STUDY TITLE: A Pilot Study to Evaluate the Efficacy and Safety of Secukinumab in the Treatment of Patients with Ichthyoses

Sub-Study: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Period, Followed by an Open-Label Maintenance Dosing Period to Evaluate the Efficacy and Safety of Secukinumab in Patients with Ichthyoses

Principal Investigator:
Amy S. Paller, M.D.
Department of Dermatology
Northwestern University
676 N. St. Clair Street, Suite 1600
Chicago, IL 60611
Telephone: (312) 695-3721
Fax: (312) 503-5900
Email: apaller@northwestern.edu

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INVESTIGATOR'S AGREEMENT

With the co-PI, I have created and read the final version of the following protocol: A Pilot Study to Evaluate the Efficacy and Safety of Secukinumab in the Treatment of Patients with Ichthyoses; and Sub-Study: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Period, Followed by an Open-Label Maintenance Dosing Period to Evaluate the Efficacy and Safety of Secukinumab in Patients with Ichthyoses, dated 14 July 2018 and agree to abide by all provisions set forth therein.

I agree to comply with the current International Conference on Harmonisation Guideline for Good Clinical Practice relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on this study.

I have received and reviewed the Full Prescribing Information for secukinumab (issued June 2018).

I agree that the study is ethical.

I agree to conduct the study as outlined and in accordance with all applicable regulations guidelines.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

This document contains confidential information, which must not be disclosed to anyone other than the recipient study staff and members of the Institutional Review Board. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of all Principal Investigators.

_____ _____

Signature of Investigator Date

_____

Printed Name of Investigator

STUDY GLOSSARY

Abbreviation/Term	Definition/Explanation
AE	Adverse Event(s)
AIC	Akaike Information Criterion
ARCI	Autosomal Recessive Congenital Ichthyosis
CMP	Comprehensive Metabolic Panel
CBC	Complete Blood Count
CIE	Congenital ichthyosiform erythroderma
CIL	Coded Identifier List
DLQI	Dermatology Life Quality Index
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
EI	Epidermolytic ichthyosis
ECG	Electrocardiogram
FDA	Food and Drug Administration
FIRST	Foundation for Ichthyosis and Related Skin Types
HIV	Human Immunodeficiency Virus
IASI	Ichthyosis Area Severity Index
IASI-E	Erythema subscore of Ichthyosis Area Severity Index
IASI-S	Scaling subscore of Ichthyosis Area Severity Index
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-treat
IQoL-32	Ichthyosis Quality of Life- 32 items
LI	Lamellar ichthyosis
LOCF	Last-Observation Carried Forward
m-CISI	Modified congenital ichthyosis severity index
mITT	modified Intention-To-Treat
MMRM	Mixed-effect Model Repeated Measures
NRS	Numerical Rating Scale
NS	Netherton syndrome
PASI	Psoriasis Area Severity Index
SAE	Serious Adverse Event
s.c.	Subcutaneous
TEWL	Transepidermal water loss

PROTOCOL SYNOPSIS

Title: A Pilot Study to Evaluate the Efficacy and Safety of Secukinumab in the Treatment of Patients with Ichthyoses

Sub-Study: A Multicenter Study with a Randomized, Double-Blind, Placebo-Controlled Period, Followed by an Open-Label Maintenance Dosing Period to Evaluate the Efficacy and Safety of Secukinumab in Patients with Ichthyoses

Investigation Type: Drug

Study Type: Randomized Control Trial

Purpose and Rationale: The ichthyoses are a group of lifelong genetic disorders which share characteristics of generalized skin thickening, scaling and underlying cutaneous inflammation. The vast majority are orphan disorders and are associated with extremely poor quality of life related to social ostracism from altered appearance, associated itchiness and discomfort, and functional limitations from the skin disease. Among the most common of these orphan disorders are autosomal recessive congenital ichthyosis (ARCI), Netherton syndrome (NS) and epidermolytic ichthyosis (EI). Therapy is time-consuming for patients or parents and is supportive, focusing on clearance of the scaling. There are no therapies based on our growing understanding of what causes the disease. We have recently found marked elevations in interleukin-17A (IL-17A) and IL-17-related cytokines in the skin of individuals with ichthyosis, likely explaining their inflammation. Psoriasis, another inflammatory skin disorder with redness and scaling, has now been shown to result from IL-17 pathway activation and IL-17A inhibition is the most effective therapy known to treat psoriasis. We propose that IL-17-targeting therapeutics will safely suppress the inflammation and possibly the other features of ichthyosis, improving quality of life. We propose to treat adults with ARCI and at least moderate erythema with subcutaneously administered anti-IL-17 antibody (secukinumab) and to serially assess clinical response to this therapy and its safety.

Primary objective: To evaluate the efficacy and safety of secukinumab in the treatment of ichthyosis (as determined by reduction in Ichthyosis Area Severity Index (IASI) at week 16, and by monitoring for the occurrence of bacterial/fungal mucocutaneous infection at week 16)

Secondary objectives:

1. To evaluate reduction in other skin severity assessments
2. To evaluate improvement in quality of life assessments
3. To evaluate the reduction in skin and blood IL-17A expression as a function of clinical response.
4. To determine response biomarkers to secukinumab in treated patients.
5. To define the cellular and molecular immune profiles of patients with ichthyoses.

These clinical indices will be assessed as per the Schedule of Assessments flowchart (Appendix 1) and require minimal input or time commitment from the study participants, but are critical to analyze trends with time.

Safety Objectives: Assess the short term (16 weeks) and long term (32 and 52 weeks) safety profile of secukinumab 300 mg s.c. in subjects with ARCI, NS and EI by monitoring for adverse events and deleterious alterations in clinical examination or clinical laboratory results.

Study Design: After the screening period (21-28 days), the study begins with a double blind trial of placebo compared to secukinumab. Subjects will be stratified by disease subtype (ARCI-CIE, ARCI-LI, EI and NS) in blocks of 4 and randomized in a 1:1 ratio of one subject treated with secukinumab to one subject treated with placebo for 15 weeks as follows: Each subject will receive secukinumab or placebo at Baseline (Day 0), weeks 1, 2, 3, 4, and every 4 weeks thereafter (week 8, week 12) until 15 weeks have elapsed. At week 16 all subjects will receive 300mg secukinumab. At week 17, 18, and 19 subjects will receive either secukinumab (if previously on Placebo) or Placebo (if on secukinumab originally), followed by open-label secukinumab 300mg every 4 weeks starting on week 20 up to week 48. The final assessment will be the end of study visit (week 52).

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
						COW1*	OLW1**	OLW4**	OLW12**	OLW20**	OLW28**	OLW32**
	Screen (28 d-21 d of Day 0)	Baseline/ Day 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 48	Wk 52
Drug supplied	0	4 doses Due on week 0, 1,2,and 3	1	1	1	4***	1	2	2	2	1	6

*Crossover Week (COW): Crossover Week 1 dosing occurs in study visit. COW2-4 dosing occurs at subject home weekly.
**Open Label Week (OLW): Open label Weeks 1, 4, 12, 20, and 28 occurs in study visits. OLW8, 16, and 24 dosing occurs at subject home every 4 weeks.
*** Because dose on week 16 is 300mg secukinumab and no placebo will be given for any patient on that week, two prescriptions must be written to differentiate the crossover dose on week 17, 18, and 19.

Multi-Center: Yes

Number of Centers: 2

Blinding:

Observer-Blind	Yes
Subject-Blind	Yes
Double-Blind	Yes

Study Duration: The clinical portion of the study will include 1.5 years for patient recruitment and up to 52 weeks of treatment, bringing the total maximum clinical study duration to 2.5 years.

Test Medication: Secukinumab 300 mg s.c. (Cosentyx®)

Control Medication: Placebo s.c. (supplied by Novartis)

Study Population: 40 evaluable subjects

Subjects must be at least 18 years of age with a diagnosis of ARCI, EI or NS and must show at least moderate erythema. These subjects will primarily come from the east coast (around New York City) and Midwest (around Chicago), but will be open to any subjects who are able to comply with study requirements and meet criteria.

Inclusion Criteria

- Subject has provided informed consent
- Subjects are at least 18 years of age or older at the time of screening.
- Female subjects must not be pregnant or breast-feeding. Female subjects of child-bearing potential with a negative urine pregnancy test and using at least one form of contraception (abstinence allowed).
- Subjects must have a confirmed diagnosis of ARCI-LI, ARCI-CIE, EI or NS (either genotype or willingness to be genotyped)
- Subjects must be clinically judged to be immunocompetent.
- Subjects will have no allergy to secukinumab, latex, or components of the product..
- Subjects will have baseline laboratory testing (normal or non-significant CMP, CBC, HIV negative, hepatitis B, C negative, QuantiFERON®-TB gold negative).
- Subjects must have an erythema score of at least 18 on IASI and an IASI-E score of 12 (at least moderate severity of erythema) at baseline

Exclusion criteria

- Subjects who are unable to give informed consent or assent.
- Subjects without a confirmed diagnosis of ARCI, EI, or NS.
- Subjects who have a known allergy to secukinumab or to latex.
- Female subjects who are pregnant or who are considering becoming pregnant.
- Subjects who have prior biologic use targeting IL-17A/IL-17 receptor A or IL-12/IL-23 or who have prior use of TNF-alpha blockers.
- Subjects who have used a systemic retinoid or systemic anti-ichthyosis agent within 4 weeks prior to initiation.
- Subjects who have used topical retinoids or keratolytics within one week prior to initiation.
- Subjects who have used emollient on the area to be biopsied in the previous 24 hours
- Subjects who have a history or diagnosis of inflammatory bowel disease
- Subjects who are on any systemic immunosuppressive agent (i.e. cyclosporine)

Duration of Treatment: 40 ichthyosis-affected adults will be studied up to 52 weeks. The study will include an initial 16 weeks 1:1 placebo: secukinumab double-blind, randomized control phase, followed by a 4 week crossover period and 32 weeks open-label phase to assure long-term safety.

Each subject will receive secukinumab or placebo at Baseline (Day 0), Weeks 1, 2, 3, 4, and every 4 weeks on week 8 and week 12. Then at Week 16 all subjects will receive 300mg secukinumab. For Weeks 17, 18, and 19, subjects if on secukinumab originally will receive 3 weekly injections of placebo. For Weeks 17, 18, and 19 subjects if previously on placebo will receive 3 weekly injections of secukinumab. During the Open label, they will continue to receive injections every 4 weeks for 32 additional weeks (up to week 48) with 4 weeks followup.

