Investigator will assure that no planned deviation from, or changes to the protocol will take place without prior agreement from the IND Sponsor and documented approval from the Institutional Review Board (IRB)/Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed ICH GCP Training.

The protocol, informed consent form(s) (ICFs) and assent form(s), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of the protocol and the consent/assent forms must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. In addition, all changes to the consent/assent forms will be IRB/EC-approved; a determination will be made regarding whether a new consent needs to be obtained from subjects who provided consent, using previously approved consent/assent forms.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ANB019 in the Treatment of Subjects with Ichthyosis

Short Title: Efficacy and Safety of ANB019 in Subjects with Ichthyosis

Study Description: This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of ANB019 compared with placebo in adolescent and adult subjects with ichthyosis. This study will also characterize the pharmacokinetic (PK) profile of ANB019 and explore the immune response to ANB019 in subjects with ichthyosis.

Written informed consent will be obtained from each subject prior to initiating any study-related procedures. Subjects will also provide consent for skin biopsy collection if they wish to participate in this test.

To be eligible for the study, subjects will need to have a diagnosis of their ichthyosis subtype (as described in Section 5.1) confirmed by genetic testing.

The expected study duration per subject is approximately 44 weeks. The study will include a screening period of up to 30 days, followed by a 16-week placebo-controlled period, a 16-week open-label extension period, and an 8-week safety follow-up period.

Of note, all subjects will receive ANB019 during the open-label extension period starting on Day 113 (Week 16) visit until Day 197 (Week 28) visit. The placebo-controlled period ends on Day 113 (Week 16) visit, before study treatment administration. Therefore, the open-label extension period starts when the study treatment is administered on Day 113 (Week 16) visit.

During the placebo-controlled period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, subcutaneously (SC) administered on 4 occasions. On Day 1, the subjects will receive a 400-mg dose of ANB019 or placebo. On Days 29, 57, and 85, the subjects will receive a 200-mg dose of ANB019 or placebo. During the open-label extension period, all subjects will receive ANB019, SC administered on 4 occasions. Subjects assigned to ANB019 during the placebo-controlled period will continue to receive a 200-mg dose of ANB019 on Days 113, 141, 169, and 197. Subjects assigned to placebo during the placebo-controlled period will receive a 400-mg dose of ANB019 on Day 113, followed by a 200-mg dose of ANB019 on Days 141, 169, and 197.

For scheduled on-site study visits, subjects will come to the study center on 13 occasions to monitor changes in disease activity, PK (if applicable), safety, and tolerability: screening and Days 1, 8, 29, 57, 85, 113, 141, 169, 197, 225, 253, and 281 (end of study [EOS]/early termination [ET]). The subjects will leave the study center following study treatment administration when all postdose assessments have been completed and with the Investigator's approval. In addition, during the placebo-controlled period, the subjects will also be contacted via telephone by study staff on Days 3, 15, 43, and 71 to inquire about potential adverse events (AEs) they experienced and any changes in concomitant medications. All procedures will be conducted in accordance with the Schedule of Activities (SoA) in Section 1.3.

Of note, all predose assessments performed on Day 113 (Week 16) will be used to evaluate the primary and secondary efficacy endpoints, as well as the safety, tolerability, and immune response of ANB019 compared with placebo.

Safety assessments will include AE/serious adverse event (SAE) monitoring, vital signs, physical examination, electrocardiograms (ECGs), and clinical laboratory tests (hematology, biochemistry, and urinalysis).

Disease activity will be evaluated for all subjects using the Ichthyosis Area Severity Index (IASI), IASI erythema (IASI-E) subscore, IASI scaling (IASI-S) subscore, Netherton Area and Severity Assessment (NASA) for subjects with Netherton Syndrome only, Investigator Global Assessment (IGA), and body surface area (BSA) involved with ichthyosis. Quality of life will be evaluated using Ichthyosis Quality of Life- 32 items (iQoL-32) in subjects ≥ 15 years of age only, Dermatology Life Quality Index (DLQI) for subjects ≥ 16 years of age, and Children's DLQI (CDLQI) for subjects <16 years of age. Subjects will also be evaluated for disease-associated characteristics, such as worst and average pruritus and pain using a Numeric Rating Scale (NRS), impression of severity using the Patient Global Impression of Severity (PGI-S) and impression of change using the Patient Global Impression of Change (PGI-C), as well as changes in transepidermal water loss (TEWL).

Blood samples to determine PK, immunogenicity (presence of anti-drug antibodies [ADA] to ANB019), and immunoglobulin E (IgE) levels (for subjects with Netherton Syndrome only) will be collected on Day 1 before the administration of the study treatment and at the other time points specified in the SoA (see Section 1.3). Tape strips and optional skin biopsies for biomarker analysis will be collected at the time points specified in the SoA. All subjects randomized in the study will be asked to participate in skin biopsy collection; however, the subject's participation is optional. In addition, photographs will be taken at selected study centers only to document skin lesions at the time points specified in the SoA.

Interim analyses (IAs) may be performed during the treatment periods (placebo-controlled period and/or open-label extension period) for

assessment of all primary and secondary efficacy endpoints, and evaluation of all safety data available.

Objectives:

Primary Objective:

- To determine the effect of ANB019 compared with placebo as measured by IASI total score

Secondary Objectives:

- To evaluate the effect of ANB019 compared with placebo on ichthyosis signs and symptoms, and quality of life in subjects with ichthyosis
- To determine the safety of ANB019 in the treatment of ichthyosis

Exploratory Objectives:

- To further evaluate the effect of ANB019 on ichthyosis signs and symptoms, and quality of life in subjects with ichthyosis
- To explore the effect of ANB019 on cutaneous biomarkers
- To explore ichthyosis-associated mutations and additional pharmacogenomic analysis
- To test for immunogenicity to ANB019
- To evaluate IgE levels in subjects with Netherton Syndrome
- To describe the PK profile of ANB019 in subjects with ichthyosis

Endpoints:

Primary Efficacy Endpoint:

- Change from Baseline in IASI total score at Week 16

Secondary Endpoints:

- Percent change from Baseline in IASI total score at Week 16
- Proportion of subjects achieving an improvement of 50% from Baseline in IASI (IASI50) at Week 16
- Change and percent change from Baseline in IASI-E and IASI-S subscores at Week 16
- Incidence of AEs, SAEs, and AEs leading to withdrawals, as well as changes in vital signs, clinical laboratory parameters (hematology, biochemistry, and urinalysis), and 12-lead ECGs

Exploratory Endpoints:

- Change and percent change from Baseline in IASI total score at Weeks 1, 4, 8 and 12
- Proportion of subjects achieving IASI50 at Weeks 1, 4, 8, and 12
- Proportion of subjects achieving an improvement of 75% from Baseline in IASI (IASI75) at Weeks 1, 4, 8, 12, and 16
- Change and percent change from Baseline in IASI-E and IASI-S subscores at Weeks 1, 4, 8, and 12

- Change and percent change from Baseline in NASA at Weeks 1, 4, 8, 12, and 16 (for subjects with Netherton Syndrome only)
- Proportion of subjects achieving an improvement of 50% from Baseline in NASA (NASA50) at Weeks 1, 4, 8, 12, and 16 (for subjects with Netherton Syndrome only)
- Change and percent change from Baseline in IGA at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects with at least 2-point decrease in IGA at Weeks 1, 4, 8, 12, and 16
- Change and percent change from Baseline in worst and average pruritus NRS at Weeks 1, 4, 8, 12, and 16
- Change and percent change from Baseline in worst and average pain NRS at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects with at least 3-point decrease in worst pruritus NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pruritus NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pruritus NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pruritus NRS of at least 4
- Proportion of subjects with at least 3-point decrease in worst pain NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pain NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pain NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pain NRS of at least 4
- Change from Baseline in BSA at Weeks 1, 4, 8, 12, and 16
- Change from Baseline in DLQI and CDLQI scores at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects in each response category for the PGI-S and PGI-C at Weeks 1, 4, 8, 12, and 16
- Change from Baseline in iQoL-32 score at Weeks 4, 8, 12, and 16
- Change from Baseline in TEWL at Weeks 4, 8, 12, and 16
- Proportion of subjects receiving rescue medication at Weeks 4, 8, 12, and 16
- Proportion of subjects achieving IASI50 from Week 20 through Week 40
- Proportion of subjects achieving IASI75 from Week 20 through Week 40
- Change and percent change from Baseline in IASI total score from Week 20 through Week 40
- Change and percent change from Baseline in IASI-E and IASI-S subscores from Week 20 through Week 40
- Change and percent change from Baseline in NASA from Week 20 through Week 40 (for subjects with Netherton Syndrome only)

- Proportion of subjects achieving NASA50 from Week 20 through Week 40 (for subjects with Netherton Syndrome only)
- Change and percent change from Baseline in IGA from Week 20 through Week 40
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) from Week 20 through Week 40
- Proportion of subjects with at least 2-point decrease in IGA from Week 20 through Week 40
- Change and percent change from Baseline in worst and average pruritus NRS from Week 20 through Week 40
- Proportion of subjects with at least 3-point decrease in worst pruritus NRS from Week 20 through Week 40 for subjects with a Baseline worst pruritus NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pruritus NRS from Week 20 through Week 40 for subjects with a Baseline worst pruritus NRS of at least 4
- Change and percent change from Baseline in worst and average pain NRS from Week 20 through Week 40
- Proportion of subjects with at least 3-point decrease in worst pain NRS from Week 20 through Week 40 for subjects with a Baseline worst pain NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pain NRS from Week 20 through Week 40 for subjects with a Baseline worst pain NRS of at least 4
- Change from Baseline in BSA from Week 20 through Week 40
- Change from Baseline in iQoL-32 score from Week 20 through Week 40
- Change from Baseline in DLQI and CDLQI scores from Week 20 through Week 40
- Proportion of subjects in each response category for the PGI-S and PGI-C from Week 20 through Week 40
- Change from Baseline in TEWL from Week 20 through Week 40
- Proportion of subjects receiving rescue medication from Week 20 through Week 40
- Skin tape strip biomarkers analysis including, but not limited to, IL-36 and Th-17
- Optional skin biopsy biomarkers analysis including, but not limited to, IL-36 and Th-17
- Presence of anti-drug antibodies to ANB019
- IgE levels evaluation (for subjects with Netherton Syndrome only)
- Serum concentration following ANB019 administration and other parameters as appropriate will be determined to describe the PK profile of ANB019

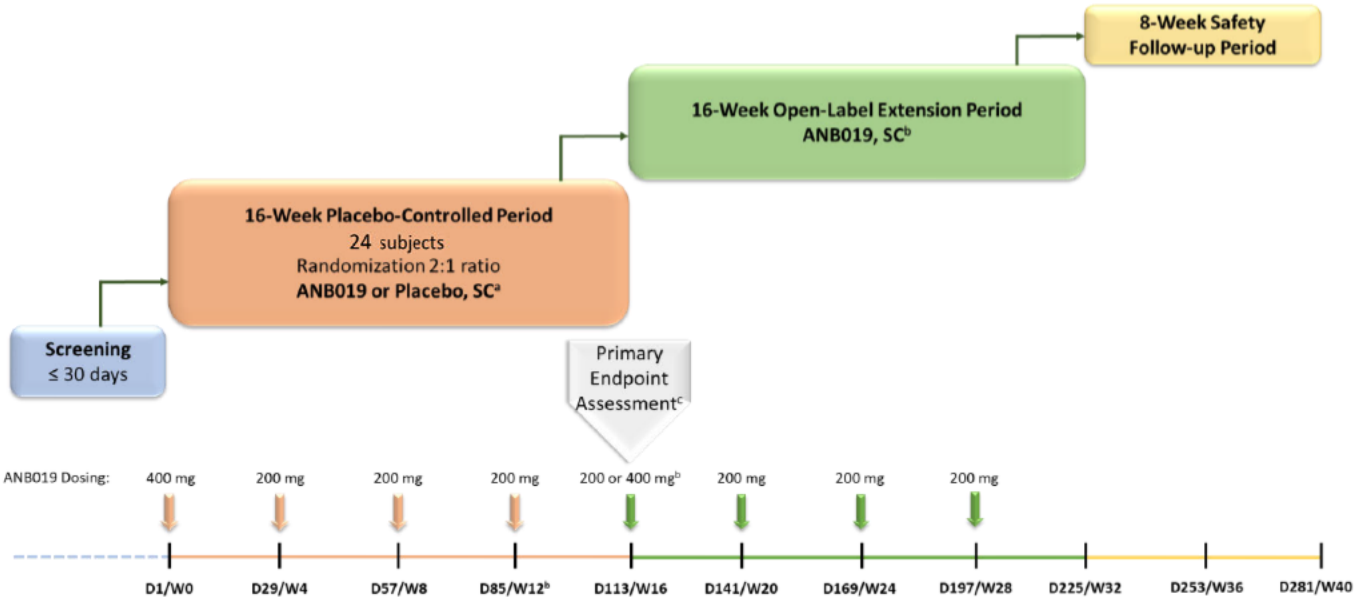
Study Population: Approximately 24 male and female subjects, aged 12 to 75 years, with clinically confirmed diagnosis of ichthyosis (as described in Section 5.1) will be enrolled in this study. To be eligible for the study, the subjects will

	need to have a diagnosis of their ichthyosis subtype confirmed by genetic testing. In addition, the subjects will have the following characteristics at Day 1: IASI total score of at least 18, erythema score of at least 2 (moderate severity) in at least 1 body region and scaling score of at least 2 (moderate severity) in at least 1 body region as evaluated by IASI, and BSA involved with ichthyosis of at least 50%.
Phase:	2
Description of Study Centers Enrolling Subjects:	Approximately 20 study centers located globally are expected to participate in this study.
Description of Study Treatments:	ANB019 will be provided in a glass vial as a sterile, colorless to yellow, and clear to slightly opalescent solution for injection. The placebo contains no active ingredient and will be provided as a sterile, colorless to slightly yellowish, and clear to very slightly opalescent solution for injection. During the placebo-controlled period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, SC administered on 4 occasions: • Day 1: 400-mg dose of ANB019 or placebo (administered as 2 SC injections of ANB019 at 200 mg each or placebo) • Days 29, 57, and 85: 200-mg dose of ANB019 or placebo During the open-label extension, all subjects will receive ANB019, SC administered on 4 occasions. Subjects assigned to ANB019 during the placebo-controlled period will continue to receive a 200-mg dose of ANB019 on Days 113, 141, 169, and 197. Subjects assigned to placebo during the placebo-controlled period will receive a 400-mg dose of ANB019 on Day 113, followed by a 200-mg dose of ANB019 on Days 141, 169, and 197. The blind will be maintained throughout the study. To keep the blind, the following measures will be taken on Day 113: • Subjects assigned to ANB019 during the placebo-controlled period will receive 2 SC injections on Day 113: 1 of ANB019 at 200 mg and 1 of placebo. • Subjects assigned to placebo during the placebo-controlled period will receive 2 SC injections on Day 113 of ANB019 at 200 mg each.
Rescue Medication:	Rescue medications (topical only) may be used starting at Week 4 provided that the criteria for rescue defined in Section 6.5.3 are met.
Study Duration:	The estimated study duration is approximately 25 months from first subject screened until completion of data analyses.

Subject Duration:	The maximum study duration per subject is approximately 44 weeks from screening to last visit (including up to 30 days for the screening period, followed by a 16-week placebo-controlled period, a 16-week open-label extension period, and an 8-week safety follow-up period).

1.2 SCHEMA

Figure 1: Study Schema



Abbreviations: D, day; SC, subcutaneously; W, week.

[a] During the placebo-controlled period, subjects will be randomized (2:1) to receive either ANB019 or placebo, SC administered on 4 occasions: 400-mg dose of ANB019 or placebo on Day 1; 200-mg dose of ANB019 or placebo on Days 29, 57, and 85.

[b] During the open label extension, all subjects will receive ANB019, SC administered on 4 occasions. Subjects assigned to ANB019 during the placebo-controlled period will continue to receive a 200-mg dose of ANB019 on Days 113, 141, 169, and 197. Subjects assigned to placebo during the placebo-controlled period will receive a 400-mg dose of ANB019 on Day 113, followed by a 200-mg dose of ANB019 on Days 141, 169, and 197.

[c] All subjects will receive ANB019 during the open-label extension period starting on Day 113 (Week 16) visit until Day 197 (Week 28) visit. The placebo-controlled period ends on Day 113 (Week 16) visit, before study treatment administration. The open-label extension period starts when the study treatment is administered on Day 113 (Week 16) visit. Predose assessments performed on Day 113 (Week 16) will be used to evaluate the primary and secondary efficacy endpoints, as well as the safety, tolerability, and immune response of ANB019 compared with placebo.

1.3 SCHEDULE OF ACTIVITIES

The screening evaluation will only be performed after the subject has agreed to participate and has signed and dated the ICF or assent. No treatment or study-related procedures will be initiated before informed consent/assent (when applicable) is signed. The Day 1 visit must be performed, at the latest, 30 days after the screening visit.

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

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

Of note, all subjects will receive ANB019 during the open-label extension period starting on Day 113 (Week 16) visit. The placebo-controlled period ends on Day 113 (Week 16) visit, before study treatment administration. Therefore, the open-label extension period starts when the study treatment is administered on Day 113 (Week 16) visit. Predose assessments performed on Day 113 (Week 16) will be used to evaluate the primary and secondary efficacy endpoints, as well as the safety, tolerability, and immune response of ANB019 compared with placebo.

Unless specified otherwise, the study assessments scheduled on Days 1, 29, 57, 85, 113, 141, 169, and 197 must be performed before study treatment administration, **except postdose PK sample collection on Day 1**. The specific order for performing the study assessments is as follows (applicable to all visits):

- Subject-reported questionnaires (worst pruritus and pain NRSs should be performed before average pruritus and pain NRSs)
- Efficacy assessments (global assessments [eg, BSA, IGA] should be performed before more quantitative assessments [eg, IASI, NASA])
- Physical examination
- ECG
- Vital signs
- Blood samples collection (for safety, PK, ADA, IgE)
- Tape stripping
- Skin biopsies, if applicable

Photography (if applicable) can be performed anytime predose provided that it is before skin samples collection.

The Coronavirus Disease 2019 (COVID-19) pandemic may impact the ability to adhere to the study procedures described in Table 1 due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines. Please refer to Section 4.2 for more details on allowable, as necessary, modifications to the protocol due to COVID-19 restrictions.