Treatment randomization scheme:

Week 0 -15	Week 16	Week 17, 18, 19	Week 20 – 48 (OLW1-28)
Randomized according to table; blinded	Open label	Crossover; blinded	Open label
A	A	B	A
B	A	A	A

*A=secukinumab B=placebo

Efficacy Assessments

- IASI: Ichthyosis Area Severity Index and subscores (IASI-E, IASI-S)
- CISI: Congenital Ichthyosis Severity Index
- A modified CISI (m-CISI), a new global assessment tool (for validation but not secondary endpoint assessment)
- Bodemer Ichthyosis Score (clinical burden of disease)
- Yale Ichthyosis Severity Index
- DLQI: Dermatology Life Quality Index
- iQoL-32: Ichthyosis-specific Quality of Life, including emotional impact
- 5-D Pruritus Scale
- Itch NRS: Numerical Rating System for pruritus
- TEWL (transepidermal water loss): Functional assessment of barrier

Note the severity assessments will be performed in tandem but blindly and without conferring by two physicians (IASI, CISI, m-CISI, Bodemer, Yale) and the CISI and m-CISI as well by the subject, allowing inter-rater reliability assessment. By doing this assessment at screening and 3-4 weeks later at baseline for those subjects who have no significant change in intervention, we will be able as well to evaluate intra-rater (test-retest) reliability.

Safety Assessments

- Adverse events and serious adverse events monitoring: adverse events of special interest include infections, particularly occurrence of bacterial or fungal mucocutaneous infection
- Laboratory assessments (e.g., hematology, clinical chemistry, urine pregnancy)
- Vital signs, physical examination

Other Assessments

- Photography

- Skin biopsy (4.5 mm) for immunohistochemistry and mRNA expression (qRT-PCR) of 4 genes (IL-17A and three IL-17A induced genes for interpretation)
- Serum samples for cytokine analysis
- Skin swabs and scrapings to evaluate skin microbiome
- Tape strips to evaluate skin proteomics and lipidomics

Data Analysis
Statistical analysis of all clinical and translational studies will be performed by a statistician at the Icahn School of Medicine at Mount Sinai and .

The data from both centers that participate in this study will be combined for analyses. The primary analysis population will be based on a modified intention-to-treat (mITT) population, which is defined as all randomized patients who received at least one dose of the randomized treatment. Because the loading dose is given at baseline, this should effectively include all the randomized patients.

Efficacy and other data will be summarized. Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects. For more details, refer to Section 9.2. The primary efficacy variable is the IASI (composite) at Week 16. The primary safety variable is the occurrence of bacterial and fungal mucocutaneous infections by Week 16. Differences in change over time between treatment and placebo will be assessed using a mixed-effect model repeated measures. Outcomes for weeks 0 to 16 for all the subjects from phase 1 and the outcomes for weeks 16 to 52 for subjects randomized with secukinumab in both phases will be considered. For more details, refer to Section 9. Safety will be evaluated by tabulations of adverse events and will be presented with descriptive statistics at each visit for each treatment group. The statistical evaluations will be organized by Treatment Phase (Weeks 0-16 and 16-48), and Post-Treatment Phase (weeks 48-52), as appropriate. AEs will be coded using the CTCAE, Common Terminology Criteria for Adverse Events, V 4.03. The number and percentage of subjects experiencing an AE/SAE will be stratified by system organ class, or a preferred term, and severity of the adverse event, and recorded and tabulated overall by each sub-strata. For more details, refer to Section 9.

Key Words: Ichthyosis, secukinumab, IL-17, biologic, monoclonal antibody

1. BACKGROUND AND RATIONALE

1.1 Disease

The ichthyoses are a group of lifelong genetic disorders which share characteristics of skin thickening, scaling and underlying cutaneous inflammation. Other than ichthyosis vulgaris (commonly associated with atopic dermatitis) and recessive X-linked ichthyosis (1:1500 boys), the >20 subtypes of ichthyosis are rare (<1:100,000 individuals). Among these rare subtypes are 3 predominant forms: i) epidermolytic ichthyosis, resulting from a mutation in one of the genes encoding suprabasal keratins; ii) Netherton syndrome, resulting from mutations in SPINK5, leading to excessive epidermal protease activity; and iii) autosomal recessive congenital ichthyosis (ARCI). This last group usually first manifests at birth as a collodion baby (Figure. 1A), in which a shiny “collodion-like” membrane encases the neonate. Within the first month of life, this membrane skin peels, revealing during the subsequent months a generalized skin

appearance ranging from variable redness (erythema) underlying darker, plate-like scaling (lamellar ichthyosis or LI, Fig. 1B) to intense erythema with fine scaling (congenital ichthyosiform erythroderma or CIE, Figure. 1C). Biallelic mutations, largely in genes encoding epidermal lipoxygenases, ichthyin, transporter ABCA12, and transglutaminase 1, lead to the ARCI phenotype. All ichthyosis types share a defective protein and lipid barrier, which manifests functionally as increased transepidermal water loss and percutaneous absorption.

These forms of ichthyosis lead to life-long disfigurement due to the highly visible erythema and scaling. The quality of life of affected children and adults is poor, not only because of their appearance and social ostracism, but also because of the frequent associated itchiness (pruritus) and functional limitations related to the inflamed, often fissured skin and limited joint mobility related to skin tightness and pain. Affected individuals also have a markedly reduced ability to sweat, restricting sports and outdoor activities in warmer weather.

Therapy for the ichthyoses is supportive and time-consuming for patients. Most use long baths, emollients and agents that peel the thick scale, specifically keratolytics and topical retinoids. Oral retinoids are most effective at removing scale and skin thickening, but tend to increase skin and mucosal inflammation and have potential side effects (most commonly hypertriglyceridemia, teratogenicity, and with chronic use hyperostosis). The high risk of systemic absorption of topical steroids (and side effects of systemic steroids) restricts their use for the cutaneous inflammation associated with these lifelong diseases. There remains a huge unmet need for more effective and safer treatments, ideally therapy that improves both the scaling and the cutaneous inflammation with its associated pruritus and discomfort.

1.2 IL-17 in Ichthyosis

While the underlying gene mutations in most forms of ichthyosis are now well delineated, explaining at least in part the barrier defect, the molecular mechanism underlying the inflammation and the skin thickening and scaling, which is presumed to be compensatory, is poorly understood. To explore the immune basis for the erythroderma, we have recently surveyed the skin of individuals with ichthyosis of known underlying genotype, characterized clinically as ARCI, Netherton syndrome or epidermolytic ichthyosis. Interestingly, all studied forms of ichthyosis showed a biomarker pattern in skin of Th17 immune skewing (Fig. 2). In these patients, the mRNA expression levels of IL-17A and other IL-17 induced genes (such as S100A's, CXCL1, CCL20, and PI3/elafin) was dramatically increased in contrast to normal skin, and almost as high and sometimes higher than that seen in lesional skin from individuals with psoriasis, a common skin disorder in which the erythema and increased scaling are now recognized to be driven by Th17. In psoriasis, neutralization of IL-17 by specific IL-17A antagonism leads to 75% disease reversal ("PASI75") in 93% of treated subjects by 16 weeks (Thaci et al 2015) and is the most effective intervention to date for psoriasis (Nast et al 2015). Antagonism of this "polar" cytokine pathway seems to produce fewer adverse effects compared to broader immune antagonism (Thaci et al 2015); (Nast et al 2015); (Langley et al 2014).

1.3 Clinical Hypotheses

We hypothesize that Th17 activation plays an important role in the erythema and possibly the thickening and scaling of ichthyosis. Furthermore, we posit that IL-17-targeting therapeutics will safely suppress the inflammation and possibly the other features, improving quality of life. We propose to treat adults with

ARCI and at least moderate erythema with subcutaneously administered anti-IL-17 antibody (secukinumab) and serially assess clinical response to therapy and its safety. Throughout the course of the intervention, we will sample blood and skin biopsies, which will support our interpretation of result and allow us to perform more comprehensive mechanistic studies. We hypothesize that: a) intervention with anti-IL-17 antibody therapy (secukinumab) will improve ARCI severity as a function of IL-17 suppression; and b) the administration of secukinumab will be well-tolerated.

1.4 Rationale for Secukinumab Use

This proposal takes a commercially available medication that is indicated for a common IL-17-driven inflammatory skin disease (plaque psoriasis) and applies it to treat an orphan disease based on our innovative discovery that IL-17 levels correlate with severity in ichthyosis. Indeed, we have biopsied upper arm skin of >20 patients with the typical generalized features of ARCI, EI or Netherton syndrome and found dramatic increases in IL-17A and IL-17A-induced cutaneous markers in ichthyotic skin (Fig. 2A). Using a severity scoring system that rates overall score (Ichthyosis Area Severity Index or "IASI"), and subscores of erythema ("IASI-E") and scaling ("IASI-S") based on intensity (0-4+) and extent (see Approach), the composite IASI (total score) and IASI-E (Fig. 2B) are highly positively correlated with levels of IL-17A and related genes. IASI-E showed the highest correlations with IL-17A ($r=0.74$, $p<0.001$) and related genes, such as CXCL1 ($r=0.74$, $p<0.001$), PI3 ($r=0.71$, $p<0.001$), S100A8 ($r=0.71$, $p<0.001$), S100A9 ($r=0.69$, $p=0.001$), S100A12 ($r=0.68$, $p=0.001$), DEFB4B ($r=.56$, $p=.01$), and LCN2 ($r=0.5$, $p=0.02$). IASI-E is also correlated with transepidermal water loss (TEWL), a functional measure of barrier deficiency ($r=0.47$, $p=0.04$). IASI was also highly correlated with IL-17A ($r=0.51$, $p=0.01$), CXCL1, ($r=0.54$, $p=0.01$), PI3 ($r=0.69$ $p=0.001$), S100A8 ($r=0.67$, $p=0.001$), S100A9 ($r=0.62$, $p=0.002$), S100A12 ($r=0.58$, $p=0.006$), and LCN2, ($r=0.55$, $p=0.01$), as well as with IASI-E ($r=0.73$, $p<0.001$). In addition to IASI-E, TEWL showed significant correlations with IL-17 related markers (e.g., DEFB4 ($r=0.65$, $p=0.004$) and S100A12 ($r=0.62$, $p=0.009$)). Finally, K16, a marker of epidermal proliferation/hyperplasia also was highly positively correlated with IASI ($r=0.63$, $p=0.002$) and IASI-E ($r=0.56$, $p=0.008$). The biomarker alterations of ichthyosis cluster distinctly without subclustering by ichthyosis subtype; the clustering of ichthyosis closely resemble that of psoriasis and is distant from atopic dermatitis (Fig 2C).

Secukinumab is commercially available, administered subcutaneously (no oral formulation), and routinely administered at a dosage of 300 mg; in the first 4 weeks, a weekly dosage is standardly given, followed by monthly administration. This dosage for psoriasis was based on dose-finding studies and has been shown to be of superior efficacy to other biologics for psoriasis (Thaci JAAD 2015). Because the drug is already available commercially (for adults with psoriasis), significant clinical improvement in this first double-blind, randomized, controlled trial of a biologic for ichthyosis can translate into rapid availability for patients. However, the proposed work has several additional innovative dimensions. First, it will better define the relationship between increases in IL-17 and the cutaneous manifestations of ARCI. These insights will be critical to understanding whether IL-17 drives the erythema, pruritus and barrier defect (increased transepidermal water loss) of the ARCI group of ichthyoses. Our limited assessment in this proposal of the effect in skin of systemically-administered IL-17 antagonism will allow us to correlate clinical improvement with reduction in IL-17-induced products, which is key for interpreting our results. Complementary biomarker assessments (performed in Dr. Guttman's laboratory) will allow us to more comprehensively correlate biomarker changes with clinical response. The proposal also gives us the

opportunity to validate 3 severity scales for ichthyosis, which will hugely facilitate future research and its interpretation.

1.5 Rationale for Choice of Comparator

A placebo arm is necessary to obtain reliable efficacy and safety measurements.

1.6 Risks and Benefits of Secukinumab

Previous studies using secukinumab have found the following risks associated with treatment:

- ***Infections***: In clinical trials, a higher rate of infections was observed in subjects treated with secukinumab (31%) compared to placebo (18%). In trials for moderate-severe plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis, higher rates of common infections such as nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with candida (1.2% versus 0.3%) were observed with secukinumab compared with placebo. Given that individuals with ichthyosis have an increased risk of staphylococcal and fungal/candidal infections of the skin, there is a possibility that there may be more skin infections (beyond the known increase in mucosal candida infections), which will require vigilance.
- ***Inflammatory Bowel Disease:*** Both exacerbations and new onset cases of this condition occurred in patients treated with secukinumab in trials for plaque psoriasis, psoriatic arthritis and ankylosing spondylitis
- ***Hypersensitivity Reactions***: Anaphylaxis and cases of rash or urticaria occurred in secukinumab treated patients in clinical trials. The removable cap of the COSENTYX Sensoready pen and the COSENTYX prefilled syringe contains natural rubber latex which may cause an allergic reaction in latex-sensitive individuals (Novartis Full Prescribing Information 2016)
- Pharyngitis, fatigue and peripheral edema were noted more in subjects receiving 3 doses of secukinumab when compared to subjects receiving 1 or 2 doses (Papp et al 2013)
- Mild to moderate (Grade 1 or 2) neutropenia was noted in 12.1% of patients receiving regular s.c. injections of secukinumab. However, there were no AEs resulting from this neutropenia and no subjects were discontinued from treatment because of this (Rich et al 2013)
- IL-17A blockade does not appear to interfere with protective antibody levels after vaccinations such as the meningococcal vaccine or the influenza vaccine (Chioato et al 2012) when comparing antibody levels in individuals who had received secukinumab s.c. to those who did not.
- Currently, there is no evidence that secukinumab imparts an increased risk of malignancy

2. STUDY ENDPOINTS

2.1 Primary and Secondary Endpoints: Double Blind and Open-Label Phases

Primary Efficacy Endpoint: Reduction at week 16 in the Ichthyosis Area Severity Index (IASI)

Primary Safety Endpoint: Occurrence of bacterial or fungal mucocutaneous infection through week 16

Secondary Efficacy Endpoints (evaluated at weeks 8, 12, 16, 32 and 52):

- Reduction in the IASI-E at weeks 8,12 and 16 (double blind portion)
- Reduction in IASI-S at weeks 8,12 and 16 (double blind portion)
- Reduction in CISI (Congenital Ichthyosis Severity Index) for skin redness/ erythema at weeks 8,12 and 16 (double blind portion) by subject and by physician assessors
- Reduction in CISI (Congenital Ichthyosis Severity Index) for skin hyperkeratosis/ scaling at weeks 8,12 and 16 (double blind portion) by subject and by physician assessors
- Reduction in composite and erythema scores of Yale Ichthyosis Severity Index at weeks 8,12 and 16 (double blind portion)
- Reduction in the IASI-E at weeks 32 and 52 as compared to baseline (open label portion)
- Reduction in IASI-S at weeks 32 and 52 as compared to baseline (open label portion)
- Reduction in CISI (Congenital Ichthyosis Severity Index) for skin redness/ erythema by subject and by physician assessors at weeks 32 and 52 as compared to baseline (open label portion)
- Reduction in CISI (Congenital Ichthyosis Severity Index) for skin hyperkeratosis/ scaling by subject and by physician assessors at weeks 32 and 52 as compared to baseline (open label portion)
- Reduction in composite and erythema scores of Yale Ichthyosis Severity Index at weeks 32 and 52 as compared to baseline (open label portion)
- A 2-point reduction in CISI for redness/erythema at weeks 16, 32, and 52
- A 2-point reduction in CISI for scale/hyperkeratosis at weeks 16, 32, and 52
- A 50% reduction in IASI at weeks 16, 32 and 52
- A 50% reduction in IASI-E or IASI-S at weeks 16, 32 and 52
- A 75% reduction in composite and individual IASIs at weeks 16, 32 and 52
- 50% Reduction in the Bodemer score, which heavily weighs associated morbidity (contractures, ectropion, mouth tightness, fissures) in addition to erythema, scaling and thickening (Bodemer et al. 2011) at weeks 16, 32 and 52
- A 3-point reduction in patient-reported itch and pain (each on a 10 point scale) at weeks 16, 32 and 52
- Improvement in the 5-D itch score
- Reduction in transepidermal water loss (TEWL), a functional measure of barrier, at weeks 16, 32 and 52
- Reduction in the Dermatology Life Quality Index (DLQI) at weeks 16, 32 and 52
- Reduction in the iQoL-32 index at weeks 16, 32 and 52

Reduction in the above assessments stratified by subtype, severity, and gender
These clinical indices will be assessed as per the Schedule of Assessments flowchart (Appendix 1) and require minimal input or time commitment from the study participants, but are critical to analyze trends with time.

2.2 Secondary Safety Endpoints

- Assess the short term (16 weeks) and long term (32 and 52 weeks) safety profile of secukinumab 300 mg s.c. in subjects with ARCI, NS and EI by monitoring for adverse events, SAE's, infections, or deleterious alterations in vital signs, other components of the physical examination, and clinical laboratory results

2.3 Exploratory Endpoints

- To explore secukinumab exposure/response relationship
- To explore the effect of treatment with secukinumab on laboratory parameters of interest (i.e. IL-17)

- To explore change in mRNA expression levels of IL-17 and IL-17 induced genes as measured by gPCR
- To explore the alterations in bacterial and fungal microbiome before and after secukinumab therapy
- To explore self-administration of secukinumab
- To explore the relationship between disease severity and evidence for metabolic disease
- To explore the inter-rater reliability for severity assessments in the use for ichthyosis

2.4 Mechanistic Endpoints:

- Change in mRNA expression levels of IL17 and IL-17-induced genes as measured by qRT-PCR.

3. INVESTIGATIONAL PLAN

3.1 Study Design

To determine the efficacy and safety of IL-17 blockade with secukinumab on the clinical severity and morbidity of ARCI, NS and EI we propose to perform a 52 week study in 40 affected adults. The study will include an initial 16-week double-blind, randomized control phase in which 1:1 placebo: secukinumab is administered through week 12 with final evaluation of effects and safety at week 16. This double blind placebo controlled phase is followed by a 4 week crossover phase in which subjects who initiated placebo will be transitioned to active intervention, then a 32 week open-label phase. In this study, the "placebo," which does not restrict bathing or emollient use, is "standard of care", since many patients do not tolerate or use retinoids.

3.2 Study Centers

This study will be performed at two sites: the Department of Dermatology at Northwestern University Feinberg School of Medicine in Chicago and the Department of Dermatology at the Mt. Sinai School of Medicine in New York. Much of the clinical component will be performed and database housed at Northwestern University. Clinical research, statistical assessments, and biomarker tissue and molecular analyses of blood and skin will be performed at Mt. Sinai.

3.3 Study Organization

In this multiple Principal Investigator (PI) project, both PIs will be responsible for protocol development, consenting of subjects, performing skin biopsies, treatment and evaluation of subjects, review of adverse events, and reporting adverse events to the DSMB. Each site will have a project manager whose duties will include protocol development, grant administration for the individual study site, purchasing, case report form and source document design and development, and oversight of the project at the study site. The project manager at Northwestern will also be responsible for grant applications and yearly reports, and a liaison to the NIAMS grant administration (including the scientific officer, clinical coordinator, and program director) and the grant administrator at Mt. Sinai. An independent study safety monitor at each site will be contracted to perform review of consents, serious adverse events, and source verification on a quarterly basis throughout the study. This independent safety monitor in each institution will also assure that the data are correctly gathered, recorded, and put together concisely and accurately for prompt submission to the DSMB. The study safety monitors will work with the statistician to complete any unblinded statistical analysis for the DSMB reports. Thus, the audit function at each site is independent of the study research team. Data will be entered by study coordinators in a central REDCap database based at

Northwestern (DCC). The Dermatology Clinical Trials Unit currently manages both international and national multisite REDCap databases. A designated data manager will manage and document all clinical data in REDCap, assuring the correct insertion and transfer of data, and aligning the institutions. The statistician will meet with the DCC every two months to discuss the progress of the study. In addition, an Executive Committee consisting of the Principal Investigators, the project managers and the study statistician will meet every other week by phone or Skype to address issues and ensure that all activities are moving forward in a coordinated manner.

3.4 Study Duration

The clinical portion of the study will include 1.5 years for subject accrual to allow up to 52 weeks of treatment duration, including followup. Complete data analysis, including limited gene expression analysis in skin, and manuscript preparation will require another 6 months, bringing the total anticipated study duration to 3 years.

3.4.1 Screening Period

The duration of the screening period will be from three to four weeks (21-28 days). Screening will be used to assess subject eligibility. Screening for infection or immunodeficiency (QuantiFERON, hepatitis B and C, HIV testing), Complete Metabolic Panel and CBC will be assessed at screening.

3.4.2 Double blind- Phase 1 (Baseline visit -- Week 15)

The double blind phase is defined as baseline visit [day 0] through week 15. At the start of the double blind phase, 6 eligible subjects with ARCI-CIE, 6 with ARCI-LI, 6 with EI and 6 with NS will be stratified by disease subtype in random blocks of 4 then randomized in a 1:1 ratio to one of two treatment arms (secukinumab 300 mg s.c. or placebo) via a randomization list. Neither subjects nor assessors will know to which group the subject is assigned. Subjects will be deemed eligible as per inclusion/exclusion criteria outlined in section 4. Secukinumab (300 mg) or placebo (2 syringes each) will be administered subcutaneously at Weeks 0, 1, 2, 3, 4, 8, and 12. Weeks 0, 4, 8, and 12 will be administered by the subject (or a doctor) in clinic during study visits. Weeks 1, 2, and 3 will be administered by the subject (or a caregiver) at home. Subjects will be examined at in clinic study visits at Weeks 0, 4, 8, and 12.