Table 1: Schedule of Activities

	Screening Period	Placebo-Controlled Period									Open-Label Extension Period					Follow-up Period	
Study visit Window (days)	**Screening** (-30 to -1)	**D1** **W0**	**D3**	**D8** **W1** (±1)	**D15** **W2** (±2)	**D29** **W4** (±2)	**D43** **W6** (±4)	**D57** **W8** (±4)	**D71** **W10** (±4)	**D85** **W12** (±4)	**D113** **W16**[a] (±4)	**D141** **W20** (±4)	**D169** **W24** (±4)	**D197** **W28** (±4)	**D225** **W32** (±4)	**D253** **W36** (±4)	**D281** **W40 (EOS/ET)**[b] (±5)
Informed consent / assent (when applicable)[c]	X																
Demographics	X																
Inclusion and exclusion criteria	X	X															
Medical and surgical history	X	X															
Height and weight[d]	X	X									X				X		X
Pain and pruritus NRSs, DLQI, CDLQI, PGI-S, PGI-C[e]		X		X		X		X		X	X	X	X	X	X	X	X
iQoL-32[e]		X				X		X		X	X	X	X	X	X	X	X
BSA[e]	X	X		X		X		X		X	X	X	X	X	X	X	X
IGA[e]		X		X		X		X		X	X	X	X	X	X	X	X
IASI assessment[e]	X	X		X		X		X		X	X	X	X	X	X	X	X
NASA[e]		X		X		X		X		X	X	X	X	X	X	X	X
Complete physical examination[f]	X	X				X		X		X	X				X		X
12-Lead ECG[g]	X	X				X					X	X			X		X
Chest X-ray[h]	X																
Vital signs[i]	X	X		X		X		X		X	X	X	X	X	X	X	X
Hematology and biochemistry[j]	X	X		X		X		X		X	X	X	X	X	X	X	X
Urinalysis[j]	X	X				X		X		X	X	X		X	X		X
TB screening (QuantiFERON®-TB Gold test)[j]	X																
Viral serology[j]	X																
Serum pregnancy test (WOCBP only)[j]	X																X
Urine pregnancy test (WOCBP only)[j]		X				X		X		X	X	X	X	X	X	X	

Table 1: Schedule of Activities (Continued)

	Screening Period	Placebo-Controlled Period									Open-Label Extension Period					Follow-up Period	
Study visit Window (days)	**Screening** (-30 to -1)	**D1** **W0**	**D3**	**D8** **W1** (±1)	**D15** **W2** (±2)	**D29** **W4** (±2)	**D43** **W6** (±4)	**D57** **W8** (±4)	**D71** **W10** (±4)	**D85** **W12** (±4)	**D113** **W16**[a] (±4)	**D141** **W20** (±4)	**D169** **W24** (±4)	**D197** **W28** (±4)	**D225** **W32** (±4)	**D253** **W36** (±4)	**D281** **W40 (EOS/ET)**[b] (±5)
FSH[j]	X																
Blood samples for PK[k]		X		X[k]		X		X		X[l]	X	X[l]	X[l]	X[l]	X	X[l]	X
Blood samples for ADA		X				X		X		I	X	X[l]			X		X
Blood sample for IgE levels evaluation[m]		X									X				X		
TEWL		X				X		X		X	X						X
Tape strips collection[n]		X				X					X		X				
Skin biopsies (optional)[n]		X				X					X		X				
Randomization		X															
Photography[o]	X	X				X					X				X		X
Telephone contact[p]			X		X		X		X								
Study treatment administration[q]		X				X		X		X	X	X	X	X			
Subject diary distribution/collection /review[r]		X				X		X		X	X	X	X	X	X	X	X
AE/SAE review	X	Continuously															
Concomitant medication review	X[s]	Continuously															

Abbreviations: ADA, anti-drug antibody; AE, adverse event; BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; D, day; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EOS, end of study; ET, early termination; FSH, follicle stimulating hormone; IASI, Ichthyosis Area and Severity Index; IGA, Investigator Global Assessment; IgE, immunoglobulin E; iQoL-32, Ichthyosis Quality of Life- 32 items; NASA, Netherton Area and Severity Assessment; NRS, Numeric Rating Scale; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity; PK, pharmacokinetics; SAE, serious adverse event; SC, subcutaneously; SoA, Schedule of Activities; TB, tuberculosis; TEWL, transepidermal water loss; W, week; WOCBP, woman of childbearing potential.

[a] All subjects will receive ANB019 during the open-label extension period starting on Day 113 (Week 16) visit until Day 197 (Week 28) visit. The placebo-controlled period ends on Day 113 (Week 16) visit, before study treatment administration. The open-label extension period starts when the study treatment is administered on Day 113 (Week 16) visit.

Table 1: Schedule of Activities (Continued)

[b] The ET visit will include all procedures to be done at the ET/EOS visit (Day 281/Week 40 visit).
[c] Adolescent subjects who reach 18 years of age during the study must be reconsented as adults.
[d] Height to be measured at screening only for subjects ≥ 18 years of age, and at screening, Day 113 (Week 16), and Day 281 (Week 40)/ET for subjects < 18 years of age.
[e] Refer to Section 8.1 for details and instructions regarding pain and pruritus NRSs (worst and average), iQoL-32 (subjects ≥ 15 years of age only), DLQI (subjects ≥ 16 years of age), CDLQI (subjects < 16 years of age), PGI-S, PGI-C, BSA, IGA, IASI, NASA, and TEWL. PGI-C is not to be performed at Day 1.
[f] Refer to Section 8.2.4 for details regarding the complete physical examination.
[g] Refer to Section 8.2.6 for details and instructions regarding the ECG. In addition to the time points specified in the SoA, ECGs may be performed at any time during the study if in the opinion of the Investigator it is clinically warranted.
[h] Bidirectional posterior-anterior view and lateral view chest X-ray, or as indicated by local treatment guidelines or practice, will be performed at screening. If a chest X-ray was performed within 6 months of screening and no clinically significant abnormality was observed, it can be skipped at screening.
[i] Refer to Section 8.2.5 for details and instructions regarding vital signs.
[j] If a negative QuantiFERON®-TB test result was obtained within 6 months of screening, it can be skipped at screening. The FSH testing is performed for women not of childbearing potential who are postmenopausal (at least 12 months of amenorrhea without an alternative medical cause). An adolescent subject who experiences menarche during the trial will be considered a WOCBP (refer to Appendix 1 for definition of WOCBP) and will be required to follow the contraceptive guidance in Appendix 1 and undergo scheduled pregnancy testing. Additional pregnancy testing may be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Refer to Appendix 10 for details and instructions regarding clinical laboratory parameters.
[k] On Day 1, samples for PK will be collected at predose and 2 hours (± 10 min) post SC administration. In addition, samples for PK will also be collected at the time points specified in Table 4.
[l] On these days, blood for PK and ADA will only be collected from adult subjects (≥ 18 years). Adolescent subjects who reach 18 years of age during the study and are reconsented as adults will follow the adult schedule for PK and ADA assessments (refer also to Table 4 and Table 5).
[m] For subjects with Netherton syndrome only.
[n] All randomized subjects will be asked to participate in the skin biopsy test; however, the subject's participation is optional. Subjects should provide their consent to participate in the skin biopsies. Tape stripping will be performed for all randomized subjects as part of this study (not optional). Tape strips and punch biopsies will be collected from the same location (if applicable) on Day 1, 29, 113, and 169 (from lesional skin).
[o] At selected study centers only.
[p] Subjects will be contacted by phone on Days 3, 15, 43, and 71, to assess for AEs and concomitant medications.
[q] During the placebo-controlled period, subjects will receive either ANB019 or placebo SC administered as follows: a 400-mg dose of ANB019 or placebo on Day 1; a 200-mg dose of ANB019 or placebo on Days 29, 57, and 85. The placebo-controlled period ends on Day 113 (Week 16) visit, before study treatment administration. All subjects will receive ANB019 on Day 113 (Week 16) visit. Subjects assigned to ANB019 during the placebo-controlled period will continue to receive a 200-mg dose of ANB019 on Days 113, 141, 169, and 197. Subjects assigned to placebo during the placebo-controlled period will receive a 400-mg dose of ANB019 on Day 113, followed by a 200-mg dose of ANB019 on Days 141, 169, and 197.
[r] Type/frequency of emollient application (if applicable) must be recorded by the subject in a diary throughout the study. Bath/shower time and duration must be recorded by the subject in a diary throughout the study.
[s] At screening, prior medications should be reviewed and documented. Refer to Section 6.5.

2 INTRODUCTION

2.1 STUDY RATIONALE

The ichthyoses are a group of rare chronic genetic disorders that share characteristics of scaling and underlying skin inflammation to varying degrees. The occurrence of scaling is thought to be a compensatory cutaneous response to the inadequate, abnormally differentiated epidermal barrier. The quality of life of affected patients is poor, particularly owing to the highly visible and disfiguring skin alterations, the frequently associated severe pruritus, and the functional limitations related to thickened skin. Therapy for the ichthyoses has been limited to use of emollients and agents that peel the thick scales, specifically keratolytics and retinoids.

Among currently available treatments, oral retinoids appear to be the most effective, but they tend to increase ichthyosis-associated skin inflammation. Use of retinoids also is associated with potential side effects; they function by removing the compensatory scales without targeting the underlying disease process. Thus, there remains a huge unmet need for effective and safe treatments for these forms of ichthyosis, ideally therapy that both improves the scaling and decreases the cutaneous inflammation with its accompanying pruritus and discomfort.

Recent studies of the skin of patients with clinically confirmed diagnosis of a variety of types of ichthyosis showed a cutaneous biomarker pattern of the Th-17 pathway with the highest levels of expression of IL-36, specifically IL-36β/γ (Paller 2017, Malik 2019, Czarnowicki 2018). Indeed, a sustained activation of the IL-36 pathway was observed in ichthyosis skin biopsies compared with normal and chronic plaque psoriasis skin biopsies, suggesting a key role of IL-36 inflammatory axis as a main driver of the disease. The increases in IL-36 cytokines, as well as their receptor (IL-36R) found in all forms of ichthyosis studied to date suggests that IL-36β/γ could play an important role in amplifying the clinical manifestations of this debilitating skin disorder.

ANB019 is a high affinity, humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) that specifically binds IL-36R and antagonizes IL-36 signaling. The IL-36 cytokines (IL-36α, IL-36β, and IL-36γ) engage with IL-36R to initiate signaling events leading to proinflammatory responses. Interleukin 36 signaling is counter balanced by IL-36R antagonist (IL- 36Ra), an IL-36 receptor antagonist that binds to IL-36R and competes with activity of IL-36 cytokines. Because IL-36 pathway has been implicated in amplifying inflammatory skin diseases, including ichthyosis, inhibition of IL-36 signaling, by targeting IL-36R with a specific mAb, may represent a novel strategy to control the pathological inflammatory cascade driven by IL-36 pathway activation. ANB019 is currently being studied as a potential first-in-class therapy for several cutaneous indications, including palmoplantar pustulosis (PPP), generalized pustular psoriasis (GPP), ichthyosis, and other inflammatory diseases where the IL-36 pathway may play a significant role in augmenting the disease. ANB019 may be beneficial in suppressing the inflammation, improving the pruritus, and possibly decreasing the scaling in patients with several types of ichthyosis.

This study is designed to evaluate the efficacy and safety of ANB019 in subjects with ichthyosis subtypes in which elevated expression of IL-36 has been confirmed (Paller 2017, Malik 2019, Czarnowicki 2018).

2.2 BACKGROUND

2.2.1 NONCLINICAL STUDIES

ANB019 exhibits strong inhibitory activity for human as well as cynomolgus monkey IL-36R (cyIL-36R) cell populations. Nonclinical data obtained from studies with ANB019 in primary human and cynomolgus monkey cells and from in vivo nonhuman primate studies demonstrated that:

- ANB019 shows reactivity with human and cynomolgus monkey IL-36R (dissociation constant [KD] of 67.9 ± 31.4 pM and 80.0 ± 49.6 pM, respectively), but not with mouse or rat IL-36R.
- In primary human and cynomolgus monkey cell populations, keratinocytes, peripheral blood mononuclear cells (PBMCs), and human whole blood, ANB019 inhibited IL-36R mediated release of IL-8.
- The terminal half-life ($t_{1/2}$) of ANB019 in cynomolgus monkeys was 304 hours after single intravenous (IV) dose administration, and 310 hours after a single SC dose administration at 10 mg/kg, with bioavailability approximately 76% consistent with the anticipated PK characteristics for a human IgG4 scaffold mAb in the cynomolgus monkey.
- Repeat-dose, Good Laboratory Practice (GLP) toxicity and toxicokinetic (TK) studies of 4, 13, and 26 weeks in duration have been conducted with ANB019 administered by weekly SC and IV injection in cynomolgus monkeys. There were only minor treatment-related injection site findings in the 4-week repeat-dose study. Treatment-related effects in the 13-week toxicity study included increased observations of nonformed feces and prolapsed rectum, and protozoa in the stomachs of cynomolgus monkeys; the latter being consistent with the mechanism of action of an immune-modulator in cynomolgus monkeys (Dubey 2002). Weekly administrations of vehicle control article, 30 mg/kg/dose ANB019 via SC injection, or 60 mg/kg/dose ANB019 via SC or IV bolus injection, to male and female sexually mature cynomolgus monkeys during the 26-week toxicity and TK study was well tolerated. ANB019-related effects were limited to a low incidence of liquid feces not considered AEs for animals administered 60 mg/kg/dose IV. Thus, the no observed adverse effect level (NOAEL) is 60 mg/kg/dose administered by SC or IV injection.

These data provide a strong scientific rationale for advancing ANB019 through clinical development.

A detailed description of the physical, chemical, and pharmaceutical properties of ANB019 and nonclinical studies is provided in the Investigator's Brochure (IB).

2.2.2 CLINICAL STUDIES

Currently, two clinical studies (ANB019-001 and ANB019-005) have been completed. Study ANB019-001 was a Phase 1, first-in-human, single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy volunteers and in subjects with psoriasis. Study ANB019-005 was a Phase 1, ethno-bridging study, a single-dose safety, tolerability, PK, and immunogenicity study of ANB019 in healthy Japanese and Caucasian subjects. A detailed description of the safety and tolerability, and PK/pharmacodynamic (PD) results of these two Phase 1 clinical studies is provided in the IB.

In addition, two Phase 2a studies (ANB019-002 and ANB019-003) to evaluate clinical activity and safety of ANB019 in GPP and PPP are ongoing. Study ANB019-002 is a single-arm, multiple-dose study to be conducted in subjects with active GPP. Study ANB019-003 is a randomized, placebo-controlled, multiple-dose study to be conducted in subjects with PPP.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

No major toxicities were observed in the 4-week repeat-dose toxicity study in cynomolgus monkeys. The main finding consisted of minor, injection site reactions associated with the SC route of administration and not considered AEs.

In cynomolgus monkeys, treatment-related effects observed in the 13-week repeat-dose toxicity study included protozoa in the stomach, an increase in nonformed feces and prolapsed rectum observations; the latter observation was not considered dose related. The increase in protozoa in the stomach has been observed in monkeys treated with immune-modulating drugs (Dubey 2002) and is consistent with the putative mechanism of action of ANB019. During the 26-week repeat-dose toxicity study, ANB019-related effects were limited to a low incidence of liquid feces. In the monkeys, the increased incidence of protozoa, nonformed feces, and prolapsed rectum were not considered AEs as they responded to veterinarian intervention. In humans, gastrointestinal infections can be clinically monitored and, in the case of most protozoa, are readily treatable even in the context of immunocompromised individuals (Farthing 2006).

One female monkey receiving 60 mg/kg ANB019 IV was found moribund on Study Day 34. The cause of death was not determined and had an uncertain relationship to ANB019 but could be due to treatment-related immune modulation. However, data published on IL-36R deficient humans shows no deleterious effect on general health, and normal immune function is broadly preserved, indicating that inhibition of IL-36R, does not generally compromise host defenses. Similar to other immune-modulating treatment paradigms, subjects should be closely monitored for any clinical gastrointestinal manifestations including infections and evaluated on an ongoing basis. If a gastrointestinal infection is suspected, the subject should be treated as clinically indicated.

In ANB019-001 study in healthy adults, single doses of ANB019 up to 750 mg administered by IV infusion or SC injection to 32 healthy adults in the SAD part of the Phase 1 study were generally well tolerated with a similar number of treatment-emergent adverse event (TEAEs) reported in subjects receiving ANB019 or placebo, 29 subjects (81%) and 11 subjects (92%), respectively. The most frequently reported AEs were upper respiratory tract infection (URTI; 10 [28%] ANB019; 6 [50%] placebo), headache (10 [28%] ANB019; 3 [25%] placebo), and viral URTI (4 [11%] ANB019; 1 [8%] placebo). Additionally, multiple doses of ANB019 up to 300 mg administered by IV infusion once weekly for 4 weeks to 18 healthy adults were also well tolerated. Overall, TEAEs occurred in 16 subjects (89%) receiving ANB019 and in 3 subjects (50%) receiving the placebo. The most common AEs were headache (7 [39%] ANB019; 1 [17%] placebo) and URTI (3 [17%] ANB019; 1 [17%] placebo).

In ANB019-005, single doses of ANB019 up to 750 mg administered by IV infusion or SC injection to 32 healthy Japanese and Caucasian adults were generally well tolerated. The most common TEAEs were alanine aminotransferase (ALT) increased (3 subjects [9.4%]) and aspartate aminotransferase (AST) increased (2 subjects [6.3%]).

To date, 1 SAE of sepsis was reported in the ongoing ANB019-002 study in subjects with GPP; the SAE was considered possibly related to the study drug. The subject had a medical history of sepsis and experienced the SAE after the 750 mg IV dose administration. Antibiotic treatment rapidly resolved the sepsis episode with complete subject recovery.

As allergic or anaphylactic reactions may occur in any subjects treated with mAbs, subjects should be observed during and after ANB019 administration. Subjects with true allergic/anaphylactic reactions

should not receive further doses of the monoclonal antibody. Symptoms of an apparent allergic reaction to the drug, also known as 'cytokine release syndrome', vary dramatically but can include:

- Mild to moderate fever, chills, headache, nausea, and vomiting
- Moderate to severe symptoms such as edema, hypotension, and pulmonary infiltrates (eg, blood and mucus in the lung)

Such reactions should be managed as clinically indicated and according to standard clinical practice.

2.3.2 KNOWN POTENTIAL BENEFITS

Subjects with ichthyosis may or may not receive direct benefit from participating in this study. An improvement in the condition as a result of participating in the study may be observed since all subjects will receive the active treatment at some point during the study.

Participation in this study also may help generate future benefit for larger groups of patients with ichthyosis if ANB019 proves to be successful in treating this disease.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

All quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical and clinical studies are considered sufficient to expect a positive benefit/risk ratio for the treatment of ichthyosis with ANB019, and therefore to initiate this study.