3.4.3 Cross-Over Phase-Phase 2 (Week 16 -- Week 19)

At Week 16, all subjects will be eligible to crossover into the second phase of the study, in which all subjects will receive secukinumab (300 mg). In order to maintain the initial blind and complete 4 months of treatment, subjects who had been randomized to secukinumab in the double blind phase will continue to receive secukinumab at a dose of 300 mg s.c. at Week 16. However, they will also receive- three placebo injections at Weeks 17, 18, and 19, so that neither the subject nor the assessor knows if the subject had received secukinumab or placebo in the double blind phase. Subjects, who had been randomized to placebo in the double blind phase, will receive four doses of secukinumab at a dose of 300 mg s.c. at Week 16 to be administered on week 16, 17, 18, and 19 for loading. Weeks 16 will be administered by the subject (or a doctor) in clinic during study visits. Weeks 17, 18, and 19 will be administered by the subject (or a caregiver) at home. At Week 16, the primary endpoint will be assessed. Complete Metabolic Panel, and CBC at will be assessed at Week 16.

3.4.4 Open Label Phase- Phase 3 (Week 20-Week 52 or End of Study)

At Week 20, subjects who have crossed over into the open label phase will receive 300 mg s.c. secukinumab at Week 20, 24, 28, 32, 36, 40, 44, and 48. Subjects will be examined at in clinic study visits at Weeks 20, 24, 32, 40, and 48. Weeks 20, 24, 32, 40, and 48 will be administered by the subject (or a doctor) in clinic during study visits. Weeks 28, 36, and 44 will be administered by the subject (or a caregiver) at home. The final in clinic study visit will be at Week 52 four weeks after the last dose for follow-up. Complete Metabolic Panel and, CBC at will be assessed at Week 32. Complete Metabolic Panel and CBC at will be assessed at Week 52 or End of Study.

3.5 Biomarker, Microbiome and Metabolic Analyses

In order to identify the molecular and cellular immune profile of the ichthyoses at baseline and identify treatment response biomarkers, we include blood analyses at screening (if on a systemic retinoid), baseline, Week 8, Week 16, Week 32, and Week 52. We will in parallel obtain punch biopsies (4.5 mm in diameter) from the upper arm (with the exception of week 8 to minimize biopsies for patients). If a patient terminates early, blood and biopsy will be obtained at that time. Of note, these patients have total body involvement (e.g., there is no “uninvolved skin”). The upper arm was chosen to be able to wrap with self-adherent wrap (such as Coban), since tape does not stick to ichthyotic skin.

Blood analyses of IL-17, IL-22 and IL-13 cytokines (by Singulex),chemokines (by MSD-a Th1, Th2 panel, and O-linked proteomics will be performed at screening (if on a systemic retinoid), baseline, Week 8, Week 16 or Early Termination visit, Week 32, and Week 52. Gene expression studies (RT-PCR and gene arrays) and immunohistochemistry of biopsy samples will be conducted. The expression levels of markers in different immune pathways, including: Th1 (IFN-gamma, CXCL10, STAT1), Th17 (IL-17, IL23p19, IL23p40, CCL20, CXCL1), Th2 (IL-13, IL-31, IL-10, CCL17, CCL18, CCL22), T22/IL-22 cytokine and IL-17/IL-22 regulated S100s genes (S100A7, A8, A9), will be evaluated using RT-PCR. We will also assess for modulation of IL-17 regulated antimicrobial peptides (i.e LL-37, elafin, lipocalin 2, hBD2. DEFB4B, inflammatory markers (i.e MMP12, S100A12), and innate immune genes (IL1b, IL-8) by RT-PCR. Skin expression studies will be correlated by cytokine/chemokine expression in the blood, as assessed by O-linked proteomic assessment of blood. Serum and RNA (Pax RNA) will be banked and frozen for later assessments based on unanticipated findings.

Skin infiltration by T-cells, DCs, and neutrophils will be assessed by immunohistochemistry. The following markers will be used: CD3 and CD8 for T cells, langerin for Langerhans cells, CD11c for myeloid DCs, neutrophil elastase to identify neutrophils, and lipocalin 2 (LCN2). Epidermal thickness will also be assessed by immunohistochemistry. Finally, gene arrays, particularly the Affymetrix U133A Plus 2 gene array platform, will also be performed. This same platform is being used in our other studies involving AD, psoriasis and alopecia areata (AA) patients.

Tape strips (noninvasive) will be taken at baseline, Week 8, Week 16 or Early Termination visit, Week 32, and Week 52 for lipidomic and proteomic assessments of the outer epidermis from the dominant arm (opposite to the nondominant arm used for TEWL, microbiome and biopsy measurements) at a site the clinically appears similar. A buccal swab will be collected and banked for future pharmacogenomics studies. Given our goal of determining whether the increases in skin Th17 cytokines reflect only a response to the barrier defect (for their antimicrobial effect) vs. pathogenic in driving inflammation – as

well as to gauge alterations in microbial organisms as Th17 activation is suppressed by treatment, we will capture swabs for future microbiome assessment. Swabs for bacteria and fungi (including candida) will be obtained from the forehead, buttock and outer arm (near the biopsy site) at each visit, beginning at baseline. In flow studies of activated lymphocytes from patients with ichthyosis, we have recently found increases in blood levels of IL-22 cytokine, providing evidence of systemic activation of the IL-23/Th17 pathway. As a result, at baseline, Week 8, Week 16 or Early Termination visit, Week 32, and Week 52 we will also evaluate fasting lipids, glucose and CRP (as well as measure waist circumference) to assess for metabolic abnormalities.

4. SUBJECT ELIGIBILITY

Subjects should be at least 18 years of age with a clinical diagnosis of ARCI-LI, ARCI-CIE, EI or NS. The enrollment goal during the double-blind 16-week period will be at least 6 subjects each with ARCI-LI, ARCI-CIE, EI and NS (total 24), and an additional 16 patients, evenly divided into placebo and secukinumab groups and ideally (but less importantly) fairly evenly divided among ichthyosis subtypes (all comers will be included).

All screened subjects initially considered for this study will be documented. Pre-screening logs will be kept at each study site, and potential subjects will be contacted by the study site in closest proximity or with which the patient has previously been affiliated. If the subject is excluded from the study, reasons for exclusion will be documented in the pre-screening log.

4.1 Inclusion Criteria

Subjects are qualified for enrollment if they meet the following criteria:

- Subject has provided informed consent
- Subjects are at least 18 years of age or older at the time of screening.
- Female subjects must not be pregnant or breast-feeding.
- Female subjects of child-bearing potential with a negative urine pregnancy test and using at least one form of contraception (abstinence allowed).
- Subjects must have a confirmed diagnosis of ARCI-CIE, ARCI-LI, EI or NS (by genotype or willingness to be genotyped).
- Subjects must be clinically judged to be immunocompetent.
- Subjects will have no allergy to secukinumab, latex, or components of the product.
- Subjects will have baseline laboratory testing (normal or non-significant CMP and CBC, and negative for HIV, hepatitis B and C, QuantiFERON®-TB gold)
- Subjects must have an erythema score of at least 18 on IASI and an IASI-E score of 12 (at least moderate severity of erythema) at baseline.

4.2 Exclusion Criteria

Participants are ineligible for enrollment if they meet any of the following criteria:

- Subjects who are unable to give informed consent or assent.
- Subjects without a confirmed diagnosis of ARCI, EI, or NS.
- Subjects who have a known allergy to secukinumab or latex.
- Female subjects who are pregnant or who are considering becoming pregnant.

- Subjects who have prior biologic use targeting IL-17A/IL-17 receptor A or IL-12/IL-23 or who have prior use of TNF-alpha blockers.
- Subjects who have used a systemic retinoid or systemic anti-ichthyosis agent within 4 weeks prior to initiation.
- Subjects who have used topical retinoids or keratolytics within one week prior to initiation.
- Subjects who have used emollient on the area to be biopsied in the previous 24 hours
- Subjects who have a history or diagnosis of inflammatory bowel disease
- Subjects who are on any systemic immunosuppressive agent (i.e. cyclosporine)

5. TREATMENT PROCEDURES

5.1 Investigational Treatment

The following study treatments will be used:

- Investigational drug
    - Secukinumab is a fully human IgG1κ monoclonal antibody that potently binds to IL-17A and not to other sequences or structurally related cytokines. In vitro, it blocks the ability of IL-17A to bind to its receptor and signal.
    - Secukinumab 300 mg, liquid formation in single-use prefilled syringes (two 150 mg pre-filled syringes for total of 300 mg dose)
- Reference therapy
    - Placebo to 300 mg secukinumab s.c. for injection will be provided in matching pre-filled syringes that contain a mixture of inactive excipients, matching the composition of the secukinumab 300 mg dose.
    - Placebo to secukinumab 300 mg, liquid formation in single-use pre-filled syringes (two syringes for placebo dose)

5.2 Double-Blind Phase-with four stratified diagnoses/subtype of EI, CIE, LI, and NS

At the baseline visit [day 0] subjects will be randomized into one of two treatment arms in a ratio of 1:1. Each arm will have at least 3 ARCI-CIE subjects, 3 ARCI-LI subjects, 3 EI subjects, and 3 Netherton syndrome subjects; there will be an additional 8 subjects in each arm with randomization designed to ensure that there is even matching by ichthyosis subtype.

5.2.1 Double-Blind Phase: Secukinumab arm

Subjects who meet eligibility criteria and have a normal baseline physical examination and laboratory testing will be enrolled in the double-blind phase. Each subject will receive 300 mg s.c. of secukinumab (administered in two pre-filled syringes) at Baseline (Day 0), Weeks 1, 2, 3, 4, 8, and 12.
Injections will be performed at the site for the initial visit to train subjects in proper aseptic and subcutaneous injection technique (per Novartis Package Insert 2016). Subjects will use the second syringe to demonstrate the ability to inject themselves. After this baseline instruction and observation of injection technique, subjects will be able to self-administer weekly or monthly injections.
We will contact subjects weekly by phone/Skype/FaceTime (subject will designate which is best) on weeks 1-3 to answer questions, assess compliance with administration, including proper disinfection of subject's hands and administration site, as well as to ensure safety and return at week 4. Subjects will keep a diary of administration dates and times (as well as use of emollients and baths), which will be

reviewed at each appointment. All subjects who receive at least one dosage will be counted in the ITT population.
Week 16 will be the final endpoint for efficacy assessment of the double-blind phase.