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

3 OBJECTIVES AND ENDPOINTS

3.1 PRIMARY OBJECTIVE AND ENDPOINT

Primary Objective	Primary Endpoint
• To determine the effect of ANB019 compared with placebo as measured by IASI total score	• Change from Baseline in IASI total score at Week 16

3.2 SECONDARY OBJECTIVES AND ENDPOINTS

Secondary Objectives	Secondary Endpoints
• To evaluate the effect of ANB019 compared with placebo on ichthyosis signs and symptoms, and quality of life in subjects with ichthyosis	• Percent change from Baseline in IASI total score at Week 16 • Proportion of subjects achieving IASI50 at Week 16 • Change and percent change from Baseline in IASI-E and IASI-S subscores at Week 16
• To determine the safety of ANB019 in the treatment of ichthyosis	• Incidence of AEs, SAEs, and AEs leading to withdrawals, as well as changes in vital signs, clinical laboratory parameters (hematology, biochemistry, and urinalysis), and 12-lead ECGs

3.3 EXPLORATORY OBJECTIVES AND ENDPOINTS

Exploratory Objectives	Exploratory Endpoints
• To further evaluate the effect of ANB019 on ichthyosis signs and symptoms, and quality of life in subjects with ichthyosis	• Change and percent change from Baseline in IASI total score at Weeks 1, 4, 8 and 12 • Proportion of subjects achieving IASI50 at Weeks 1, 4, 8, and 12 • Proportion of subjects achieving IASI75 at Weeks 1, 4, 8, 12, and 16 • Change and percent change from Baseline in IASI-E and IASI-S subscores at Weeks 1, 4, 8, and 12 • Change and percent change from Baseline in NASA at Weeks 1, 4, 8, 12, and 16 (for subjects with Netherton Syndrome only) • Proportion of subjects achieving NASA50 at Weeks 1, 4, 8, 12, and 16 (for subjects with Netherton Syndrome only) • Change and percent change from Baseline in IGA at Weeks 1, 4, 8, 12, and 16 • Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at Weeks 1, 4, 8, 12, and 16

Exploratory Objectives	Exploratory Endpoints
	• Proportion of subjects with at least 2-point decrease in IGA at Weeks 1, 4, 8, 12, and 16 • Change and percent change from Baseline in worst and average pruritus NRS at Weeks 1, 4, 8, 12, and 16 • Change and percent change from Baseline in worst and average pain NRS at Weeks 1, 4, 8, 12, and 16 • Proportion of subjects with at least 3-point decrease in worst pruritus NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pruritus NRS of at least 3 • Proportion of subjects with at least 4-point decrease in worst pruritus NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pruritus NRS of at least 4 • Proportion of subjects with at least 3-point decrease in worst pain NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pain NRS of at least 3 • Proportion of subjects with at least 4-point decrease in worst pain NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pain NRS of at least 4 • Change from Baseline in BSA at Weeks 1, 4, 8, 12, and 16 • Change from Baseline in DLQI and CDLQI scores at Weeks 1, 4, 8, 12, and 16 • Proportion of subjects in each response category for the PGI-S and PGI-C at Weeks 1, 4, 8, 12, and 16 • Change from Baseline in iQoL-32 score at Weeks 4, 8, 12, and 16 • Change from Baseline in TEWL at Weeks 4, 8, 12, and 16 • Proportion of subjects receiving rescue medication at Weeks 4, 8, 12, and 16 • Proportion of subjects achieving IASI50 from Week 20 through Week 40 • Proportion of subjects achieving IASI75 from Week 20 through Week 40 • Change and percent change from Baseline in IASI total score from Week 20 through Week 40 • Change and percent change from Baseline in IASI-E and IASI-S subscores from Week 20 through Week 40

Exploratory Objectives	Exploratory Endpoints
	• Change and percent change from Baseline in NASA from Week 20 through Week 40 (for subjects with Netherton Syndrome only) • Proportion of subjects achieving NASA50 from Week 20 through Week 40 (for subjects with Netherton Syndrome only) • Change and percent change from Baseline in IGA from Week 20 through Week 40 • Proportion of subjects achieving an IGA of clear (0) or almost clear (1) from Week 20 through Week 40 • Proportion of subjects with at least 2-point decrease in IGA from Week 20 through Week 40 • Change and percent change from Baseline in worst and average pruritus NRS from Week 20 through Week 40 • Proportion of subjects with at least 3-point decrease in worst pruritus NRS from Week 20 through Week 40 for subjects with a Baseline worst pruritus NRS of at least 3 • Proportion of subjects with at least 4-point decrease in worst pruritus NRS from Week 20 through Week 40 for subjects with a Baseline worst pruritus NRS of at least 4 • Change and percent change from Baseline in worst and average pain NRS from Week 20 through Week 40 • Proportion of subjects with at least 3-point decrease in worst pain NRS from Week 20 through Week 40 for subjects with a Baseline worst pain NRS of at least 3 • Proportion of subjects with at least 4-point decrease in worst pain NRS from Week 20 through Week 40 for subjects with a Baseline worst pain NRS of at least 4 • Change from Baseline in BSA from Week 20 through Week 40 • Change from Baseline in iQoL-32 score from Week 20 through Week 40 • Change from Baseline in DLQI and CDLQI scores from Week 20 through Week 40 • Proportion of subjects in each response category for the PGI-S and PGI-C from Week 20 through Week 40 • Change from Baseline in TEWL from Week 20 through Week 40 • Proportion of subjects receiving rescue medication from Week 20 through Week 40

Exploratory Objectives	Exploratory Endpoints
• To explore the effect of ANB019 on cutaneous biomarkers	• Skin tape strip biomarkers analysis including, but not limited to, IL-36 and Th-17 • Optional skin biopsy biomarkers analysis including, but not limited to, IL-36 and Th-17
• To test for immunogenicity to ANB019	• Presence of anti-drug antibodies to ANB019
• To evaluate IgE levels in subjects with Netherton Syndrome	• IgE levels evaluation (for subjects with Netherton Syndrome only)
• To describe the PK profile of ANB019 in subjects with ichthyosis	• Serum concentration following ANB019 administration and other parameters as appropriate will be determined to describe the PK profile of ANB019

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of ANB019 compared with placebo in adolescent and adult subjects with ichthyosis. This study will also characterize the PK profile of ANB019 and explore the immune response to ANB019 in subjects with ichthyosis.

Approximately 24 male and female adolescent and adult subjects with clinically confirmed diagnosis of ichthyosis (as described in Section 5.1) will be enrolled in this study. To be eligible for the study, the subjects will need to have a diagnosis of their ichthyosis subtype confirmed by genetic testing. In addition, the subjects will have the following characteristics at Day 1: IASI total score of at least 18, erythema score of at least 2 (moderate severity) in at least 1 body region and scaling score of at least 2 (moderate severity) in at least 1 body region as evaluated by IASI, and BSA involved with ichthyosis of at least 50%. Randomization will be stratified based on erythema severity at Baseline (highest severity [moderate {2} vs severe/very severe {3, 4}] as evaluated by IASI-E).

Written informed consent will be obtained from each subject prior to initiating any study related procedures. Subjects will also provide consent for skin biopsy collection if they wish to participate in this test.

The expected study duration per subject is approximately 44 weeks. The study will include a screening period of up to 30 days, followed by a 16-week placebo-controlled period, a 16-week open-label extension period, and an 8-week safety follow-up period.

Of note, all subjects will receive ANB019 during the open-label extension period starting on Day 113 (Week 16) visit until Day 197 (Week 28) visit. The placebo-controlled period ends on Day 113 (Week 16) visit, before study treatment administration. Therefore, the open-label extension period starts when the study treatment is administered on Day 113 (Week 16) visit.

During the placebo-controlled period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, SC administered on 4 occasions. On Day 1, the subjects will receive a 400-mg dose of ANB019 or placebo. On Days 29, 57, and 85, the subjects will receive a 200-mg dose of ANB019 or placebo. During the open label extension period, all subjects will receive ANB019, SC administered on 4 occasions. Subjects assigned to ANB019 during the placebo-controlled period will continue to receive a 200-mg dose of ANB019 on Days 113, 141, 169, and 197. Subjects assigned to placebo during the placebo-controlled period will receive a 400-mg dose of ANB019 on Day 113, followed by a 200-mg dose of ANB019 on Days 141, 169, and 197. Refer to Section 6.1.2 for additional details on study treatment administration.

For scheduled on-site study visits, subjects will come to the study center on 13 occasions to monitor changes in disease activity, PK (if applicable), safety, and tolerability: screening and Days 1, 8, 29, 57, 85, 113, 141, 169, 197, 225, 253, and 281 (EOS/ET). The subjects will leave the study center following study treatment administration when all postdose assessments have been completed and with the Investigator's approval. In addition, during the placebo-controlled period, the subjects will also be contacted via telephone by study staff on Days 3, 15, 43, and 71 to inquire about potential AEs they experienced and any changes in concomitant medications. All procedures will be conducted in accordance with the SoA in Section 1.3.

Of note, all predose assessments performed on Day 113 (Week 16) will be used to evaluate the primary and secondary efficacy endpoints, as well as the safety, tolerability, and immune response of ANB019 compared with placebo.

Safety assessments will include AE/SAE monitoring, vital signs, physical examination, ECGs, and clinical laboratory tests (hematology, biochemistry, and urinalysis).

Disease activity will be evaluated for all subjects using the IASI, IASI-E subscore, IASI-S subscore, NASA for subjects with Netherton Syndrome only, IGA, and BSA involved with ichthyosis. Quality of life will be evaluated using iQoL-32 in subjects ≥ 15 years of age only, DLQI for subjects ≥ 16 years of age, and CDLQI for subjects <16 years of age. Subjects will also be evaluated for disease-associated characteristics, such as worst and average pruritus and pain using an NRS, impression of severity using the PGI-S and impression of change using the PGI-C, as well as changes in TEWL.

Blood samples to determine PK, immunogenicity (presence of ADA to ANB019), and IgE levels (for subjects with Netherton Syndrome only) will be collected on Day 1 before the administration of the study treatment and at the other time points specified in the SoA (see Section 1.3). Tape strips and optional skin biopsies for biomarker analysis will be collected at the time points specified in the SoA. All subjects randomized in the study will be asked to participate in the skin biopsy collection; however, the subject's participation is optional. In addition, photographs will be taken at selected study centers only to document skin lesions at the time points specified in the SoA.

Interim analyses (IA) may be performed during the treatment periods (placebo-controlled period and/or open-label extension period) for assessment of all primary and secondary efficacy endpoints, and evaluation of all safety data available.

4.2 MODIFICATIONS TO STUDY CONDUCT DUE TO THE CORONAVIRUS DISEASE 2019 (COVID-19) PANDEMIC

As a consequence of the COVID-19 pandemic that had a worldwide impact, including cases in North America and Europe, control measures in place in different regions may impact the ability to adhere to some of the study procedures described in this protocol. Due to challenges that include, but are not limited to, subject preferences, site closures, travel restrictions, and quarantines, some modifications to study conduct during the COVID-19 pandemic may be necessary to ensure study continuity. The following are allowable, as necessary, modifications to study conduct during the COVID-19 pandemic:

- Prior to a study visit at the site, the subject may be contacted and screened for potential exposure or infection to COVID-19 per site, local or federal requirements. If the subject is suspected of having been or infected with COVID-19, the on-site visit should either be re-scheduled or a virtual visit may be performed, as applicable.
- In the event that a subject cannot attend their regularly scheduled study visits in person due to COVID-19 necessitating a limit on in-person contact, the Investigator may perform safety and efficacy assessments by phone or video, with home nursing visit support for procedures that cannot be done virtually. The Investigator may use the technology platform that is currently available to them. Suggested platforms include Apple FaceTime, Zoom for Healthcare, Facebook Messenger video chat, Microsoft Teams, Google Hangouts video, and Skype. Home nursing visit support may be used in addition to phone or video at visits that require procedures that cannot be done via phone or video alone, such as but not limited to, ECG, PK draws, clinical laboratory draws, and IP administration.
- Clinical laboratory tests (chemistry and hematology) and pregnancy tests may be performed by local laboratory if home nursing visits are not possible and sample collection cannot be performed

at the study site due to COVID 19-related limitations, including but not limited to site closure. Abnormal laboratory results should be promptly communicated to the Medical Monitor. Subjects' anonymity must be maintained when communicating results to the Medical Monitor.
- At home IP administration by home health nurses may be done.
- Source documentation should note that the visit was performed virtually (not face-to-face), and note the name of the local lab where laboratory tests were done.
- If certain study procedures or assessments cannot be completed per the schedule of events, the reason for the missed assessment (ie, TEWL, labs, vital signs, physical exams, etc.) must be noted in the source documentation (eg, COVID-19), captured in the protocol deviations documentation, and reported to the IRB/Ethics Committee, as applicable.

A detailed assessment of COVID-19 related risk and mitigation measures will be documented in the appropriate study plans.

4.3 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The effective treatment of ichthyosis remains an unmet medical need. The use of available treatments is limited by low efficacy and long-term adverse effects.

In this context, the development of agents with new mechanisms of action is considered important for future clinical practice. As ANB019 offers the potential for inhibition of IL-36 signaling by blocking IL-36R, it may provide a novel strategy for treatment of patients with ichthyosis. As part of this pilot study, only subtypes with confirmed elevation of IL-36 expression will be included.

The proposed design is considered appropriate for assessing the safety and tolerability of ANB019 in subjects with ichthyosis, and the efficacy of ANB019 compared with placebo in subjects with ichthyosis.

In the placebo-controlled period, randomization will ensure random allocation of subjects to treatment arms to reduce bias. Randomization will be stratified based on erythema severity at Baseline (highest severity [moderate {2} vs severe/very severe {3, 4}] as evaluated by IASI-E). Because efficacy assessments of ichthyosis have a high degree of subjectivity, the study will be double-blinded. The highest degree of subject and assessor (Investigator or designee) blinding should be sought to achieve credible inference. It is also important to have a placebo-control period in this Phase 2 study to control for confounding factors, such as potential Investigator bias, and to ensure that the statistical procedures can be appropriately applied.

4.4 JUSTIFICATION FOR DOSE

During the placebo-controlled period, ANB019 will be SC administered as a 400-mg dose on Day 1, followed by a 200-mg dose on Days 29, 57, and 85.

The doses selected for the study demonstrated a favorable safety and tolerability profile in a Phase 1 study conducted in healthy volunteers. In addition, ANB019 demonstrated linear PK with an estimated $t_{1/2}$ of approximately 28 days at all doses tested with persistent pharmacodynamic activity. The loading dose of 400 mg SC administered on Day 1 was chosen to achieve maximum observed concentration (C_{max}) soon after dosing in order to provide optimal potential benefit to ichthyosis subjects and to reach steady state concentrations rapidly following 200 mg SC dosing. The 16-week placebo-controlled period is expected to provide better clinical outcome, thus potentially benefiting subjects with ichthyosis and further assessing the long-term safety and efficacy of ANB019.

The open-label extension period was added to provide potential benefits to subjects with ichthyosis assigned to placebo during the placebo-controlled period and further assessing the long-term efficacy of ANB019.

4.5 END OF STUDY DEFINITION

A subject is considered to have completed the study if he or she has completed all period of the study including the last specified visit (Day 281 [Week 40]/ET) shown in the SoA (see Section 1.3).

The end of the study is defined as completion of the last visit or procedure shown in the SoA by the last subject included the study.

5 STUDY POPULATION

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

It is imperative that subjects fully meet all the inclusion criteria and none of the exclusion criteria.

5.1 INCLUSION CRITERIA

To be eligible to participate in this study, a subject must meet all of the following criteria, either at the screening and Day 1 visits or only at one of the specified visits (screening or Day 1) as noted in the criterion:

1. Male and female subject aged 12 to 75 years (inclusive) at the time of signing the informed consent/assent.
2. Confirmed diagnosis by genetic testing of ichthyosis of one of these subtypes:
   a) Congenital ichthyosiform erythroderma (autosomal recessive congenital ichthyosis [ARCI]);
   b) Epidermolytic ichthyosis;
   c) Netherton syndrome;
   d) Ichthyosis en confetti;
   e) Other subtypes may be included (only subtypes in which high levels of IL-36γ expression in skin were confirmed by a ribonucleic acid [RNA] analysis [eg, RNA sequencing {RNA-seq}, polymerase chain reaction {PCR}] as part of other studies).

   Note: Confirmation of genetic subtype will be obtained prior to eligibility determination.
3. IASI total score ≥ 18, erythema score ≥ 2 (moderate severity) in ≥ 1 body region and scaling score ≥ 2 (moderate severity) in ≥ 1 body region as evaluated by IASI, and BSA involved with ichthyosis of at least 50% at Day 1.
4. Subject has been using an emollient (without pharmacological active ingredients) daily for at least 1 week prior to Day 1 (except within 3 hours prior to the study visit) and agrees to continue using that same emollient daily at the same frequency throughout the study.
5. Subject meets the following laboratory criteria at screening:
   a) Hemoglobin ≥ 90 g/L (≥ 9 g/dL);
   b) White blood cell count ≥ 3.0×10^9/L (≥ 3.0×10^3/µL);
   c) Platelets ≥ 100×10^9/L (≥ 100×10^3/µL);
   d) Serum creatinine <132.6 µmol/L (< 1.5 mg/dL);
   e) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2 upper limit of normal (ULN);
   f) Total bilirubin ≤ 1.5 × ULN. Subjects with known Gilbert's disease who have serum bilirubin < 3 × ULN may be included.
6. Body mass index (BMI) within the range of 18 to 38 kg/m^2, inclusive {BMI = weight (kg)/[height (m)]^2}.
7. No clinically significant medical condition or physical/laboratory/ECG/vital signs abnormality that would, in the opinion of the Investigator, put the subject at undue risk or interfere with interpretation of study results.
8. Contraceptive use by men and women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
   Contraception and pregnancy:
   a) A male subject must agree to use contraception as detailed in Appendix 1 of this protocol during the treatment period and for at least 220 days (which includes the duration of relevant

exposure plus the duration of sperm cycle) after the last study treatment administration and refrain from donating sperm during this period.

b) Female subjects:
   i) A woman of childbearing potential (WOCBP) is eligible to participate if she has a negative serum pregnancy test (beta-human chorionic gonadotropin) at screening and a negative urine pregnancy test at Day 1 (see Appendix 1), is not breastfeeding, and agrees to follow the contraceptive guidance in Appendix 1 during the treatment period and for at least 6 months after receiving the study treatment, and refrains from donating oocytes for assisted reproduction during this period. The female subject's selected form of contraception must be effective by the time the female subject enters into the study at Day 1 (eg, hormonal contraception should be initiated at least 48 days before Day 1).
   ii) A woman not of childbearing potential as defined in Appendix 1, must have a follicle-stimulating hormone (FSH) test confirming nonchildbearing potential.
   iii) An adolescent subject who experiences menarche during the trial will be considered a WOCBP and will be required to follow the contraceptive guidance for WOCBP in Appendix 1 and undergo pregnancy testing as detailed in the SoA (Section 1.3).

9. Subject is willing to participate and is capable of giving written informed consent, which must be personally signed and dated by the subject and obtained prior to any trial-related activities. Subjects who need to provide assent, as per local requirement, need to have their parent(s) or legal representative read and sign the informed consent form prior to any study-related procedures. Adolescent subjects who reach 18 years of age during the study must be reconsented as adults.
10. Subject must be willing to comply with all study procedures and must be available for the duration of the study.

5.2 EXCLUSION CRITERIA

A subject who meets any of the following criteria at the screening and/or Day 1 visits, as applicable, will be excluded from participation in this study:

1. Concomitant dermatological or medical conditions that may interfere with the Investigators' ability to evaluate the subject's response to therapy.
2. A subject with ichthyosis vulgaris, X-linked ichthyosis, or lamellar ichthyosis will be excluded.
3. Subject has a history of clinically significant (as determined by the Investigator) cardiac, pulmonary, neurologic, gastrointestinal, endocrine, hematological, renal, hepatic, cerebral or psychiatric disease, or other major uncontrolled disease.
4. Chronic or recurrent infectious disease, including but not limited to upper and lower respiratory infection (eg, sinusitis, bronchitis, and bronchiectasis), urinary tract infection (eg, recurrent pyelonephritis) within 6 months prior to screening.
   Note: A subject with a history of localized oral or genital herpes simplex that, in the opinion of the Investigator, is well controlled will be eligible for study participation.
5. History or any evidence of active infection that required systemic treatment within 4 weeks of Day 1 (eg, bronchopulmonary, urinary, or gastrointestinal), excluding localized oral or genital herpes simplex that, in the opinion of the Investigator, is well-controlled.
6. Any factors that would predispose the subject to develop an infection in the Investigator's opinion.
7. Opportunistic infection (eg, *Pneumocystis carinii*, aspergillosis, or mycobacteria other than tuberculosis [TB]) or parasitic infections (eg, helminths, protozoa, *Trypanosoma cruzi*) within 6 months prior to screening.
8. Herpes zoster infection within 2 months prior to screening.

9. Known or suspected autoimmune disorder, including but not limited to rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, giant cell arteritis, Bechet's disease, dermatomyositis, multiple sclerosis, moderate to severe asthma, or other severe forms of atopy, any autoimmune vasculitis, autoimmune hepatitis, or any other active autoimmune disease for which a subject requires medical follow-up or medical treatment.
10. History of known or suspected congenital or acquired immunodeficiency state, or condition that would compromise the subject's immune status (eg, history of splenectomy).
11. Any major surgery within 4 weeks of Day 1.
12. History of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
13. History of any significant drug allergy or reaction (such as anaphylaxis or hepatotoxicity) and reactivity to polysorbate-20, a component of ANB019 formulation, or the inactive ingredients (excipients).
14. Subject has taken the following drugs within the specified period prior to Day 1:
    a) Topical medications (including, but not limited to, corticosteroids, keratolytics, retinoids, crisaborole, and other phosphodiesterase 4 inhibitors) within 2 weeks prior to Day 1.
    b) Topical agents or systemic agents that could affect pruritus (such as topical antipruritic agents, gabapentin, pregabalin, doxepin, and aprepitant) within 2 weeks prior to Day 1.
    Note: Other drugs that may have an effect on pruritus and that are used to treat other conditions may be allowed if started at least 4 weeks before Day 1 and are on a stable dose during the entire study.
    Note: Over the counter topical products containing pramoxine 1% are allowed during the entire study.
    c) Oral sedative H1 antihistaminic (including but not limited to diphenhydramine) within 2 weeks prior to Day 1.
    Note: Oral nonsedative H1 antihistaminic to treat allergies will be permitted during the study only if the subject has been on a stable dose for at least 2 weeks prior to Day 1 and continues to use the same agent at the same frequency throughout the study.
    d) Systemic therapy (including, but not limited to retinoids, cyclosporin, methotrexate, corticosteroids) or any other immunosuppressant or immunomodulation drugs within 4 weeks prior to Day 1.
    e) Previous treatment with anti-IL-36R, anti-IL-36, anti-tumor necrosis factor (TNF)/ IL-12/IL-23/ IL-17, or any other mAbs within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
    f) Any nonbiologic investigational drug within 4 weeks or 5 half-lives, whichever is longer prior to Day 1.
    g) Marketed or investigational biological agent within 12 weeks or 5 half-lives (whichever is longer) prior to Day 1.
    h) Antibiotic medication within 4 weeks (topical 1 week and systemic 4 weeks) prior to Day 1.
    i) Systemic antiviral medication within 4 weeks prior to Day 1.
    j) Live attenuated vaccine within 12 weeks prior to Day 1.
15. Active TB or latent TB infection as indicated by a positive QuantiFERON®-TB Gold test at screening or within 6 months prior to screening (if the test is indeterminate, it can be repeated only once), chest X-ray, and/or clinical examination, or has had active TB disease at any time in the past.
16. Clinically significant drug or alcohol abuse in the last year prior to Day 1, or other factors limiting the ability to cooperate and to comply with the study protocol, as determined by the Investigator.

17. Subject is a pregnant or lactating woman, or a woman who intends to become pregnant during the study period.
18. Subject has any other physical, mental, or medical conditions, which, in the opinion of the Investigator, make study participation inadvisable or could confound study assessments.
19. Subject has clinically significant abnormality on chest X-ray at screening or within 6 months prior to screening.
20. Subject has any clinically significant abnormalities on 12-Lead ECG at screening.
21. Subject has any evidence of clinically significant abnormality in urinalysis at screening as determined by the Investigator.
22. Subject has a positive blood screen for hepatitis C antibody, antibodies to hepatitis B core antigens, hepatitis B surface antigen, or human immunodeficiency virus 1 and 2 antibodies.
23. Subject is not able to tolerate SC drug administration.
24. For subjects consenting to biopsies only:
    a) Subject has a history of an allergic reaction or significant sensitivity to lidocaine or other local anesthetics.
    b) Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
    c) Subject has taken anticoagulant medication, such as heparin, low molecular weight (LMW) heparin, warfarin, antiplatelets (except low-dose aspirin which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies. Nonsteroidal anti-inflammatory drugs (NSAIDs) will not be considered antiplatelets and will be allowed.

5.3 LIFESTYLE CONSIDERATIONS

Subjects are allowed to take a bath/shower as desired throughout the study, but not allowed 3 hours prior to a study visit. Bath/shower time and duration must be recorded by the subject in a diary throughout the study.

5.4 SCREEN FAILURES

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects 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 reasons, eligibility criteria not met, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once after discussion with the Medical Monitor. Rescreened subjects should not be assigned the same subject number as for the initial screening. All procedures planned at the screening visit, including signature of a new consent/assent form, will be performed.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment and retention strategies for the study will be covered in other study plans.

6 STUDY TREATMENT

Study treatment is defined as any investigational treatment or placebo intended to be administered to a clinical study subject according to the study protocol.

6.1 STUDY TREATMENT ADMINISTRATION

6.1.1 STUDY TREATMENT DESCRIPTION

ANB019 is a humanized IgG4 (S228P)/kappa mAb that belongs in the class of anti-IL-36R mAb.

ANB019 will be provided in a glass vial as a sterile, colorless to yellow, and clear to slightly opalescent solution for injection. The placebo contains no active ingredient and will be provided as a sterile, colorless to slightly yellowish, and clear to very slightly opalescent solution for injection. Detailed administration instructions will be provided in the Pharmacy Manual.

During the placebo-controlled period, eligible subjects will be randomized (2:1) to receive either ANB019 or placebo, SC administered on 4 occasions:

- Day 1: 400-mg dose of ANB019 or placebo (administered as 2 SC injections of ANB019 at 200 mg each or placebo)
- Days 29, 57, and 85: 200-mg dose of ANB019 or placebo

During the open-label extension, all subjects will receive ANB019, SC administered on 4 occasions. Subjects assigned to ANB019 during the placebo-controlled period will continue to receive a 200-mg dose of ANB019 at 200 mg on Days 113, 141, 169, and 197. Subjects assigned to placebo during the placebo-controlled period will receive a 400-mg dose of ANB019 on Day 113, followed by a 200-mg dose of ANB019 on Days 141, 169, and 197.

The blind will be maintained throughout the study. To keep the blind, the following measures will be taken on Day 113:

- Subjects assigned to ANB019 during the placebo-controlled period will receive 2 SC injections on Day 113: 1 of ANB019 at 200 mg and 1 of placebo.
- Subjects assigned to placebo during the placebo-controlled period will receive 2 SC injections on Day 113 of ANB019 at 200 mg each.

Further information will be provided in the Pharmacy Manual.

6.1.2 DOSING AND ADMINISTRATION

Study treatment dosing and administration details are provided in Table 2.

Table 2: Study Treatment Details

Study Treatment Name:	ANB019 Anti-interleukin 36 receptor monoclonal antibody	Placebo
Dosage Form:	Solution for injection	Solution for injection
Source of procurement:	AnaptysBio, Inc.	AnaptysBio, Inc.
Study Treatment Description	ANB019 will be provided as a sterile, colorless to yellow, and clear to slightly opalescent solution supplied in a single use, 2R, Type I glass vial with a fill volume of 1.2 mL. Each vial contains 120 mg of ANB019 at a concentration of 100 mg/mL.	The placebo contains no active ingredient and will be provided as a sterile, colorless to slightly yellowish, and clear to very slightly opalescent solution supplied in a single use, 2R, Type I glass vial with a fill volume of 1.2 mL.
Dosage Formulation:	ANB019 study treatment is formulated as: 100 mg/mL ANB019 in 25 mM-histidine, 60 mM-NaCl, 145 mM sorbitol, and 0.02% v/v polysorbate-20 at pH 6.0.	The Placebo is formulated as: 25 mM-histidine, 60 mM-NaCl, 145 mM sorbitol, and 0.02% v/v polysorbate-20, at pH 6.0.
Unit Dose Strength(s)/ Dosage Level(s):	Placebo-controlled period: Subjects assigned to ANB019 during the placebo-controlled period will receive the following doses: • Day 1: 400-mg dose, administered as 2 mL × 2 SC injections of ANB019 at 200 mg each. • Days 29, 57, and 85: 200-mg dose, administered as 2 mL × 1 SC injection of ANB019 at 200 mg. Open-label extension period: • Day 113 for subjects assigned to placebo during the placebo-controlled period: 400-mg dose, administered as 2 mL x 2 SC injections of ANB019 at 200 mg each. • Day 113 for subjects assigned to ANB019 during the placebo-controlled period: 200-mg dose, administered as 2 mL x 2 SC injections; 1 SC injection of ANB019 at 200 mg and 1 SC injection of placebo. • Days 141, 169, and 197 for all subjects: 200-mg dose, 2 mL × 1 SC injection.	Placebo-controlled period: Subjects assigned to placebo during the placebo-controlled period will receive an equivalent volume of placebo SC administered on Days 1, 29, 57, and 85. • Day 1: 2mL × 2 SC injections of placebo. • Days 29, 57, and 85: 2 mL × 1 SC injection of placebo. Open-label extension period: There will be no placebo administration during the open-label extension period.
Route of Administration:	SC injection (4 doses during the placebo-controlled period and 4 doses during the open-label extension period)	SC injection (4 doses during the placebo-controlled period, none during the open-label extension period)

Table 2: Study Treatment Details (Continued)

Dosing Instructions:	ANB019 and placebo should be administered by clinic staff trained in best practices for SC administration of study treatments. For SC injections, ANB019 and placebo should be prepared by drawing up the required dosing volume into suitable sized syringe and attaching a dosing needle. No further dilution is required. The preferred anatomical site of SC administration is the abdomen; however, the injection may be made in the upper arm, if needed. The same anatomical site should be used throughout the entire study for a given subject (ie, do not administer one dose into the upper arm and at a subsequent visit or dose, administer the next dose into the abdomen). Subsequent doses should be rotated within an anatomical site (ie, if the upper left abdominal quadrant is used as the initial site of administration, then the next administration at a subsequent visit should be rotated to the upper right quadrant). Subcutaneous injections should not be given into moles, scars, tattoos, or areas where the skin is tender, bruised, red, hard, or not intact. Prior to SC needle insertion, the skin will be pinched between the thumb and index finger to separate the subcutaneous layer from the muscle. The needle is to be injected at a 90-degree angle to the fat pad. The plunger will be pressed gently until the entire dose is delivered to the SC space and the needle will be held in place (fully depressed) for 10 seconds after the injection is administered. The needle will be removed and then the skin pinch released; any leakage or backflow of fluid from the administration site onto the surface of the skin will be noted and documented in the eCRF. The site of administration is NOT to be massaged by either the clinic staff or by the subject for at least 60 minutes after drug administration.

Abbreviations: eCRF, electronic case report form; NaCl, sodium chloride; SC, subcutaneous.

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

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatments received, and any discrepancies are to be reported and resolved before use of the study treatment.

Only subjects randomized in the study may receive study treatment and only authorized study center staff may supply or administer study treatment. Further guidance and information for the administration of the study treatment are provided in the Pharmacy Manual.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized study center staff.

ANB019 vials must be refrigerated at 2°C to 8°C (36°F to 46°F) until the day of use. ANB019 must not be used beyond the re-test or expiration date provided by the manufacturer. Vial contents should not be frozen or shaken. ANB019 vials undiluted may be stored at room temperature (8°C to 25°C [46°F to

77°F]) for up to 8 hours. Vials are intended for single use only; therefore, any remaining solution should not be used and should be discarded after study treatment accountability and reconciliation.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

The Investigator, a member of the study center staff, or a hospital Pharmacist must maintain an adequate record of the receipt and distribution of all study medication using the Drug Accountability Form. These forms must be available for inspection at any time.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

This study includes a randomized, double-blind, placebo-controlled period followed by an open-label period. The blind will be maintained throughout the study with limited and controlled access to the randomization code.

All subjects will be assigned a unique 'subject identification number' at the time of screening. On Day 1, after verification that all inclusion and no exclusion criteria have been met, the subjects will be randomized in a 2:1 ratio to receive ANB019 or placebo. As subjects become eligible, they will be assigned unique randomization numbers, which will be used to assign the allocated treatment based on a randomization schedule. Randomization will be stratified based on erythema severity at Baseline (highest severity [moderate {2} vs severe/very severe {3, 4}] as evaluated by IASI-E).

The Sponsor, Investigator, and subjects will be blinded to treatment assignment of ANB019 or placebo. An unblinded Pharmacist will be responsible for study treatment dispensing.

Once the subject has provided an informed consent and meets all inclusion and no exclusion criteria, the study center will request the treatment assignment using a central Interactive Web Response System (IWRS).

The process for breaking the blind will be handled through the IWRS. Unblinding is undertaken by a predetermined process to ensure that participating subject and study team are not unblinded unnecessarily and the study results are not compromised. Unblinding of treatment assignment during the study should occur only if it is necessary to know what treatment the subject received during the placebo-controlled period. Unblinding should occur if the Investigator deems identification of the study treatment is necessary for the purpose of providing urgent subject care, and knowledge of the subject's treatment assignment (ANB019 or placebo) will alter subsequent care (emergency unblinding).

In the event that emergency unblinding is necessary, the Investigator must ensure that the unblinding of the treatment code is performed in a discrete manner and the treatment is disclosed only to those persons involved with the direct medical care of the subject. The Investigator must provide the reason for unblinding to the Sponsor's Medical Monitor according to the Sponsor instructions following emergency unblinding.

The Sponsor and the contract research organization (CRO) must be notified when a subject and/or Investigator is unblinded during the study. The IWRS will create the blinded and/or unblinded notification when the blind is broken, which can be sent via email as per the user role of IWRS. The unblinding will be captured in the IWRS audit trail. Pertinent information regarding the circumstances of unblinding of a subject's treatment code must be documented in the subject's source documents.

6.4 STUDY TREATMENT COMPLIANCE

Study treatment compliance in this study will be under the direct control of the Investigator; the study treatments will be administered on site.

The prescribed dosage, timing, and mode of administration may not be changed. Any departures from the intended regimen must be recorded in the eCRFs.

For the study treatment administrations, date/time of administration, site of administration, and dose administered (entire dose/incomplete dose) will be documented in the eCRF.

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over the counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment and receives during the study must be recorded on the eCRF along with:

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

In addition, all prior medications used to treat ichthyosis disease conditions and any other medications taken within 6 months prior to enrollment must be recorded in the eCRF. The concomitant treatments for other indications that are not listed in the prohibited therapies or procedures section (see Section 6.5.2) must be on a stable dose for at least 4 weeks before study treatment administration (Day 1). Dose adjustments of these treatments should be avoided during the study.

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 PERMITTED THERAPIES

During the study, subjects must apply an emollient of their choice (without pharmacological active ingredient, refer to Section 5.2 for additional information) on their skin, including on lesions. The emollient use must be initiated at least 1 week prior to Day 1 and subjects must continue using it at the same frequency throughout the study. However, emollient must not be applied 3 hours prior to the study visits.

Every effort should be made to keep the same emollient throughout the study for the same body region. However, the chosen emollient may differ depending on the body region (eg, body vs face). The commercial name of the selected emollient(s) will be recorded in the source document and the electronic case report form (eCRF). No other products may be applied to the lesions during the study.

Type/frequency of emollient application must be recorded by the subject in a diary throughout the study.

6.5.2 PROHIBITED MEDICATIONS OR PROCEDURES

Prohibited medications/therapy are listed below. The use of a prohibited medication/therapy (unless conditions for use of rescue medications have been met, see Section 6.5.3) is a protocol violation and must be recorded in the eCRF. Subjects who start prohibited medications or therapies that have been demonstrated to be effective for treatment of ichthyosis during the study will be withdrawn from study treatment. Subjects who start any other prohibited medications or therapies during the study may be withdrawn from study treatment if an impact on efficacy assessment or safety of the subjects is

expected. If in any doubt, Investigator is advised to discuss medications with the Medical Monitor. In addition, the Investigator must notify the Medical Monitor in order to make a decision as to whether the subject will be withdrawn from the study.

All treatments likely to have efficacy in ichthyosis need to be discontinued prior to treatment initiation (prior to Day 1) with washout periods as stipulated in Table 3. All medications listed in Table 3 are also restricted during the study period. If treatment with any of these prohibited treatments is essential, then the subject must notify the study team.

Table 3: List of Prohibited Medications

Treatment	Washout period
Topical medications (including, but not limited to, corticosteroids, keratolytics, retinoids, other medicated topical agents)	2 weeks prior to Day 1
Topical agents or systemic agents that could affect pruritus (such as topical antipruritic agents, gabapentin, pregabalin, doxepin, and aprepitant) within 2 weeks prior to Day 1. Note: Other drugs that may have an effect on pruritus and that are used to treat other conditions may be allowed if started at least 4 weeks before Day 1 and are on a stable dose during the entire study. Note: Over the counter topical products containing pramoxine 1% are allowed during the entire study.	2 weeks prior to Day 1
Oral sedative H1 antihistaminic (including but not limited to diphenhydramine) Note: Oral nonsedative H1 antihistaminic to treat allergies will be permitted during the study only if the subject has been on a stable dose for at least 2 weeks prior to Day 1 and continues to use the same agent at the same frequency throughout the study.	2 weeks prior to Day 1
Systemic therapy (including but not limited to retinoids, cyclosporin, methotrexate, corticosteroids) or any other immunosuppressant or immunomodulation drugs	4 weeks prior to Day 1
Anti-IL-36R, anti-IL-36, anti-TNF/IL-12/IL-23/IL-17, or any other mAbs	12 weeks or 5 half-lives (whichever is longer) prior to Day 1
Any nonbiologic investigational drugs	4 weeks or 5 half-lives (whichever is longer) prior to Day 1
Marketed or investigational biological agent	12 weeks or 5 half-lives (whichever is longer) prior to Day 1
Antibiotic medication	Topical: 1 week prior to Day 1 Systemic: 4 weeks prior to Day 1
Systemic antiviral medication	4 weeks prior to Day 1
Live attenuated vaccine	12 weeks prior to Day 1

Abbreviations: IL, interleukin; IL-36R, IL-36 receptor; mAb, monoclonal antibody; TNF, tumor necrosis factor.

6.5.3 RESCUE MEDICATION

To evaluate the need of rescue medication, the Investigator will be required to perform an IASI assessment and the subject will have to evaluate pruritus using the worst pruritus and pain NRS. Rescue medication can be initiated if subjects have worsened by at least 25% as per IASI and/or reported intolerable symptoms. The Investigator should make every attempt to conduct efficacy and safety assessments (eg, disease severity scores, safety laboratory tests) immediately before administering any rescue medication. An unscheduled visit may be used for this purpose, if necessary.