5.2.2 Double-Blind Phase: Placebo arm
Subjects who meet eligibility criteria and have a normal baseline physical examination and laboratory testing will be enrolled in the double-blind phase. Each subject will receive 300 mg s.c. of placebo using two pre-filled syringes at Baseline (Day 0), Weeks 1, 2, 3, 4, 8 and 12.
Injections will be performed at the site for the initial visit to train subjects in proper subcutaneous injection technique. Subjects will use the second syringe to demonstrate the ability to inject themselves. After this baseline instruction and observation of injection technique, subjects will be able to self-administer weekly or monthly injections.
We will contact subjects weekly by phone/Skype/FaceTime (subject will designate which is best) on weeks 1-3 to answer questions, assess compliance with administration, including proper disinfection of patient's hands and administration site, and ensure safety and return at week 4. Subjects will keep a diary of administration dates and times (as well as use of emollients and baths), which will be reviewed at each appointment. All subjects who receive at least one dosage will be counted in the ITT population.
Week 16 will be the final endpoint for efficacy assessment of the double-blind phase and, at week 16, we will switch placebo-treated patients to secukinumab as all patients enter the open-label phase.

5.3 Crossover Phase
Because patients and investigators cannot know if they received secukinumab or placebo initially and the subjects who crossover need to receive weekly injections in the first month, all subjects will receive secukinumab 300mg at Week 16, followed by 3 weekly (week 17, 18, 19) administrations (2 syringes) of either placebo (if on secukinumab originally) or secukinumab (if previously on placebo).

5.3.1 Open Label Phase
All subjects will then continue with injections of secukinumab 300mg at week 20 and every 4 weeks thereafter through 48 weeks, with the final assessment at 52 weeks (Appendix 1). In person study visits will occur at Weeks 20, 24, 32, 40, 48, and 52.

5.4 Treatment Assignment, Randomization
At the baseline visit [day 0] eligible subjects will be randomized. A randomization number will be assigned to the subject which will be used to link the subject to a treatment arm.

Subject Identification
Subjects are numbered sequentially. Each subject will be assigned a unique number and will keep this number for the duration of the study. Subject numbers will not be reassigned or reused for any reason. Subjects should be identified only by their assigned identified code number. The investigator must maintain a subject master log linking the subject number to the subject's name. The investigator must follow all applicable privacy laws in order to protect a subject's privacy and confidentiality.

Randomization

A centralized randomization system will be implemented at NU. After fulfilling the enrollment criteria, study participants will be randomized on day 0/baseline to secukinumab or placebo in a 1:1 ratio. Randomization will be stratified by disease subtype (ARCI-CIE, ARCI-LI, EI and NS) in random blocks of 4. We will not stratify by center due to the small sample size.

Codes will be sent from the data coordinating center (NU) and distributed to a licensed pharmacist at each study site. Records of the code/seed used to generate the randomization will be kept. The pharmacy and data management personnel will keep clinical Investigators blind through the study until all clinical data has being collected and recorded. A revision and quality control assessment of the collected data will be carried out. Once all data quality issues are sorted out, the data analysis stage will start and investigators will be unblinded. Laboratory personnel conduction assays for the mechanistic studies will be blinded.

5.5 Treatment Blinding

Subjects, investigator/site staff, individuals performing the assessment will not know the treatment assignment for individual subjects. This will be assured via the following methods:

- The randomization schema will be kept confidential until implementation.
- During the trial, all study personnel will be kept blinded except for the pharmacist.
- In order for study participants to remain blinded, a research pharmacist at each site will be assigned the responsibility of an unblinded dispenser and give the test article to the investigator or designee for administration.
- The research pharmacist may not administer the test article to study subjects.
- Contact between the unblinded dispenser and study subjects would be kept to a minimum.
- The investigator, study coordinator, and any study participants other than the unblinded dispenser must not be allowed to know the test article assigned to any study subject and must not be allowed to see the randomization chart, test article containers, or treatment records.
- The packaging, labeling, schedule of administration and appearance of secukinumab and placebo will be identical.
-

Unblinding

In case of an emergency, when knowledge of the test article assignment is required for the medical management of an individual subject, the subject will be unblinded. The code should be broken only in the event of a medical emergency, when knowing the treatment assignment is absolutely necessary. The investigators will notify the DSMB within 24 hours after determining that it is necessary to unblind the treatment assignment. The DSMB can also decide to unblind. The investigator must also indicate in source documents and in the case report form that the blind was broken and provide the date, time, and reason for breaking the blind. Any AE or SAE associated with breaking the blind must be recorded and reported as specified in this protocol.

A clinical data manager will assemble all the subject data by groups (treatment versus placebo) and the data safety monitoring board or the biostatistician may request the unblinding of subject treatment assignment for analyzing safety data, upon the appearance of unequal adverse events.

5.6 Dispense and Use of Investigational Treatment

5.6.1 Dispensing the Investigational Treatment

Both study sites will be supplied by Novartis with secukinumab and placebo.

Secukinumab (AIN457) and placebo syringes from Novartis will be shipped to a designated, licensed pharmacist at the investigational pharmacy of each study site. The blinded study drug will be supplied as AIN457 150mg/1ml or placebo with 2 syringes per box. A removable tear-off label will be found on each box that identifies whether the box contains active drug or placebo. The Pharmacy will remove that label before the syringes are dispensed. Only the pharmacy staff and unblinded DCC staff will be aware whether the subject is receiving active drug or placebo for the blinded portion of the study. The subject and research physician will be blinded until completion of the study. The randomized code will be broken in the case of a Serious Adverse Event and unblinding for an individual subject may occur.

Open label drug will be provided for the open label portion of the study as Cosentyx ® 150mg/1ml with one syringe per box.

When delivery of a test medication is received at the investigational site, the Pharmacist, or a member of their staff specifically authorized and delegated by the Investigator, will check for accurate delivery and acknowledge receipt by signing (or initialing) and dating the required documentation and returning it as instructed. The date, time and condition of the package should also be documented at the time of receipt. A copy of this documentation will be retained for the Investigator file. Packaging, syringes, and medication appearance will be identical with the exception of the unique medication number on the label of the treatment packaging. This individual must store the treatment according to instructions specified on the packaging. An accurate record of the shipment and dispensing of these study agents will be kept by the respective pharmacist at each site. All unused study material will be returned by study subjects to the dispensary site.

5.6.2 Instructions for prescribing and taking study treatment

Throughout the study, treatment (either secukinumab or placebo) will be administered subcutaneously either by the subject or by an approved individual. Prefilled syringes will be provided by the site staff to the subject. Initial injections will be performed at the site to train subjects in proper subcutaneous injection technique. Study personnel will perform first injection with subject observing, then subjects will use the second syringe to demonstrate the ability to inject themselves. After this instruction and observation, subjects will be able to self-administer weekly or monthly injections.

We will contact subjects weekly by phone/Skype/FaceTime (subjects will designate which is best) on weeks 1-3 to answer questions, assure adherence to administration, and ensure safety and return at week 4. Subjects will keep a diary of administration dates and times, which will be reviewed at each appointment. All subjects who receive at least one dosage will be counted in the ITT population.

Injections are to be administered at a different anatomic location (such as dominant upper arm, thigh, or any quadrant of the abdomen except for 2 inches around the navel area) than the previous injection. Subjects may not self-inject upper outer arm but this area may be used by caregiver or healthcare provider for injection. Injections should not be given in areas where the skin is tender, bruised, erythematous, or indurated if possible.

5.6.3 Prohibited treatment

Subjects should not receive live vaccines during this study. They may not use any topical agent for the treatment of ichthyosis other than over the counter emollients. They may not be on any systemic agents for the treatment of ichthyosis. Subjects who experience skin infection requiring antibiotics during the study will not be discontinued from study drug or withdrawn from the study. The therapies they require will be noted by investigator on the case report form.

5.7 Subject Withdrawal/Discontinuation

Subjects will be evaluable if they complete all required assessments and visits through and including Week 16. If subjects fail to return for study visits, or become lost to follow up, subjects will be considered withdrawn. The PI and/or designated study staff will attempt to follow up with these individuals to discern the reason for their non-compliance. Similarly, if subjects choose to discontinue their participation in the study, study staff will attempt to contact the subject to determine their reason for discontinuation. The subject may also be discontinued by the PI for lack of efficacy.

Study treatment must be discontinued and the subject withdrawn if the investigator believes that continuation would compromise the subject's well-being. Treatment must be discontinued under the following circumstances:

- Occurrence of any AEs determined by the PI to prevent subject continuation with treatment
- Neutrophil count is less than 1000 or less than 1500 accompanied with fever
- Pregnancy
- Use of prohibited treatment
- Emergency unblinding

Subjects who discontinue study treatment will return at next scheduled visit to undergo an end of study visit and then be discontinued from the trial.

5.8 Study Completion and Post-study Treatment

Study participation is completed for the subject at the conclusion of their week 52 study visit. Adverse events that occur within 30 days of this visit must be documented and reported by the PI.

The study as a whole will be completed when all 40 randomized subjects have completed their 52 week treatment course as per the protocol and the complete data analysis, including limited gene expression analysis in skin has been performed.

Upon completion of their study participation, subjects will return to individual treatment, as determined by their regular treating physician.

6. VISIT SCHEDULE AND ASSESSMENTS

Appendix 1 lists the assessments and indicates with an "X" when the visits are performed. Subjects should be seen for all visits on the designated day or as close as possible to the original planned visit schedule (recommended visit windows are provided in Appendix 1). Special respect and effort for the baseline, week 8, week 16, week 32, and week 52 visits should be made.

In the event that subjects do not present for their study visit, study staff will document their attempts to contact these individuals.

6.1 Screening Visit

The screening visit is to be performed within 21-28 days of baseline visit [day 0]. After providing informed consent, subjects will be assessed for study eligibility at the screening visit (day -28 to day -21), which includes blood tests, infection screening, assessment of vital signs, assessment of skin severity scores, genotyping, photography, skin swabs and scrapings, and pregnancy test (if applicable).

6.1.1 Consent

Consent will be obtained by the study investigator or by approved study staff at the screening visit (visit 1) as indicated in Appendix 1. All participants will be given time to read the pre-approved consent forms, and ask any questions they may have. The consenter will emphasize that the study is voluntary. Consent forms will be kept in a designated study office in a locked drawer.

6.1.2 Medical and Medication History

A PI or designated study staff member will collect information regarding relevant medical history/current medical conditions excluding ARCI-LI, ARCI-CIE, NS or EI at every study visit as indicated in Appendix 1. All collected information will be documented. When possible, diagnoses (rather than symptoms) will be recorded. The history regarding ARCI-CIE, ARCI-LI, NS or EI will also be obtained including date of diagnosis and prior treatments. Medications including current medications and those taken within six months preceding enrollment will be recorded. Particular attention must be paid to any history of joint pain and IBD (history of diarrhea/constipation, bloody/painful stool, increased gas/bloating). Attention should also be paid to current treatments for ichthyosis (including bleach baths, any recent topical or systemic antibiotic use, skin care regimen and use of any topical or systemic medication).

6.1.3 Vital Signs and Height

Vital signs, including blood pressure, pulse, respiratory rate, temperature, weight will be collected at every study visit for all subjects as indicated in Appendix 1. Height will be recorded at the first visit as indicated in Appendix 1.