Rescue medication is defined as a treatment, other than emollient, taken to control intolerable symptoms of ichthyosis. A subject will be allowed to use topical rescue medications (including low/medium potency topical steroids [eg, hydrocortisone, triamcinolone] or topical calcineurin inhibitor) starting at Week 4. However, topical retinoids and high-potency topical steroids (eg, clobetasol and betamethasone dipropionate), as well as systemic medications listed in Table 3, will not be permitted.

Subjects who take permitted topical rescue medication can continue taking study treatment and continue in the study, if the topical rescue medication is started at Day 29 (Week 4) or later, and for a duration of at most 2 weeks (multiple use less than 2-week duration may be allowed after confirmation with the Medical Monitor). However, subjects who take prohibited topical rescue medication or systemic rescue medication, start taking a permitted topical rescue medication prior to Day 29 (Week 4), or used permitted topical rescue medication for more than 2 weeks may be discontinued from study treatment, but they will be asked to complete the follow-up period. The Investigator must notify the Medical Monitor in order to make a decision as to whether the subject should be withdrawn from the study.

Rescue medication will be directed by the Investigator as needed. Rescue medication may be used at the Investigator's discretion only if medically indicated for the wellbeing of the subject. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded. The study team will dispense rescue medication that will be obtained locally and will be reimbursed.

6.6 DOSE MODIFICATION

No dose modification is allowed in this study. Study treatment can be interrupted temporarily or permanently if deemed necessary as per the Investigator's discretion.

6.7 TREATMENT AFTER THE END OF THE STUDY

All subjects will return to the study center for the EOS (Day 281/Week 40) or ET visit for final safety and EOS assessments. After this visit, subjects should be treated according to the clinical judgment of the subject's physician. Care after EOS/ET will not be provided by AnaptysBio, Inc. Any SAE or pregnancy occurring through the EOS visit should be reported to the pharmacovigilance unit (see Section 8.2.1) and followed up until an outcome is determined.

7 STUDY TREATMENT DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY TREATMENT

The subject's eligibility criteria will be checked prior to administration of the study treatment on Day 1. If a clinically significant finding or AE/SAE is identified after enrollment, the Investigator or qualified designee will determine if the subject can receive the study treatment and continue in the study and if any change in subject management is needed.

Discontinuation from study treatment does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. In case of early withdrawal from the study treatment and study, the subject will be required to attend the ET visit.

7.1.1 TEMPORARY INTERRUPTION

Study treatment can be interrupted temporarily for any individual subject in case of an AE as per the Investigator's discretion. The Medical Monitor should be informed. Re-starting of study treatment can be done after discussion with the Medical Monitor.

7.1.2 RE-CHALLENGE

The study treatment can be reintroduced at the next scheduled administration visit at the Investigator's discretion and after discussion with the Medical Monitor. Study treatment will be reintroduced at the 200 mg dose. In case of positive re-challenge, the study treatment should be withdrawn permanently.

7.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

A subject may withdraw from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.

In case of early withdrawal from the study treatment and the study, the subject will be required to attend the ET visit (see the SoA in Section 1.3). After the ET visit, additional follow-up visits may be scheduled to follow any ongoing AE. Subjects must be withdrawn from the study under the following circumstances, any SAE or significant AE which, in the opinion of the Investigator, warrant study discontinuation for safety reasons, or pregnancy occurring through the EOS, which should be followed up until outcome.

The following events are considered sufficient reasons for discontinuing a subject from the study treatment and/or the study:

- Pregnancy (Refer to Appendix 1 and Section 8.2.1.8)
- Significant deviation/lack of compliance with protocol
- Any significant AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject in the opinion of the Investigator
- Disease progression which requires discontinuation of the study treatment
- Withdrawal of consent
- Lost to follow-up
- Use of any prohibited medication or treatment that in the opinion of the Investigator necessitates the subject being withdrawn (Refer to Section 6.5.2)

- Termination of the subject participation by the Investigator or Sponsor

The reason for subject discontinuation or withdrawal from the study will be recorded on the eCRF.

If a subject withdraws from the study, he or she may request destruction of any samples taken and not tested, and the Investigator must document this in the study center study records.

See SoA (see Section 1.3) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

Subjects withdrawing from the study prematurely for reasons other than a study treatment-related AE may be replaced at the discretion of the Sponsor.

7.3 LOST TO FOLLOW-UP

A subject 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 center.

The following actions must be taken if a subject fails to return to the clinic for a required study visit (unless this is required by the COVID-19 situation and virtual visits are scheduled instead):

- The study center must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study. If the re-scheduled visit falls within the next visit's window, then the visit should be considered a missed visit and the subject should come in for the next scheduled visit as planned. Missed visits must be captured in the eCRFs and will be recorded as a protocol deviation.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (see Section 1.3). Assessments scheduled on the day of study treatment administration must be performed prior to the study treatment administration unless otherwise noted. There are visits where the protocol requires more than 1 procedure to be completed at the same time point. When indicated, the procedures must follow the specific order of events; see Section 1.3 for instructions.

Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue in the study.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening purposes provided the procedures met the protocol specified criteria and were performed within the time frame defined in the SoA (see Section 1.3).

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Clinical evaluations of ichthyosis will be performed by an experienced and qualified dermatologist (board certified or equivalent) or other suitably qualified and experienced designee. To assure consistency and reduce variability, the same assessor should perform all assessments on a given subject, whenever possible (especially at Day 1 and Week 16).

8.1.1 SUBJECT ASSESSMENTS OF PRURITUS AND PAIN

The intensity of pruritus and pain will be assessed at the visits specified in the SoA (see Section 1.3) using worst and average NRSs. This will be evaluated by asking subjects to assign a numerical score representing of the worst intensity over the last 24 hours or the average intensity over the last 7 days of their symptoms (pruritus or pain) on a scale from 0 to 10, with 0 indicating no symptoms and 10 indicating the worst imaginable symptoms.

These assessments will be completed by the subject on a worksheet prior to any safety and efficacy evaluations at every study visit. Of note, worst pruritus and pain NRSs should be performed before average pruritus and pain NRSs. The 4 scales are presented in Appendix 2.

8.1.2 ICHTHYOSIS QUALITY OF LIFE- 32 ITEMS

The iQoL-32 questionnaire will be assessed in subjects ≥ 15 years of age (on Day 1) at the visits specified in the SoA (see Section 1.3). The IQoL-32 questionnaire will not be administered to subjects who turn 15 years of age following their Day 1 visit. It is a simple 32-question specific and validated questionnaire for ichthyosis (Dreyfus 2013). Each item is scored from 0 to 4 for a total score that may therefore vary between 0 and 128.

The aim of this subject-reported questionnaire is to measure how much ichthyosis has affected the subject's quality of life during the past 4 weeks. The iQoL-32 will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The iQoL-32 is presented in Appendix 3.

8.1.3 DERMATOLOGY LIFE QUALITY INDEX / CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX QUESTIONNAIRES

The DLQI/CDLQI questionnaires will be assessed at the visits specified in the SoA (see Section 1.3). They are simple 10-question validated questionnaires (Finlay 1994; Lewis-Jones 1995). The DLQI/CDLQI score ranges from 0 (no effect on the subject's life) to 30 (extremely large effect on the subject's life). The aim of these subject-reported questionnaires is to measure how much the skin condition has affected the subject's quality of life during the previous week.

The CDLQI will be administered to subjects < 16 years old and the DLQI will be administered to subjects ≥ 16 years old. Subjects will be administered the same questionnaire during the entire study based on their age at Day 1.

The DLQI/CDLQI will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaires are self-explanatory and will be filled in by the subjects without the need for a detailed explanation. The DLQI and CDLQI are presented in Appendix 4 and Appendix 5, respectively.

8.1.4 PATIENT GLOBAL IMPRESSION OF SEVERITY

The PGI-S will be assessed at the visits specified in the SoA (see Section 1.3). It is a single-item question, which asks the subject to rate the current severity of ichthyosis. The response options are "Clear skin", "Mild", "Moderate", "Severe".

The PGI-S will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The PGI-S (modified from Yalcin 2003) is presented in Appendix 6.

8.1.5 PATIENT GLOBAL IMPRESSION OF CHANGE

The PGI-C will be assessed at the visits specified in the SoA (see Section 1.3). The PGI-C is a single-item, self-administered questionnaire, which ask the subject to rate the change in their symptom severity ("Very much better" to "Very much worse").

The PGI-C will be completed by the subject on a worksheet prior to any safety and efficacy evaluations. The questionnaire is self-explanatory and handed to the subject who is asked to fill it in without the need for a detailed explanation. The PGI-C (modified from Yalcin 2003) is presented in Appendix 7.

8.1.6 BODY SURFACE AREA

The overall BSA affected by ichthyosis will be evaluated (from 0% to 100%) at the visits specified in the SoA (see Section 1.3). The palmar surface of one hand (using the subject's hand and including the fingers) represents 1% of his or her total BSA (Thomas 2007). To be eligible, subjects must have a BSA ≥ 50% at Day 1.

8.1.7 INVESTIGATOR GLOBAL ASSESSMENT

The IGA of ichthyosis severity will be assessed at the visits specified in the SoA (see Section 1.3). The IGA will be used to evaluate the current state of ichthyosis on the entire body. It is a 5-point morphological assessment of overall ichthyosis severity: 0, clear; 1, almost clear; 2, mild; 3, moderate; 4, severe. The IGA is a global evaluation that should be performed at arm's length distance from the subject and must be performed before the IASI and NASA.

8.1.8 ICHTHYOSIS AREA SEVERITY INDEX

The IASI will be assessed at the visits specified in the SoA (see Section 1.3). The IASI quantifies the severity of a subject's ichthyosis based on the severity of erythema or scaling, and the percentage of BSA affected (Paller 2017, Malik 2019, Czarnowicki 2018). The IASI is a composite score ranging from 0 to 48 that takes into account the degree of erythema and scaling (each scored from 0 to 4 separately) for each of four body regions, with adjustments for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. The IASI is presented in Appendix 8. To be eligible for this study, subjects must have an IASI total score ≥ 18, with erythema score ≥ 2 (moderate severity) in ≥ 1 body region and scaling score ≥ 2 (moderate severity) in ≥ 1 body region as evaluated by IASI at Day 1 visit.

8.1.9 NETHERTON AREA AND SEVERITY ASSESSMENT

The NASA will be assessed in subjects with Netherton Syndrome at the visits specified in the SoA (see Section 1.3). The NASA quantifies the severity of subjects' ichthyosis based on the severity of erythema, infiltration/papulation, lichenification, and scaling, and the percentage of BSA affected (Yan 2010). The NASA is a composite score ranging from 0 to 72 that takes into account the degree of erythema, infiltration/papulation, lichenification, and scaling (each scored from 0 to 3 separately) for each of four body regions, with adjustments for the percentage of BSA involved for each body region and for the proportion of the body region to the whole body. The NASA is presented in Appendix 9.

8.1.10 TRANSEPIDERMAL WATER LOSS

The TEWL will be evaluated at the visits specified in the SoA (see Section 1.3). The TEWL evaluates the amount of water that passively evaporates through skin to the external environment. It will be used in the study to evaluate the clinical severity of ichthyosis and the associated effect on skin barrier function.

At Day 1, the Investigator will select an anatomical region (as specified in the SRM) with representative ichthyosis lesions for each subject and perform 3 readings; the location will be recorded. TEWL readings will be taken in standard room ambient conditions (22°C to 25°C, 40% to 60% relative humidity); the mean of the TEWL measurements will be used for the analyses.

8.2 SAFETY ASSESSMENTS

8.2.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.2.1.1 DEFINITION OF ADVERSE EVENTS

An AE is any untoward medical occurrence in a subject temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

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 study treatment that does not necessarily have a causal relationship with this treatment.

8.2.1.1.1 EVENTS MEETING THE ADVERSE EVENT DEFINITION

Events meeting the AE definition include:

- Any abnormal laboratory test results (hematology, biochemistry, or urinalysis) or other safety assessments (eg, ECG, vital signs measurements), including those that worsen from Day 1, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of 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.

8.2.1.1.2 EVENTS NOT MEETING THE ADVERSE EVENT DEFINITION

Events not meeting the AE definition include:

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

8.2.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An AE or suspected adverse reaction is considered "serious" if, in the view of either the Investigator or Sponsor, it results, at any dose, in any of the following outcomes:

- **Death**
- **Life-threatening adverse event** – The term ‘life-threatening’ in the definition of “serious” refers to an event in which the subject 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.

- **Inpatient hospitalization or prolongation of existing hospitalization** – In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions** – 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.
- **Congenital anomaly/birth defect**
- **Other important medical events** – Events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
  Examples of such medical events include invasive or malignant cancers, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

8.2.1.3 CLASSIFICATION OF AN ADVERSE EVENT

8.2.1.3.1 SEVERITY OF EVENT

The intensity of an AE is an estimate of the relative severity of the event. The Investigator will make an assessment of intensity for each AE and SAE reported during the study based on his or her clinical experience and familiarity with the literature. The following definitions are to be used to rate the severity of an AE:

- **Mild** – Events require minimal or no treatment, is easily tolerated by the subject, causing minimal discomfort, and do not interfere with the subject's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning and sufficient discomfort to the subject.
- **Severe** – Events interrupt a subject's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious". An AE that is assessed as severe should not be confused with a 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.

8.2.1.3.2 RELATIONSHIP TO STUDY TREATMENT

All AEs must have their relationship to study treatment assessed by the Investigator who examines and evaluates the subject based on temporal relationship and his or her clinical judgment. Alternative

causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated. The Investigator will also consult the IB in his or her assessment. The degree of certainty about causality will be graded using the categories below. In a clinical study, the study treatment must always be suspect.

- **Unrelated** – Clinical event incontrovertibly not related to the study treatment.
- **Unlikely to be related** – Clinical event with an incompatible time relationship to study treatment administration which makes a causal relationship improbable, and in which an underlying condition or other drugs or chemicals provides plausible explanations.
- **Possibly related** – Clinical event with a reasonable time relationship to study treatment administration, and that is unlikely to be attributed to concurrent condition or other drugs or chemicals.
- **Related** – Clinical event with plausible time relationship to study treatment administration and that cannot be explained by concurrent condition or other drugs or chemicals.

For each AE/SAE, the Investigator must document in the medical notes that he or 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 pharmacovigilance unit. 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 pharmacovigilance unit within 24 hours of awareness of the event.

The Investigator may change his or her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

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

8.2.1.3.3 EXPECTEDNESS

The pharmacovigilance unit will be responsible for determining whether an AE is expected or unexpected as interpreted through the IB. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study treatment.

8.2.1.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

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

All AEs including local and systemic reactions will be captured on the appropriate eCRF. Information to be collected includes event description, date of onset, clinician's assessment of severity, seriousness, relationship to study treatment (assessed only by those with the training and authority to make a diagnosis), action taken, and outcome of the event. All AEs occurring while on study must be documented appropriately regardless of relationship (see Section 8.2.1.3.2). All AEs will be followed to adequate resolution.

Study site personnel will note the occurrence and nature of each subject's medical condition(s) present prior to the informed consent signature in the appropriate section of the source document and eCRF. During the study, site personnel will note any change in the condition(s) and the occurrence and nature of any AE. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

Should a subject experience an AE at any time after the screening visit informed consent signature until the end of participation in the study, the event will be recorded as an AE in the source document and eCRF. Any SAE related to the study participation (eg, screening procedure) will be recorded in the source document and eCRF from the time consent is given to participate in the study until the end of participation in the study (EOS/ET visit).

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the pharmacovigilance unit.

Any medical condition that is present at the time that the subject is screened will be considered as medical history and not reported as an AE. However, if the study subject's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE/SAE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The Investigator is responsible for appropriate medical care of subjects during the study. After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. The Investigator also remains responsible for following through with an appropriate health care option for all AEs that are ongoing at the end of the study. The subject should be followed until the event is resolved or stable. If an AE is ongoing at the end of study, the follow-up duration is left to the discretion of the Investigator. Follow-up frequency will be performed at the discretion of the Investigator.

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

8.2.1.5 ADVERSE EVENT REPORTING

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information (including event term, start and stop dates, severity, relationship to study treatment, outcome, if serious or non-serious) in the eCRF. Each event must be recorded separately.

It is not acceptable for the Investigator to send photocopies of the subject's medical records to the pharmacovigilance unit in lieu of completion of the AE/SAE eCRF page.

There may be instances when copies of medical records for certain cases are requested by the pharmacovigilance unit. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the pharmacovigilance unit.

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.

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 pharmacovigilance unit 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.

New or updated information will be recorded in the originally completed eCRF.

8.2.1.6 SERIOUS ADVERSE EVENT REPORTING

Prompt notification by the Investigator to the pharmacovigilance unit of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study treatment under clinical investigation are met. All SAEs will be recorded and reported to the pharmacovigilance unit within 24 hours of awareness. The Investigator will submit any updated SAE data to the pharmacovigilance unit within 24 hours of receipt of the information as outlined in the Safety Reporting Instructions that will be provided to the sites and in the study Safety Management Plan.

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

The Sponsor or designee has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor or designee will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC, and Investigators.

Investigator safety reports must be prepared for suspected unexpected SAEs according to local regulatory requirements and pharmacovigilance unit policy, and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the pharmacovigilance unit will review and then file it along with the IB and will notify the IRB/EC, if appropriate according to local requirements.

If a subject dies while participating in the study, the Investigator will provide the pharmacovigilance unit with a copy of any postmortem findings.

8.2.1.6.1 REPORTING VIA AN ELECTRONIC DATA COLLECTION TOOL

The primary mechanism for reporting an SAE to the pharmacovigilance unit will be the EDC clinical database.

If the electronic system is unavailable, then the study center will use the back-up paper SAE Report Form. The study center will then enter the SAE data into the EDC system as soon as it becomes available.

After the study is completed and the database is locked, the tooled system will be taken off-line to prevent the entry of new data or changes to existing data.

If a study center receives a report of a new SAE from a subject or receives updated data on a previously reported SAE after the EDC system is locked, then the study center can report this information on a paper SAE form and email the form to the pharmacovigilance unit.

Contacts for SAE reporting can be found in SAE form and Safety Reporting Instructions that will be provided to the sites.

8.2.1.6.2 REPORTING VIA PAPER CASE REPORT FORM

In rare circumstances, and in the absence of EDC or email, notification by facsimile or telephone is acceptable for notifying the pharmacovigilance unit of an SAE. Once the EDC is available, the SAE must be reported in the system within 24 hours of it becoming available.

Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in Safety Reporting Instructions that will be provided to the sites.

8.2.1.7 REPORTING EVENTS TO SUBJECTS

Not applicable.

8.2.1.8 REPORTING OF PREGNANCY

If a female subject or a female partner of a male subject becomes pregnant during the study and up to 28 days after the end of the study, the subject should inform the study center as soon as possible.

If a pregnancy is reported, the Investigator should inform the pharmacovigilance unit within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 1.

If a pregnancy occurs, it will be followed up to determine the outcome, but no longer than 6 to 8 weeks after the estimated delivery date, where consent has been obtained to do so.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs and must be reported in 24 hours of awareness as described in Section 8.2.1.6.

8.2.1.9 TREATMENT OF OVERDOSE

For this study, any dose of ANB019 or placebo administered in a volume exceeding the planned dosing detailed in Table 2 (Dose Strength[s]/Dosage Level[s]) will be considered an overdose. For ANB019, this means a dose greater than 400 mg received within a 24-hour time period on Day 1 and Day 113 (for subjects assigned to placebo during the placebo-controlled period) and greater than 200 mg on Days 29, 57, 85, 113 (for subjects assigned to ANB019 during the placebo-controlled period), 141, 169, and 197.

In the improbable event of a suspected overdose, the following procedures should be executed:

- Administration is to be discontinued.
- The subject is to be monitored clinically.
- Supportive measures are to be undertaken as clinically indicated.
- Electrocardiography and clinical laboratory evaluations (ie, blood glucose, hepatic enzymes, creatinine, blood urea nitrogen, creatine kinase (CK), and complete blood count) are to be performed and followed until all values return to Baseline levels and AEs subside, if applicable.

No information on overdose, maximum tolerated dose, or dose-limiting toxicities for ANB019 has been established at this time and since there are no known antidotes for ANB019, the treatment of overdose is at Investigator's discretion.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities and follow-up until resolution.
3. Obtain a serum sample for PK analysis soon after the dose for SC administration.
4. Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

8.2.2 HEIGHT AND WEIGHT

Height (cm) and weight (kg) will be collected to calculate the BMI. Height and weight will be measured at the time points specified in the SoA (see Section 1.3).

8.2.3 CHEST X-RAY

Bidirectional posterior-anterior and lateral view chest X-ray, or as indicated by local treatment guidelines or practice, will be performed at screening (see Section 1.3). If a chest X-ray was performed within 6 months of screening and no clinically significant abnormality was observed, it can be skipped at screening.

8.2.4 PHYSICAL EXAMINATIONS

Complete physical examinations will be performed at the time points indicated in the SoA (see Section 1.3).

A complete physical examination will include assessments of general appearance; skin; head/neck; pulmonary, cardiovascular, gastrointestinal, lymphatic, and musculoskeletal system; extremities; eyes; nose; throat; and neurologic status.

A detailed examination of the skin should be performed at the time points indicated in the SoA for the efficacy assessments (eg, IASI).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.5 VITAL SIGNS

Body temperature (°C), pulse rate (bpm), blood pressure (mmHg), and respiratory rate (breath/min) will be assessed at the time points specified in SoA (see Section 1.3).

Blood pressure and pulse rate will be assessed in a seated position with a completely automated device. Manual techniques will be used only if an automated device is not available.

Blood pressure and pulse rate measurements should be preceded by at least 5 minutes of rest for the subject in a quiet setting without distractions (eg, television, cell phones).

Vital signs including body temperature, respiratory rate, and pulse rate (after at least 5 minutes rest) should be measured once. Arterial blood pressure should be measured twice (at intervals of at least 5 minutes), using a validated device.

8.2.6 ELECTROCARDIOGRAMS

A single 12-lead ECG will be obtained at the time points specified in the SoA (see Section 1.3) using a validated ECG machine that automatically calculates the heart rate and measures RR, PR, QRS, QT, and QTcF intervals.

Additional information will be provided in a separate manual.

The ECG will be reviewed by the Investigator or an authorized representative who is experienced in the evaluation of ECGs and assessed for clinical significance.

The ECG individual data (including clinical significance that will be reported as AE) will be entered into the electronic data capture (EDC).

8.2.7 CLINICAL SAFETY LABORATORY ASSESSMENTS

See Appendix 10 for the list of clinical laboratory tests to be performed and the SoA (see Section 1.3) for the timing and frequency of the tests.

A central laboratory will be used to perform all laboratory tests except urine pregnancy dipstick which will be assessed by the study center staff. However, local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately and the Investigator needs to make an immediate decision for any safety concerns based on laboratory results. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.

For screening laboratory assessments, if any laboratory results are outside of the upper or lower limits listed in Section 5.1, final determination of eligibility will be at the Investigator's discretion following consultation with the Medical Monitor and Sponsor.

All laboratory tests with values considered clinically significantly abnormal during the study and including the subject's last study visit (EOS) should be repeated until the values return to normal or Baseline or are no longer considered clinically significant or judged medically stabilized 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.

All protocol-required laboratory assessments, as defined in Appendix 10, must be conducted in accordance with the Laboratory Manual and the SoA.

If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE), then the results must be recorded in the eCRF.

8.2.8 TELEPHONE CONTACT

At Days 3, 15, 43 and 71, subjects will be contacted by phone to assess for safety. Study staff will review for any new AEs or changes in concomitant medications. Any new/changed AEs and concomitant medications will be recorded on the eCRF.

8.3 OTHER ASSESSMENTS

8.3.1 PHOTOGRAPHY

Photography (of total body and representative lesion[s] of skin scaling and erythema) will be performed at selected study centers only at the time points mentioned in the SoA (see Section 1.3) for documentation purposes only.

Additional information on photography will be described in the manual provided to sites.

8.3.2 PHARMACOKINETICS

Whole blood will be obtained for the determination of ANB019 concentration in human serum. Samples will be collected according to the SoA (see Section 1.3) and Table 4. Whole blood will be obtained from each subject for PK assessments during the study. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up). Samples collected for analyses of ANB019 serum concentration may also be used to correlate exposure to safety or efficacy as well as supportive analysis for dose justification.

The actual date and time (24-hour clock) of the blood sample collection will be recorded in the subject's eCRF. The details of blood sample collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate manual.

The measurement of the concentrations of ANB019 will be performed using a validated assay method under the supervision of the Sponsor. The analytical methods used to measure concentrations of ANB019 will be described in a separate bioanalytical report.

Only samples within the stability window of the assay will be analyzed.

While PK samples must be collected from subjects assigned to the placebo arm to maintain the blinding of treatment assignment, PK assay results for these subjects are not needed for the safe conduct or proper interpretation of this study. These samples may not be analyzed unless needed to investigate if a dosing error has occurred. Personnel at the bioanalytical laboratory performing PK assays will be unblinded, the clinical study team members, and study center staff (with the exception of the unblinded Pharmacist) will remain blinded to treatment for the duration of the study. Data may be de-identified for quality review. Additional details on de-identification or unblinding of the PK data, if applicable, will be described in a separate plan.

Drug concentration information that may unblind the study will not be reported to study centers or blinded personnel until the study has been unblinded.

Table 4: Pharmacokinetic Sample Collection and Time Points

Study Visit	Pharmacokinetic Sample Time Point (Serum)	Adults (≥ 18 years)	Adolescents (≥ 12 to < 18 years)[a]
Day 1	Predose	X	X
	2 hrs (± 10 min) postdose	X	X
Day 8	Anytime	X	
Day 29	Predose	X	X
Day 57	Predose	X	X
Day 85	Predose	X	
Day 113	Predose	X	X
Day 141	Predose	X	
Day 169	Predose	X	
Day 197	Predose	X	
Day 225	Anytime	X	X
Day 253	Anytime	X	
Day 281	Anytime	X	X

Abbreviations: hrs, hours; min, minutes.

[a] Adolescent subjects who reach 18 years of age during the study and are reconsented as adults will follow the adult schedule of assessments.

8.3.3 IMMUNOGENICITY ASSESSMENTS

Anti-drug antibodies (ADA) to ANB019 will be evaluated in serum samples collected from all subjects according to the SoA (see Section 1.3) and Table 5. Additionally, serum samples should also be collected at the final visit from subjects who discontinued study treatment or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee. Each serum sample will be divided into 2 aliquots (1 each for primary and a back-up).

The detection and characterization of antibodies to ANB019 will be performed using a validated assay method by or under the supervision of the Sponsor.

Serum samples will be tested in a multi-tiered approach. A validated screening assay for antibodies binding to ANB019 will be initially used to assess serum samples. Samples that are determined putative positive in the screening assay will then be subjected to a confirmatory assay to demonstrate that antibodies are specific to ANB019. Samples that are identified as positive in the confirmatory assay will be further characterized in a validated titer assay and the titer of confirmed positive samples will be reported. Other analyses may be performed to verify the stability of antibodies to study treatment and/or to further characterize the immunogenicity of study treatment.

Samples that are confirmed positive for antibodies binding to ANB019 may be further characterized for their ability to neutralize the activity of the study treatment using a validated neutralizing antibody assay method and the presence and/or titer of ADA may be correlated to safety and PK data.

Table 5: Anti-Drug Antibodies Sample Collection and Time Points

Study Visit	Anti-Drug Antibodies Sample Time Point (Serum)	Adults (≥ 18 years)	Adolescents (≥ 12 to < 18 years)[a]
Day 1	Predose	X	X
Day 29	Predose	X	X
Day 57	Predose	X	X
Day 85	Predose	X	
Day 113	Predose	X	X
Day 141	Predose	X	
Day 225	Anytime	X	X
Day 281	Anytime	X	X

[a] Adolescent subjects who reach 18 years of age during the study and are reconsented as adults will follow the adult schedule of assessments.

8.3.4 IMMUNOGLOBULIN E LEVELS EVALUATION

Whole blood will be obtained from subjects with Netherton Syndrome for the evaluation of IgE levels. Samples will be collected according to the SoA (see Section 1.3). The quantification of IgE will be performed by the Sponsor or Sponsor's designee using a validated method. Samples collected for IgE levels evaluation may also be used to correlate with safety or efficacy results.

The actual date and time of the sample collection will be recorded in the subject's eCRF. The details of blood sample collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate manual.

8.3.5 BIOMARKERS ANALYSIS

8.3.5.1 TAPE STRIPPING

Tape strips samples will be collected according to the SoA (see Section 1.3) to measure cutaneous biomarkers including but not limited to IL-36R, Th-17 cytokines such as IL-17A, and markers of neutrophils and dendritic cells infiltration.

The actual date and time of the sample collection will be recorded in the subject's eCRF. The details of tape strips collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate Laboratory Manual.

The measurement of tape strips biomarkers may be performed by an additional third party (eg, a university Investigator) designated by the Sponsor.

8.3.5.2 OPTIONAL SKIN BIOPSY

Optional skin biopsy samples will be collected according to the SoA (see Section 1.3) to measure skin biopsy biomarkers including but not limited to IL-36R, Th-17 cytokines such as IL-17A, and markers of neutrophils and dendritic cells infiltration.

The actual date and time of the sample collection will be recorded in the subject's eCRF. The details of skin biopsy collection, sample tube labeling, sample preparation, storage, and shipping procedures will be described in a separate Laboratory Manual.

The measurement of skin biopsy biomarkers may be performed by an additional third party (eg, a university Investigator) designated by the Sponsor.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary analysis for this study is to compare the mean IASI score for ANB019 with placebo during the double-blind treatment period, at a two-sided alpha = 0.05 level. Any testing being performed for secondary or exploratory endpoints will be considered exploratory in nature based on a 2-sided alpha = 0.05

H_0: $\mu_{ANB019} - \mu_{Placebo} = 0$ vs. H_A: $\mu_{ANB019} - \mu_{Placebo} \neq 0$

9.2 SAMPLE SIZE DETERMINATION

The primary efficacy endpoint is the change from Baseline of the IASI score at Week 16. The null hypothesis (H_0) to be tested is that the mean change in IASI score from Baseline is the same for ANB019 and placebo. Assuming a 0.5 correlation between Baseline IASI and Week 16 IASI, a common standard deviation (SD) of 9, and a 11% dropout rate, an enrollment of 16 subjects (leaving 14 after dropout) in the ANB019 treatment arm and 8 subjects (leaving 7 after dropout) will have at least 80% power to detect the overall treatment effect for a two sample t-test using a 2-sided significance level of 0.05, where the difference in the mean reduction form Baseline between one of the ANB019 groups and the placebo group is assumed to be 12.3 points. A placebo response is anticipated for this study sample and assumed to be an approximate 10% improvement from the Baseline in the IASI score. If the mean Baseline IASI score is 30, this represents a 3-point reduction in the score for the placebo group. The ANB019 group is assumed to achieve a mean reduction of 15.3 points, assuming the same Baseline mean score of 30.

9.3 POPULATIONS FOR ANALYSES

The analysis sets are defined in Table 6.

Table 6: Analysis Sets

Analysis Set	Description
ITT Analysis Set	The ITT analysis set will include all randomized subjects. In this analysis set, treatment will be assigned based upon the treatment arm to which subjects were randomized regardless of which treatment they receive.
Safety Analysis Set	The safety analysis set will include all randomized subjects who receive 1 dose of ANB019 or placebo. The safety analysis set will be used for all safety analyses. Subjects will be analyzed as treated.
Per Protocol Analysis Set	The per protocol analysis set will include all subjects in the ITT analysis set who do not have major protocol violations that would affect the evaluation of the primary efficacy endpoint.
PK Analysis Set	The PK analysis set will include all ANB019 treated subjects in the safety analysis set who have at least 1 quantifiable postdose PK sample available and who do not have events or protocol deviations or events with the potential to affect PK concentrations. The PK analysis set will be used for all PK analyses.

Abbreviations: ITT, intent-to-treat; PK, pharmacokinetic.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The statistical analysis will be performed using statistical analysis system (SAS®) Version 9.4 or higher. All details regarding the statistical analysis and the preparation of tables, listings, and figures will be described in the Statistical Analysis Plan (SAP) and approved by the Sponsor before database lock and any analysis is undertaken.

The default summary statistics for continuous variables include number of contributing observations, mean, SD, median, minimum, and maximum. For PK parameters, coefficient of variation (CV) and geometric mean will also be presented, as appropriate.

For categorical variables, the number and percentage (percentage of subjects in each category relative to the total number of subjects in the relevant analysis set or relative to the total number of subjects in the relevant analysis set with assessments available [where appropriate]) in each category will be the default summary presentation.

Unless otherwise specified, "Baseline" is defined as the last observed value of the parameter of interest prior to the first intake of study treatment (this includes unscheduled visits). For numerical variables, change from Baseline will be calculated as the difference between the value of interest and the corresponding Baseline value.

Unless otherwise specified, all formal statistical tests will be 2-sided at the 5% significance level. Point estimates of treatment differences will be accompanied with 2-sided 95% confidence intervals (CIs), where applicable.

In the case of normality assumption violations, appropriate nonparametric methods may be used for analysis.

All data will be presented in by-subject listings.

9.4.2 SUBJECT DISPOSITION

A tabular presentation of the subject disposition will be provided. It will include the number of subjects screened, randomized, treated, completed as well as the number of dropouts with reasons for discontinuation, and major protocol deviations or violations.

A listing will be presented to describe dates of screening, assigned treatment, screen failed with reason, completion or early withdrawal, and the reason for early discontinuation, if applicable, for each subject. A list of protocol deviations/violations will be identified and discussed with the Investigator/Sponsor in dry run to categorize as major or minor with decisions of exclusion from analysis sets prior to unblinding.

During the COVID-19 pandemic, protocol deviations related to COVID-19 will be documented and information on how they will be handled in the analyses will be detailed in the SAP.

9.4.3 BASELINE DESCRIPTIVE STATISTICS

Subject characteristics obtained at Baseline will be summarized for all subjects taking ANB019 or placebo.

Summaries will include descriptive statistics for continuous variables (sample size [n], mean, SD, median, minimum, and maximum) and for categorical variables (n, frequency, and percentage).

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) latest version and listed for all subjects.

9.4.4 CONCOMITANT MEDICATION

All medications will be coded using the World Health Organization (WHO) Drug Dictionary and Anatomical Therapeutic Chemical (ATC) system. Each medication will be classified as prior medication if it is stopped prior to the first dose of study treatment, or as concomitant medication if it is ongoing at the time of the first dose or is started after the first dose of study treatment. Prior, concomitant, and rescue medications will be summarized descriptively with a by-subject listing.

9.4.5 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT

The primary efficacy endpoint is the change from Baseline in IASI total score at Week 16.

A general linear mixed model repeated measures (MMRM) analysis will be used to estimate the least-squares means (LSM) and associated standard errors for the change from Baseline in IASI total score to Week 16. The model will include change from Baseline in IASI total score at Week 16 as the dependent variable, fixed effects for treatment arm, categorical time point, and the treatment by time point interaction, and the Baseline IASI total score as a covariate. An appropriate covariance structure will be described in the SAP prior to database lock. Should the initial model not converge, alternate covariance structures or inclusion of fewer postBaseline visits (eg, Week 8 and Week 16 only) will be considered. Full details will be described in the SAP. The difference between LSMs (ANB019 – placebo) at Week 16 will be presented along with the associated 95% CI and p-value.

Possible effect of any other covariates as well as investigation of variables through sub-group analysis may also be investigated. Details of such analyses will be described in the SAP. Details of specific alternative statistical methods will be documented in the SAP.

In addition, descriptive statistics (n, mean, SD, median, minimum, and maximum) will be presented by visit.

9.4.6 ANALYSIS OF THE SECONDARY EFFICACY ENDPOINTS

Following are the secondary efficacy endpoints:

- Percent change from Baseline in IASI total score at Week 16
- Proportion of subjects achieving IASI50 at Week 16
- Change and percent change from Baseline in IASI-E and IASI-S subscores at Week 16

9.4.6.1 CATEGORICAL ENDPOINTS

Frequency and percentages for each response Yes/No for categorical endpoints related to IASI will be presented separately by visit for both treatment arms. Subjects with missing scores at a given visit will be considered to have not met the criteria of interest (ie, nonresponse). Estimates of the difference between treatments (ANB019 – placebo) will be presented along with exact 95% CIs. Treatment arms will be compared using an exact test, as described in the SAP.

9.4.6.2 CONTINUOUS ENDPOINTS

Summary statistics will be provided for absolute scores of IASI, IASI-E, and IASI-S, , as well as for change from Baseline by visit and treatment arm. A by-subject listing will be presented for each assessment, by visit.

Summary statistics will be provided for TEWL scores as well as for change from Baseline by visit and treatment arm.

Analyses involving endpoints of percent change will be implemented descriptively.