6.1.4 Complete Physical Examination

A complete physical examination will be performed by a physician or a qualified, licensed healthcare professional. A full examination will occur at the screening and baseline visits, as well as Weeks 16, 32, and 52; a full skin exam including measurement of TEWL will occur at visits 2-12 as indicated in Appendix 1. TEWL will be measured at upper outer arm near biopsy site and upper buttock. Waist circumference will be measured at baseline, weeks 16, 32, and 52. Additional exam components and maneuvers may be necessary depending on presenting symptomatology and are at the discretion of the PI or study staff. Results will be documented in the Medical History if present before signing the informed consent. If examination shows abnormal findings that meet criteria for an AE after the informed consent form has been signed and the subject has been enrolled with study drug initiation, these findings will be documented as such in the subject's file.

6.1.5 Genotyping & Genetic testing

At Northwestern University, all patients must either have known genotype available to the investigator or agree to be separately consented to undergo saliva-based DNA testing as offered at no cost by Dr. Keith Choate at Yale on a research basis; the investigator will know the mutated gene, but not the exact mutation and will be able to report this information to the subject. Consent will be per Lurie Children's Hospital Institutional Review Board-approved project STU00202786 under Dr. Paller. Sampling for Dr. Choate will be performed by saliva collection.

At Mt. Sinai, subjects' genotype information will be collected only if already available (i.e. subject can provide documentation).

In addition, buccal swabs will be collected at screening visit for banking (e.g., potential pharmacogenomics) at both sites.

6.1.6 Infectious Disease Testing

Testing for HIV, hepatitis B and C, and quantiferon gold testing for tuberculosis (TB) will be performed at the site of screening (Northwestern or Mt. Sinai) for all subjects at visit 1 as indicated in Appendix 1. A blood draw by a trained phlebotomist will be necessary for HIV, hepatitis B and C testing. Subjects must have negative testing for all infectious diseases tested to be randomized. If the subject has an indeterminate QuantiFERON®-TB gold, the test may be repeated once. If the result is positive or remains indeterminate, the subject may not participate in the study. Patients will be referred for any positive or indeterminate rest result to an appropriate physician for management. If the subject has been treated in the past for active or latent TB, they will be excluded from the study.

Should there be suspicion of an infectious complication (such a bacterial or fungal/candida infection), the area will be photographed for documentation, and infection confirmed by culture as appropriate.

6.1.7 Pregnancy Testing

All female study subjects will be tested for pregnancy at the baseline and end study visits as indicated in Appendix 1. Urine HCG testing will be obtained. Any woman with a confirmed positive pregnancy test during screening is not eligible for randomization and participation in this study.

6.1.8 Complete Blood Count and Clinical Chemistry Testing

A blood draw by a trained phlebotomist at visits 1, 2, 4, 6, 9, and 12 as indicated in Appendix 1. As per the schedule, hemoglobin, hematocrit, platelet count and white blood cell count with differential will be measured. Additionally, hepatic transaminases, blood urea nitrogen, creatinine, sodium, potassium, chloride, bicarbonate and glucose will be measured. At visits 2, 4, 6, 9, and 12 fasting lipids, glucose and C-reactive protein (CRP) will be measured.

6.1.9 Severity Evaluations (Appendices 2-6, 9, 10)

Severity evaluations will be performed at every study visit. Severity assessments will be performed by: Ichthyosis Area and Severity Index (IASI), Congenital Ichthyosis Severity Instrument (CISI), a modified CISI (m-CISI), the Bodemer scoring system (Bodemer et al 2011), and the Yale Ichthyosis Severity

Index. CISI is a validated score that assesses individual scores for erythema, scaling and alopecia, but is limited in that it is not a single score, includes a feature found in the minority of patients (alopecia) and includes non-uniform Likert scales (0-4+ or 0-5+). M-CISI eliminates the alopecia score, adopts a 5-point Likert for erythema and scaling, and averages the erythema and scaling scores for a single global assessment; it is a new scale that is being validated herein but will not be used for endpoints. IASI is a composite score based on the global CISI score that captures differences in severity in different body regions as a function of their body surface area and also standardizes the number of choices within the Likert scales for erythema and scaling. As in the EASI score for AD and the PASI score for psoriasis, IASI evaluates erythema and scaling as 0-4+ in severity at each of 4 locations: head and neck (including scalp); arms (including palms); legs (including soles); and trunk, prorated based on body surface area in these sites and the percentage of involvement in each of these sites (total possible score for each is 24 and total composite score is 48). To include a patient-reported severity score, we will use the Congenital Ichthyosis Severity Index, which has been validated for patient use (Kamalpour et al 2010), and the m-CISI. We will also pilot in the US a complex, non-validated burden of disease scoring system proposed by Bodemer et al in France, which heavily weighs associated morbidity (contractures, ectropion, mouth tightness, fissures) in addition to other measures of severity. All investigators/ sub-investigators will be trained based on photographs before study initiation to uniformly assign CISI, m-CISI, Bodemer, and IASI scores. A huge issue is the paucity of validated scores for ichthyosis severity. Our evaluations will be performed concurrently (but without conferring) by two investigators to allow inter-rater reliability, as well as at screening and again at baseline (at 3-4 weeks to minimize recall bias) for assessing test-retest reliability. As such, we hope to use this opportunity to assess reliability in these un-validated instruments. Patient-reported itch will be quantified on a 0-10 numerical rating scale (NRS) and by 5-D itch score (Elman et al 2009); a 1-10 score pain assessment is part of the Bodemer scale. The Yale Severity Index was recently developed and tested at a recent meeting of the Foundation for Ichthyosis and Related Skin Types. It includes a 0-4+ scale for erythema and for scaling, and provides pictorial representations for comparison, dividing scaling into lamellar and keratoderma scale scores. This study is the first time it will be applied to patients in an investigation.

6.1.10 TEWL and Tape Strips

TEWL will be performed at the biopsy and skin swab sites (nondominant arm and upper buttocks) to assess the skin barrier at visits 2-12. Tape strips will be also be obtained from ichthyosis subjects at baseline and weeks 8, 16, 32 and 52. Tape strips are purchased from CuDerm. Tape stripping will be performed on the dominant upper outer arm (same sites serially) using circular 2x2 or 3x3 cm transparent tape strips at lesional skin sites for each patient or unaffected skin site for controls. The tape strips will be used for detection of alterations of epidermal lipids and proteins in the outer stratum corneum of epidermis. We will be sending tape strips for proteomics and lipidomics analysis to the laboratories at Mt. Sinai/Rockefeller University medical center under the supervision of Dr. Emma Guttman and other designated laboratories. Alternating tape strips will be obtained for these analyses. Equal pressure will be applied to affected areas for 10 seconds. Up to 32 tape strips will be serially extracted on skin sites. Tape stripping is painless and, in our experience and that of the literature, has no adverse sequelae.

6.1.11 Photography (Appendix 11)

Photography will be done at study visits 1-12 as indicated in Appendix 1. Photos will be labeled using subject's study ID as well as subject visit number and date of the photo. Photos will be uploaded to a

secure, password-locked file per institutional Data security Plan and deleted from the camera memory card as soon as possible.

6.1.12 Skin Swabs and Scrapings for Microbiome (Appendix 12)

Skin swabs and scrapings will be collected at visits 1-12. Subjects will be instructed to not bathe, shower, or apply any topical product to the area that will be tested 24 hrs before the visit. Vigorous activity will also be minimized for several hours prior to swab. A questionnaire will be administered along with swabs. Swabs and scrapings will be collected from the nondominant side at upper outer arm (at biopsy and TEWL site), upper buttock, and scalp. Swabs will be labeled with the subject's study ID, study visit number, and visit date.

6.2 Data Collection at Subsequent Study Visits

Study visits including baseline visit [day 0] and visits 1-12 will occur at one of the study sites (Appendix 1)

6.2.1 Complete Skin Examination

A targeted exam (necessary components determined by PI or qualified study staff) will occur at visits 2-12 as indicated in Appendix 1. Additional exam components and maneuvers may be necessary depending on presenting symptomatology and are at the discretion of the PI or study staff. If exam findings occur after the informed consent form has been signed and meet the criteria for an AE, they will be documented as such in the subject's file.

6.2.2 Blood Samples for Biomarkers

A blood sample will be collected at screening (if on a systemic retinoid) and visits 2, 4, 6, 9, and 12 as indicated in Appendix 1 for biomarkers and RNA analysis. A blood draw by a licensed phlebotomist will be collected by study staff. Serum samples will be labeled with the subject's study ID, study visit number, and visit date and stored at -80^{o}C until analysis for cytokines is performed.

6.2.3 DLQI and iQoL-32 (Appendices 7,8)

DLQI and iQoL-32 will be obtained at the baseline visit, Visit 4 (week 8), visit 6 (week 16), visit 9 (week 32), and visit 12 (week 52) as indicated in Appendix 1. DLQI is the most commonly used and first dermatology-specific quality of life assessment tool (Basra et al 2008). It can be used to assess various dermatologic conditions and has been a reliable measure of quality of life (Finlay 1994). IqoL-32 is a validated, 32-item quality of life questionnaire that is specific to ichthyosis and has been shown to be highly correlated to clinical severity (Dreyfus et al 2013).

6.2.4 Skin Biopsy

Skin biopsies will be obtained from the non-dominant upper outer arm and will occur during the baseline visit, visit 6 (week 16), visit 9 (week 32), and visit 12 (week 52) as indicated in Appendix 1. Subjects will be instructed to not bathe, shower, or apply any topical product to the area that will be biopsied 24hrs before the visit. The area will be marked and then cleaned with an antiseptic wash. A 4.5 mm punch biopsy will be obtained and bisected for immunohistologic and qRT-PCR studies. The defect will be closed with a suture and dressed with a self-adherent compression dressing. The subject will be provided with instructions for wound care and suture removal.

6.2.5 Adverse Event Assessment
Adverse event assessments will occur at visits 1-12. Additionally, subjects will be queried by study coordinator about tolerability and any adverse events during the weekly phone or Skype sessions during weeks 1-3 of the study. Adverse event definitions are detailed in section 7.

6.3 Unscheduled Visits
In the event of a suspected AE that needs evaluation by the PI or needs laboratory testing or intervention, a subject may schedule a visit at any time. During their baseline visit, instructions will be provided detailing how to schedule a visit. These instructions will include a phone number and office address that subjects may use to contact the study group. During unscheduled visits, study treatment will not be administered and assessments will not be performed.

6.4 Sample Collection, Preparation, Labeling and Shipment

6.4.1 Sample collection
All samples will collected as specified in the schedule of events flowchart and as per SOP of the respective institution.

6.4.2 Labeling and de-identifying specimens
Specimens will not have patient identifiers attached to them (i.e., name, initials, DOB, or social security number). They will be labeled with a unique patient ID number or code and date of visit. The key to the code will be kept at each institution in a password —protected computer, to be accessed only by the clinical staff at each institution delegated to this task. Should a specimen be transported to Mount Sinai Medical Center with any patient identifiers, the specimen will be returned to Northwestern for proper labeling.

6.4.3 Transporting specimens to Mount Sinai Medical Center
All specimens will be transported to Mt. Sinai either by hand by a member of the investigative staff (if acquired at Mt. Sinai) or by competent courier (eg. Fedex) for the frozen skin and blood samples. Biobanked serum and PAX RNA samples, swabs for microbiome and a buccal swab for future pharmacogenomics will be retained in the Paller lab. The shipment will be traceable and that the chain of custody will be documented. The specimens will be delivered to a competent member of the study team, who will assure that the specimens have been properly de-identified and stored/transported in the proper environment (see above).

6.4.4 Specimen management

Specimens will be logged into a password protected electronic database by a qualified member of the research team. Samples will stored at the storage facility for a period of at least 5 years following the date the analysis is complete and used solely for objectives outlined in this study. After this date, residual sera will be destroyed. Patient confidentiality will be maintained. Results of all experiments will be reviewed by one of the PIs and the source of the data will be verified. Regular meetings of the specimen/data analysis team will occur. Regular study monitoring will also occur by qualified members of the research

team. The samples will be retained for 5 years from the end of the clinical completion of the study. In addition, samples can be destroyed at any time at the request of the subject.

7. SAFETY DATA COLLECTION, RECORDING AND REPORTING

7.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence experienced by a subject after completing written informed consent to participate in a clinical study. AEs may not be causally or temporally associated with the investigational product or procedure. Lack of drug effect is not considered an AE because the purpose of the study is to establish drug effect.

All AEs and SAEs will be recorded and reported from the time the subject signs the informed consent form to 4 weeks after administration of the last dose of test article. Subjects will be instructed to report AEs and SAEs during this time period. The investigators will follow up on all AEs and SAEs until the events have subsided, returned to baseline, or in case of permanent impairment, until the condition stabilizes.

Aggregated AEs will be evaluated monthly by the PI/research teams. Safety data will be reviewed by the investigators, study teams, biostatisticians and a monitor unrelated to the study approximately every 3 months, depending on the number of subjects enrolled. A DSMB will be organized to assess safety and overall risk to benefit ratio throughout the study. The DSMB will meet via phone conference quarterly or as deemed necessary by the PIs. The first DSMB meeting via a phone conference will be assembled after the first 3 months (or 8 patients, whichever is first) are enrolled to assure that the study is proceeding according to expectations and no changes in the protocol and consent are needed. An independent safety monitor in each institution will assure that the data is correctly gathered, recorded, and assembled concisely and accurately for DSMB review.

Most notable side effects per secukinumab Full Prescribing Information include increased risk of infection (including but not limited to nasopharyngitis, upper respiratory tract infection, and mucocutaneous infections with candida), exacerbations and new cases of inflammatory bowel disease, and hypersensitivity reactions. Adverse reactions reported by greater than 1% of subjects also include diarrhea, rhinitis, oral herpes, pharyngitis, urticaria, and rhinorrhea. Adverse reactions reported by less than 1% of subjects include sinusitis, tinea pedis, conjunctivitis, tonsillitis, oral candidiasis, impetigo, otitis media, otitis externa, increased liver transaminases, and neutropenia. There is an increased prevalence of staphylococcal and fungal cutaneous infections in ichthyosis, and patients respond normally to traditional anti-bacterial and anti-fungal agents when detected. Investigators will be vigiliant to the possibility that patients with ichthyosis will experience an increased incidence of these infections; if discovered, mucocutaneous infection will be treated with standard measures.

7.2 Unblinding and Followup of Subjects with Adverse Events

If a subject develops an adverse event that requires early termination, then we will document whether they were receiving secukinumab or placebo.

If subjects are experiencing unresolved adverse events at the time of study completion or early termination, then the investigator will schedule a follow-up visit to determine the outcome of the adverse event.

7.3 Serious adverse events

7.3.1. Definition of SAE

A serious adverse event (SAE) is any adverse event which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to indication under study and has not worsened since signing the informed consent
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - social reasons and respite care in the absence of any deterioration in the subject's general condition
- is medically significant, i.e., defined as an event that jeopardizes the subject or may require medical or surgical intervention

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk ofdeath at the time of the reaction; it does not refer to a reaction that hypothetically might havecaused death if more severe or ongoing.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above.
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All AEs (serious and non-serious) are captured on the case report form; SAEs also require individual reporting to DSMB and to Novartis Medical Affairs as per Section 7.2.2.

7.3.2. SAE Reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit, must be reported to the DSMB within 24 hours of learning of its occurrence. SAE must also be reported to Novartis by the DSMB within 15 days per federal prompt reporting requirements. Any SAEs experienced after the 30-day period should be reported to DSMB if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted to the DSMB within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded on the paper Serious Adverse Event Report Form. The investigator must assess the relationship of each SAE to study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours after awareness of the SAE to the DSMB. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the subject's source documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Full Prescribing Information, (new occurrence) and is thought to be related to the study treatment, the DSMB may urgently require further information from the investigator. An Investigator Notification (IN) may need to be issued to inform investigators involved in any study with the same study treatment that this SAE has been reported

Deaths or any serious adverse events will be reported to the DSMB and Novartis within 24 hours of becoming aware of the event. This information will be communicated by the PI via email. The DSMB will confirm receipt by email. All serious adverse events will be reported to the IRB of each institution according to their policies, and these events will also be reported by the DSMB and Novartis. Non-serious adverse events will be reported to each Institution's IRB per their IRB's policies. SAEs will be reported to PI immediately, and if the number of subjects experiencing AEs exceeds the pre-determined threshold, a meeting will be called to evaluate and determine if an early termination is needed.

7.4. Pregnancy Reporting

To ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported the DSMB within 24 hours of learning of its occurrence, and to Novartis Medical Affairs within 15 days. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital

abnormalities, or maternal and/or newborn complications. This includes both cases of pregnancy with paternal or maternal exposure to investigational products.

Pregnancy should be recorded on the Clinical Trial Pregnancy Form and be reported by the investigator/qualified site staff to DSMB. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy must be reported on the SAE Report Form.

8. DATA REVIEW AND DATABASE MANAGEMENT

In this multicenter project, both PIs (or their designee) will be responsible for protocol development, consenting of subjects, performing skin biopsies, treatment and evaluation of subjects, review of adverse events, and reporting adverse events to the DSMB. Each site will have a project manager whose duties will include protocol development, grant administration for the individual study site, purchasing, case report form and source document design and development, and oversight of the project at the study site. An independent study safety monitor at each site will be contracted to perform review of consents, serious adverse events, and source verification on a quarterly basis throughout the study. This independent safety monitor in each institution will also assure that the data are correctly gathered, recorded, and put together concisely and accurately for prompt submission to the DCC. Thus, the audit function at each site is independent of the study research team. Data will be entered by study coordinators in a central REDCap database based at Northwestern. The Dermatology Clinical Trials Unit currently manages both international and national multisite REDCap databases. A designated data manager will manage and document all clinical data in REDCap, assuring the correct insertion and transfer of data, and aligning the institutions. The statistician will meet with the DCC every two months to discuss the progress of the study. In addition, an Executive Committee consisting of the Principal Investigators, the project managers and the study statistician will meet every other week by phone or Skype to address issues and ensure that all activities are moving forward in a coordinated manner. The DSMB will assess safety and overall risk to benefit ratio throughout the study. The DSMB will meet every 3 months to review aggregate adverse events, with additional meetings and conference calls if deemed necessary by the PIs. The first meeting via a phone conference will be assembled after the first 3 subjects are enrolled, in order to assure that the study is proceeding according to expectations and no changes in the protocol or consent are needed.

8.1. Site Monitoring

The Project Manager at Mt. Sinai will remotely monitor the Northwestern site, and the Project Manager at Northwestern will monitor the Mt. Sinai site. Sites will also be monitored internally by the Data Coordinating Center and remotely by the Data Safety Monitoring Board.

8.2. Data Collection

Demographics, medical information, and data points will be recorded. Once collected by the study staff, data for each subject will be transferred to a secure REDCap database.

8.3 Data Disclosure and Subject Confidentiality

Each subject will be given a unique identifier code. The subject's name and code will be maintained on a password protected Coded Identifier List (CIL), on a password protected computer, in a secured building.

An additional spreadsheet with the unique identifier codes will be maintained and used for data collection. Only authorized study staff will have access to the spreadsheets.

Subject medical information obtained as a result of this study is considered confidential and disclosure to third parties other than the principal investigators and the study team is prohibited. Data generated as a result of this study will be available for inspection on request by the Institutional Review Board (IRB). Subjects' personal information collected from medical records will be maintained on the CIL. An additional spreadsheet will be maintained with only the subjects' unique codes. These spreadsheets will be maintained on password-protected computers, in password protected network folders per institutional Data Security Plan.

9. DATA ANALYSIS

Statistical analysis of all clinical and translational studies will be performed by statistician at the Icahn School of Medicine at Mount Sinai and Northwestern University. Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects.

9.1. Analysis Sets

Definition of Trial Analysis Sets: All subjects who provide informed consent and are registered in the trial will be accounted for in the clinical trial report. The inclusion/exclusion of subjects and/or subject data from the trial analysis sets will be documented in the statistical analysis plan before breaking the randomization code.

'Modified Intention-to-Treat' Analysis Set: The primary analysis population will be based on a modified intention-to-treat (mITT) population, which is defined as all randomized patients who received at least one dose of the randomized treatment. Because the loading dose is given at baseline, this should effectively include all the randomized patients.

9.2. Subject Demographics and Other Baseline Characteristics

Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects. Demographics include age, sex, race, ethnicity, and skin type. Other baseline characteristics include height, weight, and vital signs, concurrent diagnoses (from medical history and indications for concomitant medication), concomitant medications, and previous treatments.

9.3. Efficacy Analyses:

All data will be analyzed after the 16-week double blinded portion of the study is completed. However, all patients and blinded study personnel will remain shielded from any information regarding the data after these analyses until the conclusion of the study.

Analysis of primary efficacy endpoint

The primary efficacy endpoint is the change from baseline to week 16 in the composite IASI score. Differences in change over time in the composite IASI score between treatment and placebo will be assessed using a mixed-effect model. The model will include treatment and treatment-by visit interaction as fixed effects and study subjects as random effects. Orthogonal contrasts will be used to test differences in the treatment effect at the different time points. This model produces unbiased treatment effect, even if

some subjects have missing values (provided that the missing data is missing at random). Besides the change in the composite IASI score, final results will be presented as percent changes from baseline, calculated from the least square means of the model above (Vickers et al, 2001).