9.4.7 ANALYSIS OF THE EXPLORATORY EFFICACY ENDPOINTS

Following are the exploratory efficacy endpoints:

- Change and percent change from Baseline in IASI total score at Weeks 1, 4, 8 and 12
- Proportion of subjects achieving IASI50 at Weeks 1, 4, 8, and 12
- Proportion of subjects achieving IASI75 at Weeks 1, 4, 8, 12, and 16
- Change and percent change from Baseline in IASI-E and IASI-S subscores at Weeks 1, 4, 8, and 12
- Change and percent change from Baseline in NASA at Weeks 1, 4, 8, 12, and 16 (for subjects with Netherton Syndrome only)
- Proportion of subjects achieving NASA50 at Weeks 1, 4, 8, 12, and 16 (for subjects with Netherton Syndrome only)
- Change and percent change from Baseline in IGA at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects with at least 2-point decrease in IGA at Weeks 1, 4, 8, 12, and 16
- Change and percent change from Baseline in worst and average pruritus NRS at Weeks 1, 4, 8, 12, and 16
- Change and percent change from Baseline in worst and average pain NRS at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects with at least 3-point decrease in worst pruritus NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pruritus NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pruritus NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pruritus NRS of at least 4
- Proportion of subjects with at least 3-point decrease in worst pain NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pain NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pain NRS at Weeks 1, 4, 8, 12, and 16 for subjects with a Baseline worst pain NRS of at least 4
- Change from Baseline in BSA at Weeks 1, 4, 8, 12, and 16
- Change from Baseline in DLQI and CDLQI scores at Weeks 1, 4, 8, 12, and 16
- Proportion of subjects in each response category for the PGI-S and PGI-C at Weeks 1, 4, 8, 12, and 16
- Change from Baseline in iQoL-32 score at Weeks 4, 8, 12, and 16
- Change from Baseline in TEWL at Weeks 4, 8, 12, and 16
- Proportion of subjects receiving rescue medication at Weeks 4, 8, 12, and 16
- Proportion of subjects achieving IASI50 from Week 20 through Week 40
- Proportion of subjects achieving IASI75 from Week 20 through Week 40
- Change and percent change from Baseline in IASI total score from Week 20 through Week 40
- Change and percent change from Baseline in IASI-E and IASI-S subscores from Week 20 through Week 40

- Change and percent change from Baseline in NASA from Week 20 through Week 40 (for subjects with Netherton Syndrome only)
- Proportion of subjects achieving NASA50 from Week 20 through Week 40 (for subjects with Netherton Syndrome only)
- Change and percent change from Baseline in IGA from Week 20 through Week 40
- Proportion of subjects achieving an IGA of clear (0) or almost clear (1) from Week 20 through Week 40
- Proportion of subjects with at least 2-point decrease in IGA from Week 20 through Week 40
- Change and percent change from Baseline in worst and average pruritus NRS from Week 20 through Week 40
- Proportion of subjects with at least 3-point decrease in worst pruritus NRS from Week 20 through Week 40 for subjects with a Baseline worst pruritus NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pruritus NRS from Week 20 through Week 40 for subjects with a Baseline worst pruritus NRS of at least 4
- Change and percent change from Baseline in worst and average pain NRS from Week 20 through Week 40
- Proportion of subjects with at least 3-point decrease in worst pain NRS from Week 20 through Week 40 for subjects with a Baseline worst pain NRS of at least 3
- Proportion of subjects with at least 4-point decrease in worst pain NRS from Week 20 through Week 40 for subjects with a Baseline worst pain NRS of at least 4
- Change from Baseline in BSA from Week 20 through Week 40
- Change from Baseline in iQoL-32 score from Week 20 through Week 40
- Change from Baseline in DLQI and CDLQI scores from Week 20 through Week 40
- Proportion of subjects in each response category for the PGI-S and PGI-C from Week 20 through Week 40
- Change from Baseline in TEWL from Week 20 through Week 40
- Proportion of subjects receiving rescue medication from Week 20 through Week 40

Methods for analyzing the above categorical and continuous efficacy endpoints will mirror the methods described in Section 9.4.6.1 and 9.4.6.2, respectively.

9.4.8 SAFETY ANALYSES

Following are the primary safety and tolerability endpoints:

- Assessment of AEs, SAEs, and AEs leading to withdrawal.
- Vital signs.
- 12-Lead ECG.
- Clinical safety laboratory tests (hematology, biochemistry, and urinalysis).

All safety analyses will be performed on the safety analysis set.

9.4.8.1 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A TEAE is defined as:

- A new event that occurs during or after first dose of study treatment or,
- Any event present at Baseline that worsens in either intensity or frequency after first dose of study treatment.

Adverse events will be coded using the MedDRA and only TEAEs will be summarized. Number of events and percentage will be tabulated by preferred term (PT) and system organ class (SOC). Multiple occurrences of an AE for a subject will only be counted once per SOC and PT. Percentages will be determined relative to the subjects in the safety analysis set for the given treatment arm.

If the intensity or seriousness of the AE changes, the overall intensity or seriousness will be the maximum intensity or seriousness of the multiple occurrences. The TEAEs, SAEs, TEAEs leading to treatment discontinuation, and TEAEs leading to withdrawal of subject will be tabulated for each treatment arm.

All AE data will be listed for each subject.

Summaries over SOC and PT of TEAEs, TEAEs leading to death, SAEs, and TEAEs that led to discontinuation from the study or study treatment will be presented by treatment. Summaries will also be presented by relatedness to the study treatment and the severity of the TEAE.

9.4.8.2 12-LEAD ELECTROCARDIOGRAM, VITAL SIGNS, AND CLINICAL SAFETY LABORATORY TESTS

Summaries and listings of data for vital signs and safety laboratory tests result (hematology, biochemistry, and urinalysis) will be presented. Appropriate descriptive statistics will be summarized for the observed value at each scheduled assessment and for the corresponding change from Baseline.

For hematology and biochemistry tests, listings of subject data will also flag up any abnormal or out-of-range values. Clinically significant changes in the laboratory test parameters will be summarized and listed. Hematology and biochemistry data will be reported in System International units.

Descriptive statistics will be used to present the safety outcomes including, weight, BMI, 12-Lead ECG, vital signs, and clinical laboratory test results.

Change from Baseline will also be summarized for vital signs, and clinical laboratory tests results.

All ECG data results (normal/abnormal) will be summarized using frequency and percentage, and parameter values will be summarized descriptively. Clinically significant abnormalities will be presented in by-subject listings.

9.4.9 PHARMACOKINETIC ANALYSES

Limited ANB019 PK parameter analysis will be evaluated by assessment of drug concentrations in serum. These drug concentrations will be listed and summarized for each sampling time point using appropriate descriptive statistics. The PK parameters will be summarized using appropriate descriptive statistics.

9.4.9.1 DERIVATION OF PHARMACOKINETIC PARAMETERS

Where possible, PK parameters will be derived using noncompartmental methods. The actual sampling times will be used in the PK parameter calculations. Further details of PK analysis, data handling, analysis procedures, and data reporting will be detailed in a separate analysis plan.

9.4.9.2 PHARMACOKINETIC CONCENTRATION DATA ANALYSIS

A subject listing of all concentration-time data following SC injections will be presented by subject and scheduled sample collection time.

Concentration data of ANB019 will be summarized by day and nominal time point using the number of observations, arithmetic mean, SD, CV, minimum, median, maximum, and geometric mean.

Graphs for mean concentration-time data following SC administration will be presented. Individual subject concentration-time plots will also be presented.

Mean trough concentrations-time data will be graphically displayed for samples collected at the visits specified in the SoA (see Section 1.3) to visually assess time to attainment of steady state. Time to steady state may also be explored by using inferential statistics, if deemed appropriate. Other presentations of data may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in a separate analysis plan.

9.4.9.3 PHARMACOKINETIC PARAMETER DATA ANALYSIS

Where possible, PK parameters will be summarized using number of observations, arithmetic mean, SD, CV, minimum, median, maximum, geometric mean, and geometric CV, with the exception of time to maximum observed concentration (T_{max}), which should be reported with n, minimum, median, and maximum only.

Graphs of parameters may be added at the discretion of the PK scientist, as appropriate, and will be described in detail in a separate analysis plan.

9.4.9.4 POPULATION PHARMACOKINETICS ANALYSIS

Pharmacokinetic data from the study may also be used for population PK and PK/response analyses. If done, a separate analysis plan will be prepared, and results will be reported separately from the Clinical Study Report (CSR).

9.4.10 IMMUNOGENICITY ANALYSES

Observed values for ADA levels/status will be listed by-subject and summarized with descriptive statistics based on the safety analysis set. If data permits, correlation will be analyzed between ADA levels, serum concentration, and safety and efficacy endpoints.

Frequency and percentage of ADA response will be presented and listed and correlated to safety and PK endpoints.

9.4.11 IMMUNOGLOBULIN E LEVEL ANALYSES

Observed values for IgE levels will be listed by-subject (for subjects with Netherton Syndrome only) and summarized with descriptive statistics based on the safety analysis set. If data permits, correlation will be analyzed between IgE levels, serum concentration, and safety and efficacy endpoints.

9.4.12 BIOMARKER ANALYSES

Tape strip and optional skin biopsy biomarkers (including but not limited to IL-36R and Th-17 cytokine) analysis will be performed by a third party designated by the Sponsor. A separate analysis plan will be created for the biomarker analyses.

9.4.13 PLANNED INTERIM ANALYSIS

Interim analyses (IA) may be performed during the treatment periods (placebo-controlled period and/or open-label extension period) for assessment of all primary and secondary efficacy endpoints, and evaluation of all safety data available.

The rationale for these analyses is to assist in making decisions for potential future development of this treatment. No adjustments to the current protocol are planned as a result of the interim analyses; therefore, overall alpha in the analyses of the primary analysis is expected to be maintained at 0.05, two-sided.

Full details of the interim analysis, including procedures for maintaining the study blind for key personnel and the confidentiality of the results will be described in the SAP.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

After reading the protocol, each Investigator will sign the protocol signature page and send a copy of the signed page to the Sponsor or representative. The study will not start at any study center at which the Investigator has not signed the protocol.

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

An ICF, and assent when required, describing in detail the study treatments, study procedures, and risks will be given to the subjects, and written documentation of informed consent is required prior to starting any study-related procedures. The following materials will be submitted to the IRB/EC with this protocol: subject self-reported questionnaires, ICF, IB, and other relevant documents (eg, advertisements).

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Each informed consent document must adhere to the ethical principles stated in the Declaration of Helsinki and will include the elements required by FDA regulations in 21 CFR Part 50, as well as the elements required by the ICH GCP guideline, and applicable federal and local regulatory requirements. The consent form will be IRB/EC -approved, and the subject will be asked to read and review the document. An assent is to be obtained from subjects who need to provide assent, as per local requirements, and their parent(s) or legal representative has to sign and date the ICF.

The Investigator or his/her representative will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent/assent document prior to any procedures being done specifically for the study.

Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent/assent document will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The medical record must include a statement that written informed consent was obtained before the subject was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF/assent.

Subjects must be re-consented to the most current version of the ICF(s)/assent(s) during their participation in the study. Subjects who are rescreened are required to sign a new ICF/assent.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study subjects, Investigator, the IND Sponsor, and regulatory authorities, as applicable. If the study is prematurely terminated or suspended, the Investigator will promptly inform study subjects and the IRB/EC and will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

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

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/EC and/or regulatory authorities.

10.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in a setting as private as possible. The Investigator must assure that the subjects' anonymity will be maintained and that subjects' identities are protected from unauthorized parties. On CRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The Investigator should keep a subject log relating codes with the names of subjects. The Investigator should maintain in strict confidence documents not for submission to the Sponsor (eg, subjects' written consent forms).

The study monitor, other authorized representatives of the Sponsor, and representatives of the IRB/EC, regulatory agencies, or pharmaceutical company supplying study treatment may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

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

Study subject research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the data management company responsible for data management, analysis, and reporting. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical study centers and by data

management research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. Authorized regulatory officials and Sponsor personnel (or their representatives) will be allowed full access to inspect and copy the records. All study investigational product, subject bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor. Subjects will only be identified by unique subject numbers on eCRFs. Every subject will be given a copy of each version of the ICF that he or she signs before and during the study. Each ICF may also include authorization allowing the institution, Investigator, and Sponsor to use and disclose personal health information in compliance with the Health Information Portability and Accountability Act (HIPAA).

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

With the subject's approval and approval by IRB/EC, de-identified biological samples will be stored at a certified, licensed central laboratory. During the conduct of the study, a subject may choose to withdraw consent to have biological specimens stored for future research. Once samples have been analyzed specimens will be destroyed. If no analyses have been completed within 5 years following EOS, samples will be destroyed.

10.1.5 MEDICAL MONITOR

Medical monitoring will be conducted to ensure the early recognition, identification and reporting of issues impacting on subjects' health and well-being throughout the trial. Details of medical monitoring with contact information of the Medical Monitors will be documented in a Medical Monitoring Plan.

10.1.6 SAFETY OVERSIGHT

No Data and Safety Monitoring Board is required as part of this study.

10.1.7 CLINICAL MONITORING

All aspects of the study will be monitored by the Sponsor or authorized representatives of the Sponsor according to GCP and Standard Operating Procedures (SOPs) for compliance with applicable government regulations, (ie, Informed Consent Regulations [US 21CFR, Part 50] and Institutional Review Board regulations [US 21CFR, Part 56.103]).

Access to all records, both during the study and after study completion, should be made available to the Sponsor at any time for review and audit to ensure the integrity of the data. The Investigator must notify Sponsor immediately if the responsible IRB/EC has been disqualified or if proceedings leading to disqualification have begun.

The Investigator must conduct the protocol in accordance with applicable GCP regulations and guidelines; applicable informed consent regulations (US 21CFR, Part 50); and in compliance with the Declaration of Helsinki. Every attempt must be made to follow the protocol and to obtain and record all data requested for each subject at the specified times. If data are not recorded per protocol, the reasons must be clearly documented on the eCRF/records.

Before study initiation, at a study center initiation visit or at a meeting with the Investigator(s), a representative from the Sponsor will review the protocol and study eCRFs with the Investigator(s) and their staff. During the study, the study monitor will visit the study center regularly to check the completeness of subject records, the accuracy of entries on the eCRFs, the adherence to the protocol

and to GCP, the progress of enrollment, and to ensure that consent is being sought and obtained in compliance with applicable regulations, and that the study drug is being stored, dispensed and accounted for according to specifications.

The Investigator and key study personnel must be available to assist the monitor during these visits. The Investigator must give the monitor access to relevant hospital or clinical records, to confirm their consistency with the eCRF entries. No information in these records about the identity of the subjects will leave the study center.

Monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the eCRFs will be performed according to the study-specific Monitoring Plan.

The Investigator must promptly complete the eCRFs after the subject's visit. The monitor is responsible for reviewing them and clarifying and resolving any data queries. A copy of the eCRFs will be retained by the Investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the IB, and any protocol amendments.

The Investigator must provide the Sponsor and the responsible IRB/EC with a study summary shortly after study completion, or as designated by the Sponsor.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

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

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

Following written SOPs, the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (eg, GLP, Good Manufacturing Practices [GMP]).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by IRB/EC and local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

All protocol-specified data will be recorded in site source documents. Study data will be entered within the clinical database eCRFs from the original source documents. Upon each subject's completion of the study, the Investigator is required to sign and affirm the data entered in the subject CRF along with a statement attesting that all pages of the subject's case report have been reviewed. All Investigator data attestation signatures will be made through the 21 CFR Part11 compliant EDC system. Signature stamps and "per signatures" are not acceptable.

It is the Sponsor's policy that study data be verifiable with the source data which necessitates access to all original recordings, laboratory reports, and other records for each subject. The Investigator must therefore agree to allow access to subjects' records, and source data must be made available for all

study data. Subjects (or their legal representatives) must also allow access to their medical records. Subjects will be informed of the importance of increased record access and permission granted by signature on the informed consent document prior to screening.

Checks will be performed to ensure quality, consistency, and completeness of the data. Instances of missing or uninterpretable data will be resolved with the Investigator or study coordinator. Data queries, documented within the clinical database, will be accessible to the research facility through the EDC system. Study center personnel will be responsible for providing resolutions to the data queries and for correcting the eCRFs, as appropriate.

The Investigator must keep written or electronic source documents for every subject participating in the clinical study. for the appropriate document retention period. The subject file that identifies the study in which the subject is participating must include the subject's available demographic and medical information including:

- Name
- Contact information
- Year of birth
- Sex
- Medical history
- Concomitant therapies/medication
- Study visit dates
- Performed examinations, evaluations, and clinical findings
- Investigational product administration
- AEs, SAEs, or pregnancy (as applicable)

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment must be included in the subject's source document (eg, laboratory value listings). All these documents must have at least the subject's study number, and the date of the evaluation.

The data recorded during the course of the study will be documented in the eCRF and/or the study-specific forms. Before or at study termination, all data must be forwarded to the Sponsor. The data will then be recorded, evaluated, and stored in anonymous or coded form in accordance with data-protection regulations.

Subjects will authorize the use of their protected health information during the informed consent process in accordance with the applicable privacy requirements. Subjects who deny permission to use and disclose protected health information will not be eligible to participate in the study.

The Investigator will ensure that the study documents forwarded to the Sponsor, and any other documents, contain no mention of subject names. Any amendments and corrections necessary will be undertaken in both the source documents and eCRFs (as appropriate), and countersigned by the Investigator, or documented designee, stating the date of the amendment/correction. Errors must remain legible and may not be deleted with correction aids. The Investigator must state his/her reason for the correction of any data. In the case of missing data/remarks, the entry spaces provided in the eCRF should be cancelled out so as to avoid unnecessary follow-up inquiries.

Electronic CRFs will be kept by the Sponsor or an authorized designee in a secured area. Clinical data will be recorded in a computer format for subsequent statistical analyses. Data files will be stored on electronic media with a final master data file kept by the Sponsor after descriptive and statistical analyses and reports have been generated and are complete.

It is the responsibility of the Investigator to ensure that the study center file is maintained in accordance with the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, Section 8 – Essential Documents for the Conduct of a Clinical Trial.

10.1.9.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study treatment. These documents should be retained for a longer period, however, if required by local regulations or as specified in the study agreement, whichever retention period is longer.

If the Investigator withdraws from the study (eg, relocation, retirement) all study-related records should be transferred to a mutually agreed upon designee. Notice of such transfer will be provided to the Sponsor in writing. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol or ICH GCP requirements. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly. Protocol deviations related to COVID-19 pandemic will be identified and documented accordingly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, Sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, Section 5.1.1
- 5.20 Noncompliance, Sections 5.20.1, and 5.20.2.

It is the responsibility of the Investigator to use continuous vigilance to identify and report deviations as soon as possible. All deviations must be addressed in study source documents, and applicable deviations must be sent to the reviewing IRB/EC per their policies. The Investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements. Further details about the handling of protocol deviations will be included in the Protocol Deviation Plan, Data Management Plan, Medical Monitoring Plan, blind data review documentation, and SAP.

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the Investigator (or a designee, appropriately trained professional designated by the Investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the Investigator or designee must contact the Medical Monitor and the Sponsor at the earliest possible time by telephone. This will allow an early joint decision regarding the subject's continuation in the study. This decision will be documented by the Investigator and the Medical Monitor. Please refer to Section 4.2 for allowable, as necessary, modifications to the protocol due to COVID-19 restrictions.

The monitor must ensure that a prompt action is taken to secure compliance. If a noncompliance that significantly affects or has the potential to significantly affect human subject protection or reliability of trial results is discovered, the CRO and the Sponsor should perform a root cause analysis and implement appropriate corrective and preventive actions.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations: It is understood by the Investigator that the information generated in this study will be used by the Sponsor in connection with the development of the product. To allow for the use of information derived from the study, it is understood that the Investigator is obliged to provide the Sponsor with complete test results, all study data, and access to all study records.

Any results of medical investigations with Sponsor's products and/or publication/lecture/manuscripts based thereon, shall be exchanged and discussed by the Investigator and Sponsor representative(s), 30 days before submission for publication or presentation. Due regard shall be given to Sponsor's legitimate interests for example, manuscript authorship, obtaining optimal patent protection, coordinating and maintaining the proprietary nature of submissions to health authorities, coordinating with other ongoing studies in the same field, and protecting confidential data and information. The Sponsor shall be furnished with a copy of any proposed publication. Comments shall be rendered without undue delay.

In cases of publications or presentations of material arising from multicenter clinical investigations, the Sponsor is to serve as coordinator and referee. Individual Investigators who are part of a multicenter investigation may not publish or present data that are considered common to a multicenter investigation without the consent of the other participating Investigators and the prior review of the Sponsor.

Results from investigations shall not be made available to any third party by the investigating team outside the publication procedure as outlined previously. The Sponsor will not quote from publications by Investigators in its scientific information and/or promotional material without full acknowledgment of the source (ie, author and reference).

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, financial interest, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this study. The Sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

10.2.1 ETHICS AND RESPONSIBILITY

This study must be conducted in compliance with the protocol, the ICH Guidance for Industry E6(R2) GCP: Consolidated Guidance, the Declaration of Helsinki, IRB/EC requirements, and all applicable national and local regulatory requirements. Investigators must submit all essential regulatory documentation, as required by local and national regulations (including approval of the protocol and ICF by a Health and Human Services [HHS]-registered IRB/EC) to the Sponsor before investigational product will be shipped to the respective study centers.

10.2.2 AMENDMENT POLICY

Only the Sponsor (or designee) may modify the protocol. Amendments must be approved by all applicable national and local committees including, but not limited to, the government regulatory

authorities and/or regional IRB/EC before implementation. The only exception is when an Investigator considers that a subject may be harmed, and immediate action is necessary. Under these circumstances, approval of the chairman of the IRB/EC, or an authorized designee, must be sought immediately. The Investigator should inform the Sponsor, and the full IRB/EC, no later than 5 working days after the emergency occurs. Protocol-specified safety reporting requirements must be adhered to, independent of any other variables.

10.2.3 INSURANCE

Sponsor will provide insurance in accordance with local guidelines and requirements for the subjects in this study. The terms of the insurance will be kept in the study files.

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12 APPENDICES

Appendix 1: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   a) Documented hysterectomy.
   b) Documented bilateral salpingectomy.
   c) Documented bilateral oophorectomy.
   Note: For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
   Note: Documentation can come from the study center personnel's review of the subject's medical records, medical examination, or medical history interview.
3. Postmenopausal female:
   a) A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range will be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   b) Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance:

Male subjects

Male subjects with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 5.1):

- Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.
- Agree to use a male condom plus partner use of a contraceptive method with a failure rate of < 1% per year when having penile-vaginal intercourse with a WOCBP who is not currently pregnant.

In addition, male subjects must refrain from donating sperm for the duration of the study and for 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment.
Male subjects 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 for the

duration of the study and for 220 days (which includes the duration of relevant exposure plus the duration of sperm cycle) after the last dose of study treatment.

Female subjects

Female subjects of childbearing potential are eligible to participate if they agree to use highly effective methods of contraception consistently and correctly as described in the table below and during the protocol-defined time frame in Section 5.1, and refrain from donating oocytes for assisted reproduction during this period.

Highly Effective Contraceptive Methods:

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral. • Intravaginal. • Transdermal.
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral. • Injectable.
Highly Effective Methods That Are User Independent [a]
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Implants inserted beneath the skin Bilateral tubal occlusion.
Vasectomized Partner *A vasectomized partner is a highly effective birth control 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 treatment. 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 subject.*
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 subjects participating in clinical studies.

Pregnancy Testing:

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test at screening and urine pregnancy test on Day 1 (prior to study treatment administration).

Additional pregnancy testing should be performed as mentioned in the SoA (see Section 1.3).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected. Positive urine pregnancy test result should be confirmed with serum test.

Collection of Pregnancy Information

Male subjects with partners who become pregnant

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

After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate pregnancy form and submit it to the pharmacovigilance unit within 24 hours of learning of the partner's pregnancy. 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 fetal status (presence or absence of anomalies) or indication for the procedure.

Any SAEs associated with the pregnancy in the male subject's partner should also be reported to the pharmacovigilance unit within 24 hours of the event using the back-up Paper Report Form.

Female Subjects who become pregnant

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the pharmacovigilance unit within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject 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 after the delivery date. Any termination of pregnancy will be reported, regardless of 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 will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor as described in Section 8.2.1.8. While the Investigator is not obligated to actively seek this information in former subjects, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will be withdrawn from the study.

Appendix 2: Pruritus and Pain Numeric Rating Scales

Worst Pruritus Numeric Rating Scale:

On scale from 0 ("no itch") to 10 ("worst imaginable itch"), how was your *WORST* itch in the past 24 hours? Please select one number.

Numeric Rating Scale
0 1 2 3 4 5 6 7 8 9 10
No itch ... Worst imaginable itch

Source: Phan 2012, Verweyen 2019
http://www.pruritussymposium.de/numericalratingscale.html

Worst Pain Numeric Rating Scale:

Select the number that best describes your *WORST* pain (with regards to your ichthyosis) during the past 24 hours? Please select one number.

Numeric Rating Scale
0 1 2 3 4 5 6 7 8 9 10
No pain ... Worst imaginable pain

Source: modified from Farrar 2001

Average Pruritus Numeric Rating Scale:

In the past 7 days, how intense was your itch in general?

Numeric Rating Scale
0 1 2 3 4 5 6 7 8 9 10
No itch ... Worst imaginable itch

PROMIS® Item Pool v1.0 – Itch-Severity – PIQSeverity05
7 May 2018

https://www.healthmeasures.net/index.php?option=com_instruments&view=measure&id=908&Itemid=992

Average Pain Numeric Rating Scale:

In the past 7 days, how would you rate your pain on average?

Numeric Rating Scale
0 1 2 3 4 5 6 7 8 9 10
No pain — Worst imaginable pain

PROMIS® Numeric Rating Scale v.1.0 – Pain Intensity 1a
5 October 2017

https://www.healthmeasures.net/index.php?option=com_instruments&view=measure&id=896&Itemid=992

Appendix 3: Ichthyosis Quality of Life- 32 Items

The following questions concern different periods of time. There are no right or wrong answers. Answer each as spontaneously as possible by ticking the proposed answer that seems closest to your opinion. If a question does not concern you, tick the corresponding box.

	In the past 4 weeks…	Tremendously (4)	A lot (3)	A little (2)	Not at all (1)	Not applicable (0)
1.	has your skin been red?	☐	☐	☐	☐	☐
2.	has your skin been sensitive or painful (tense, uncomfortable)?	☐	☐	☐	☐	☐
3.	have you had dry or thick skin, with a lot of scales (dead skin)?	☐	☐	☐	☐	☐
4.	has your skin been itchy?	☐	☐	☐	☐	☐
5.	has your skin hurt because of cracking?	☐	☐	☐	☐	☐
6.	because of your ichthyosis, have your eyes bothered you (dryness, pain, watering, impaired vision, redness)?	☐	☐	☐	☐	☐
7.	because of your ichthyosis, have your ears bothered you (earwax plug, impaired hearing, pain, itching)?	☐	☐	☐	☐	☐
8.	did your skin have trouble adapting to temperature and/or weather changes?	☐	☐	☐	☐	☐
9.	have you been bothered by the smell of your skin?	☐	☐	☐	☐	☐
10.	have you felt like your skin was unsightly because of your disease?	☐	☐	☐	☐	☐
11.	does the disease make you feel dirty?	☐	☐	☐	☐	☐
12.	have you felt uncomfortable performing certain everyday actions (such as writing, moving) because of the pains or stiffness caused by ichthyosis?	☐	☐	☐	☐	☐
13.	have you felt 'fatigue' in connection with your ichthyosis?	☐	☐	☐	☐	☐

14.	has your scalp bothered you (combing, hair care, pain, or itching)?	☐	☐	☐	☐	☐
15.	have you changed your vacation plans or the places you go because the planning required by your ichthyosis was too complicated?	☐	☐	☐	☐	☐
16.	have you felt that your ichthyosis was a handicap (aesthetic or physical), even if you do not consider yourself a handicapped person?	☐	☐	☐	☐	☐
17.	have you experienced mood swings because of ichthyosis?	☐	☐	☐	☐	☐
18.	Have you felt sad, discouraged or powerless in the face of your disease?	☐	☐	☐	☐	☐
19.	have you felt lonely or withdrawn because of the disease?	☐	☐	☐	☐	☐
20.	have you experienced a feeling of anger, being 'fed up', a sense of injustice because of your disease?	☐	☐	☐	☐	☐
21.	have you felt afraid of the future (treatments losing their effectiveness, worsening, difficulty applying the creams with age)?	☐	☐	☐	☐	☐
22.	have you felt afraid that the disease could restrain a romantic/sexual relationship?	☐	☐	☐	☐	☐
23.	have you had the unpleasant feeling of being stared at or avoided by others?	☐	☐	☐	☐	☐
24.	have you been afraid of being rejected or humiliated by others?	☐	☐	☐	☐	☐
25.	have you felt afraid that others find your skin oily, sticky or rough?	☐	☐	☐	☐	☐
26.	have you had bothersome side effects because of the medications?	☐	☐	☐	☐	☐
27.	has the disease hampered you in performing your work or going about your studies?	☐	☐	☐	☐	☐

28.	has your ichthyosis influenced the way you dress?	☐	☐	☐	☐	☐
29.	have you had a surplus of household chores because of your ichthyosis (skin flakes, oily clothes)?	☐	☐	☐	☐	☐
30.	have you found caring for your skin difficult and unpleasant?	☐	☐	☐	☐	☐
31.	has the care taken too much of your time each day?	☐	☐	☐	☐	☐
32.	has the ichthyosis caused you significant expenses or inconvenient administrative procedures?	☐	☐	☐	☐	☐

Appendix 4: Dermatology Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self-conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	☐ ☐	Not relevant ☐
	If "No," over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	 Not relevant ☐

Please check you have answered EVERY question. Thank you.

If two or more questions are left unanswered the questionnaire is not scored. If two or more response options are ticked, the response option with the highest score should be recorded. If there is a response between two tick boxes, the lower of the two score options should be recorded.

Appendix 5: Children's Dermatology Life Quality Index

The aim of this questionnaire is to measure how much your skin problem has affected you OVER THE LAST WEEK. Please tick ☑ one box for each question.

1.	Over the last week, how **itchy**, **"scratchy"**, **sore** or **painful** has your skin been?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
2.	Over the last week, how **embarrassed** or **self conscious**, **upset** or **sad** have you been because of your skin?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
3.	Over the last week, how much has your skin affected your **friendships**?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
4.	Over the last week, how much have you changed or worn **different** or **special clothes/shoes** because of your skin?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
5.	Over the last week, how much has your skin trouble affected **going out**, **playing**, or **doing hobbies**?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
6.	Over the last week, how much have you avoided **swimming** or **other sports** because of your skin trouble?		Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
7.	Last week, was it **school time?** ⇨	**If school time**: Over the last week, how much did your skin affect your **school work**?	Prevented school ☐ Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐
	OR		
	was it **vacation time?** ⇨	**If vacation time**: How much over the last week, has your skin problem interfered with your enjoyment of the **vacation**?	Very much ☐ Quite a lot ☐ Only a little ☐ Not at all ☐

8.	Over the last week, how much trouble have you had because of your skin with other people **calling you names**, **teasing**, **bullying**, **asking questions** or **avoiding you**?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
9.	Over the last week, how much has your **sleep** been affected by your skin problem?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been?	Very much Quite a lot Only a little Not at all	☐ ☐ ☐ ☐

Please check that you have answered EVERY question. Thank you.

Appendix 6: Patient-Global Impression of Severity

Overall, how would you rate the **severity** of your ichthyosis now?

1. ☐ Clear Skin
2. ☐ Mild
3. ☐ Moderate
4. ☐ Severe

Appendix 7: Patient-Global Impression of Change

Overall, how would you rate the change in severity of your ichthyosis compared with how it was before you started taking the medication in this study?

1. ☐ Very much better
2. ☐ Much better
3. ☐ A little better
4. ☐ No change
5. ☐ A little worse
6. ☐ Much worse
7. ☐ Very much worse

Appendix 8: Ichthyosis Area Severity Index

The IASI (Paller 2017, Malik 2019, Czarnowicki 2018) incorporates extent through the techniques used for assessment in the Eczema Area and Severity Index (EASI) and Psoriasis Area and Severity Index (PASI) scores for atopic dermatitis and psoriasis, respectively.

The steps for the IASI are as follows:

a) Determine mean **INTENSITY** of erythema and scaling separately within four body regions (A1 = head and neck; A2 = upper limbs; A3 = trunk; A4 = lower limbs) as seen on the day of the examination. The intensity of redness/erythema and scaling of the ichthyosis is assessed using a 5-point scale (can be integer or with .5):

0	**None**
1	**Mild**
2	**Moderate**
3	**Severe**
4	**Very Severe**

b) Determine what percentage of **AREA** within a body region is affected by ichthyosis (B1 = percentage within head and neck; B2 = percentage within upper limbs; B3 = percentage within trunk; B4 = percentage within lower limbs). The area affected by ichthyosis within a given body region is estimated as a percentage of the total area of that body region and is assigned a numerical value according to the degree of ichthyosis involvement as follows:

% involvement	**0**	**1-9%**	**10 - 29%**	**30 - 49%**	**50 - 69%**	**70 - 89%**	**90 - 100%**
Region score	**0**	**1**	**2**	**3**	**4**	**5**	**6**

c) Determine **TOTAL EXTENT** by using a multiplier that takes into account the percentage of the total body surface area represented by each body region (C1 = 0.1 for head and neck; C2 = 0.2 for upper limbs; C3 = 0.3 for trunk; C4 = 0.4 for lower limbs).

The **ISAI-E** is obtained by using the formula below:

IASI-E = A1 erythema x B1 x C1 + A2 erythema x B2 x C2 + A3 erythema x B3 x C3
+ A4 erythema x B4 x C4

The **ISAI-S** is obtained by using the formula below:

IASI-S = A1 scaling x B1 X C1 + A2 scaling x B2 x C2 + A3 scaling x B3 x C3 + A4 scaling x B4 x C4

The **IASI TOTAL SCORE** (max potential 48) = IASI-E (max potential = 24) + IASI-S (max potential = 24).

Appendix 9: Netherton Area and Severity Assessment

The NASA (Yan 2010) incorporates extent through the techniques used for assessment in EASI scores for atopic dermatitis. The NASA assigns proportionate BSA to the head and neck (10%), trunk (30%), upper extremities (20%), and lower extremities (40%). This is roughly consistent with the rule of 9. The area of involvement (affected by inflammation, not including dry skin) of each of the 4 body regions is represented by a 7-point numeric coded value (0-6) as shown in the following tabulation (the investigator is required to record the percentage of the area [0-100%], and it is suggested to record to the nearest 5%):

Region score	0	1	2	3	4	5	6
Area of involvement, %	No eruption	< 10	10 - 29	30 - 49	50 - 69	70 - 89	90 - 100

The head, trunk, upper limbs, and lower limbs are assessed separately for erythema (E), infiltration/papulation (I), lichenification (L), and scaling (S). The average degree of severity of each sign in each of the 4 body parts is assigned a score of 0 to 3 indicating no involvement (0) or mild (1), moderate (2), or severe (3) expression of the clinical sign. Half steps are allowed.

Further practical details to aid the assessment are as follows:

- The lower extremities region includes the buttocks.
- The trunk region includes the internal/medial axillae and groin.
- The head/neck region comprises the face and the anterior and posterior neck.
- The upper extremities region includes the hands and external axillae.

The definitions of the scoring signs of NASA are the following:

Erythema (E)	
0	None
1	Mild; faintly detectable erythema: very light pinpoint dots
2	Moderate; full red, clearly distinguishable
3	Severe; deep/dark red
Infiltration/papulation (I)	
0	None
1	Mild; barely perceptible elevation
2	Moderate; clearly perceptible elevation but not extensive
3	Severe; marked and extensive elevation
Lichenification (L)	
0	None
1	Mild; slight thickening of the skin discernible only by touch and with skin markings minimally exaggerated
2	Moderate; definite thickening of the skin with skin markings exaggerated so that they form a visible criss-cross pattern
3	Severe; thickened indurated skin with skin markings visibly portraying an exaggerated criss-cross pattern
Scaling (S)	
0	None
1	Mild
2	Moderate
3	Severe

The calculation of NASA score is performed as follows (where the area is defined on the 7-point ordinal scale):

Location	Scoring
Head/Neck	(E + I + L + S) x Area X 0.1
Trunk	(E + I + L + S) x Area X 0.3
Upper limbs	(E + I + L + S) x Area X 0.2
Lower limbs	(E + I + L + S) x Area X 0.4
NASA score equals:	**Sum of the above 4 body areas**

Appendix 10: Clinical Laboratory Tests

The tests detailed in Table 7 will be performed by the central laboratory. The time points are specified in the SoA (see Section 1.3).

Local laboratory tests will be allowed in the event that the central laboratory results will not be available immediately, and the Investigator needs to take an immediate decision for any safety concerns. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Urine pregnancy dipstick will be performed at the study center prior to study treatment administration.

Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.

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

Investigators must document their review of each laboratory safety report.

Table 7: Protocol-required Safety Laboratory Assessments by Central Laboratory

Laboratory Assessments	Parameters	
Hematology	Hemoglobin	Red blood cell (RBC) count
	Hematocrit	White Blood Cell (WBC) count with Differential:
	Packed cell volume (PCV)	Neutrophils
	Mean cell hemoglobin (MCH)	Lymphocytes
	Mean cell volume (MCV)	Monocytes
	Mean cell hemoglobin concentration (MCHC)	Eosinophils
	Platelet count	Basophils
Biochemistry	Alanine aminotransferase (ALT)	Creatinine
	Albumin	Gamma glutamyl transferase (GGT)
	Alkaline phosphatase (ALP)	Glucose
	Aspartate aminotransferase (AST)	Potassium
	Bicarbonate	Phosphate (Inorganic)
	Bilirubin (Total)	Protein (Total)
	Bilirubin (Direct-only if total is elevated)	Sodium
	Calcium	Blood urea nitrogen (urea)
	Chloride	Creatine kinase (CK)
	Uric acid	Triglycerides
	Lactate dehydrogenase	human C-reactive protein (hsCRP)
	Troponin	Total cholesterol (fractions)
Serum pregnancy	Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)	
Follicle stimulating hormone (FSH)	In women of nonchildbearing potential only (postmenopausal woman with at least 12 months of amenorrhea without an alternative medical cause)	

Laboratory Assessments	**Parameters**	
Urinalysis	Bilirubin	pH
	Blood	Protein
	Glucose	Specific gravity
	Ketones	Urobilinogen
	Leukocytes	
		Microscopy (At discretion of Investigator based on urinalysis results)
	Nitrites	
Viral serology	Antibodies to hepatitis B core antigens	
	Hepatitis B surface antigen	
	Hepatitis C antibody	
	Human immunodeficiency virus antibodies	
Tuberculosis (TB) screening	QuantiFERON-TB Gold® In-Tube, the third-generation test (If the test indeterminate it can be retested only once)	
NOTES: Please see SoA for laboratory tests time points. All blood samples must be drawn prior to administration of the study treatment, unless otherwise specified. The date and exact time of sample collection must be recorded.		