Analysis of primary safety endpoint

Safety analyses will be presented rates of bacterial or fungal mucocutaneous infection in each treatment group from baseline through week 16. The rate of infections will be compared using poisson regression. The proportion of subjects experiencing bacterial or fungal mucocutaneous infection during the study period in each treatment group will also be reported and compared using a Fisher exact test.

Analysis of secondary efficacy endpoint

We anticipate that, given the small sample size, a formal subgroup analysis (for ARCI-LI vs ARCI-CIE vs. EI vs. NS) will not be possible. However, we will report means and 95% confidence interval to descriptively compare the performance of the treatment across the four subgroups.

To compare secukinumab to placebo according to the proportion of patients who achieve IASI50/IASI75 at week 16, a Fisher´s exact test for contingency tables analysis will be used. The same approach will be used for all other binary outcomes, including a 2-point reduction in CISI, 50% (or 75%) reduction in IASI-E, EASI-S, a 3-point reduction in patient-reported itch or pain (each on a 10 point scale); and a 50% reduction in TEWL.

Mechanistic Endpoints: mRNA expression values will be normalized to housekeeping gene hARP and log2-transformed for analysis. Measurements under the limit of detections will be imputed as 20% of the minimum value observed for that gene. Similar to the IASI score, qRT-PCR expression data was modeled using a mixed effect models.

9.4 Safety Variables

Safety will be evaluated by tabulations of adverse events and will be presented with descriptive statistics at each visit for each treatment group. The statistical evaluations will be organized by Treatment Phase (Weeks 0-16) and Crossover/Open-label phase (16-52). The number and percentage of subjects experiencing an AE/SAE will be stratified by system organ class, or a preferred term, and severity of the adverse event, and recorded and tabulated overall by each sub-strata. Each subject will be counted only once within a system organ class or a preferred term using the adverse events with the highest severity within each category. All information pertaining to adverse events noted during the study will be listed by subject, detailing verbatim given by the investigator, preferred term, system organ class, date of onset, date of resolution, severity, and relationship to treatment. A tabulation of Serious Adverse Events (SAEs), will be provided by subject within treatment groups. The proportion of subjects in each treatment group reporting adverse events that occur in ~ 5% in either treatment group will be compared using the Fisher's exact test.

The specific system organ classes and preferred terms analyzed will be those that are reported by at least five percent of the subjects in either treatment group.

9.5. Sample size Justification:

Sample size estimation for this trial is based on the comparison of the change in the composite IASI score from baseline to 16 weeks post treatment between the secukinumab and placebo arms. Data from our cohort

of 21 adolescents and adults was used to estimate the sample size. The mean composite IASI score in this cohort was 28.9 with a standard deviation of 9.0. Assuming a correlation between the pre and post treatment IASI scores of 0.55, we estimated the standard deviation of the baseline to week 16 change at approximately 8.5. Fixing the type I error at 0.05 for a two tailed t-test, a sample size of 16 subjects per group provides 80% power to detect a treatment effect of 30% for change in the IASI composite score (40% reduction in the secukinumab vs. an 10% reduction in the placebo arm). To account for an anticipated 20% dropout rate, 20 subjects in each treatment group (total 40) will be randomized.

9.6. Analysis of Reliability

To determine inter-rater reliability, the two trained blinded investigators at each medical center will perform all assessments. To study intra-rater (test-retest) reliability, measures will be carried out by the subject (for the patient-reported severity outcome) and by the same two physicians (for the disease scores) at both screening and baseline visits, which will be separated by 3-4 weeks to minimize recall bias. Intra-rater and inter-rater reliability will be assessed by the intraclass correlation (ICC) for agreement (Shrout and Fleiss, 1979) and will be calculated within the linear mixed-effects model framework (Eldridge et al, 2009). The ICC for the inter-rater agreement will be calculated in the random coefficient model with covariates center and random intercepts for the patient and the physician. Bland-Altman plots will also be used to study patterns of agreements. As per Cicchetti (Cicchetti et al, 1994), interpretation for kappa or ICC for inter-rater agreement measures will be as follows: poor <0.40; fair 0.40-0.59; good 0.60-0.74; excellent 0.75-1.00.

10. ETHICAL CONSIDERATIONS.

10.1. Informed Consent

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, and with the ethical principles laid down in the Declaration of Helsinki.

10.2. Consent Forms

Prior to study entry, a written informed consent must be obtained from the subject (≥ 18 years old). A copy of the subject's signed consent form must be retained in the study file. Documentation of consent process will be placed in source document for each study subject.

10.3. Responsibilities of the Investigator and IRB

A periodic review will be submitted to the IRB at least once per year. The IRB will be notified of completion of the study. After study completion or termination, a final report will be provided to the IRB to close the study. The investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted. Serious Adverse Events that are reported to Novartis will be submitted promptly to the IRB per IRB guidelines.

At least once per year, the IRB will review and give written approval in order to continue the study. This trial will be conducted in accordance with Good Clinical Practices and the Declaration of Helsinki.

10.4. Publication of Study Protocol and Results

The Principal Investigator and co-investigators may publish the results of this study in conjunction with appropriate scientific and medical personnel of either institution. Information obtained from this study may be used for teaching, research, publications, or presentations at scientific meetings. If individual results are discussed, subject identities will be protected by using a subject number rather than name or other identifying information.

11. PROTOCOL ADHERENCE

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented. All significant protocol deviations will be recorded and reported.

11.1. Protocol Amendments

All changes must be submitted to the IRB. Protocol modifications that impact subject safety or the validity of the study must be approved by the IRB and Novartis Medical Affairs before initiation.

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13.

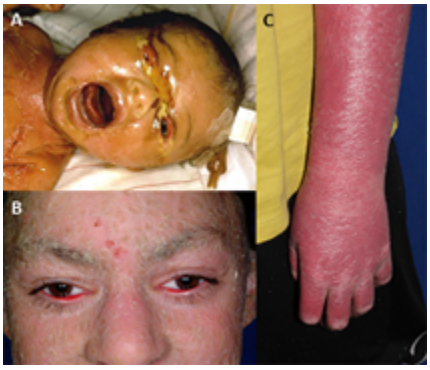


Fig. 1 (left)**. A**. Most patients with ARCI are *collodion babies* at birth. **B-C**. The extent of redness (erythema) and scaling varies within ARCI, ranging from lamellated scaling, generally with less visible erythroderma (**B,** *lamellar ichthyosis* (ARCI-LI)) to intense redness with finer scale (**C,** c*ongenital ichthyosiform erythroderma* (ARCI-CIE))
Fig. 2 (below). Biomarker expression in ichthyosis skin shows IL-17 skewing. A. mRNA expression of IL-17A and IL-17A-induced genes is increased in ichthyosis, including ARCI (CIE/LI) vs.controls. *p<.05; *p<.01; ***p<.001. **B**. Highly positive correlation of IL-17A mRNA levels with IASI-Erythema (B) and IASI (not shown). **C**. Ichthyosis patients cluster in their expression patterns, and are closest to psoriasis patients.

Appendix 1: Schedule of Assessments Flowchart

Phase 1 (double-blind): Visits 1-5;
Crossover: Visit 6
Open label: Visits 7-12

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12
						COW1	OLW1	OLW4	OLW12	OLW20	OLW28	OLW32
	Screen (28 d-21 d of Day 0)	Baseline/ Day 0	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 32	Wk 40	Wk 48	Wk 52
Visit Window			±3 days	±3 days	±1 wk	±3 days	±3 days	±1 wk	±1 wk	±1 wk	±1 wk	±1 wk
Consent	X											
Demographics	X											
Inclusion/Exclusion	X	X										
Medical History	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X
AE Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination	X	X				X			X			X
Full Skin Examination		X	X	X	X	X	X	X	X	X	X	X
Vital Signs (incl. weight)	X	X	X	X	X	X	X	X	X	X	X	X
Height	X											
Waist circumference		X				X			X			X
Randomization		X										
Saliva Genotyping (if unknown) [2]	X											
Buccal swab	X											
Blood Biomarkers	X[1]	X		X		X			X			X
PAX RNA	X[1]	X		X		X			X			X
QuantiFERON®-TB gold	X											X
Hep B/C, HIV testing	X											
Urine HCG(if applicable)	X											X
Chem-20, CBC	X					X			X			X
Lipid panel, glucose, CRP (fasting)		X				X			X			X
Severity evaluations	X	X	X	X	X	X	X	X	X	X	X	X
TEWL		X	X	X	X	X	X	X	X	X	X	X
Tape Strips		X		X		X			X			X
Itch scores		X	X	X	X	X	X	X	X	X	X	X
DLQI and iQoL-32		X				X			X			X
Skin Biopsy (4.5 mm)		X				X			X			X
Photography	X	X	X	X	X	X	X	X	X	X	X	X
Skin Swabs	X	X	X	X	X	X	X	X	X	X	X	X
Injection & Teaching		X										
Dispense study treatment		X	X	X	X	X	X	X	X	X	X	
Review Subject Diary			X	X	X	X	X	X	X	X	X	X

1. To be drawn at screening if the patient is on systemic retinoid
2. At Northwestern only.

All investigators will be trained by Dr. Paller before initiation.

Appendix 2: Ichthyosis Area and Severity Index (IASI)

The **IASI** (**I**chthyosis **A**rea and **S**everity **I**ndex) is a modification of the global CISI score (see Appendix 2) that incorporates extent through the techniques used for assessment in the EASI and PASI scores for eczema (AD) and psoriasis, respectively. IASI takes only a few minutes to assess and the totals are calculated automatically in spreadsheets. All investigators will be trained by Dr. Paller before initiation and with the first few patients using representative examples of different scores in different skin tones and body sites. While this is not a validated score to date, the proposed study is an opportunity to validate this scoring instrument.

The steps for the IASI are as follows:

a) Determine mean **INTENSITY** of erythema or scaling in a body region (A1 = head and neck; A2 = upper limbs; A3 = trunk; A4 = lower limbs) through either selecting a representative area of ichthyosis or averaging the intensity within a body region. The intensity of redness/ erythema and scaling of the ichthyosis is assessed as none (0), mild (1), moderate (2), severe (3) or very severe (4).

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. In each region, the area is expressed as nil (0), 1-9% (1), 13-29% (2), 30-49% (3), 50-69% (4), 70-89% (5) or 90-100% (6). Many with ichthyosis have generalized involvement with 100% of area affected (e.g., score of 6), but it is possible that areas may be spared (e.g., palms or soles). The mean intensity score (A1-A4 for each site) is multiplied by the number correlating with the percentage within a region with ichthyosis (B1-4).

% 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 **FINAL SCORE** for **each intensity measure** (IASI-E or IASI-S) is thus the composite of (A1+B1)xC1) + (A2+B2)xC2) + (A3+B3)xC3) + (A4+B4)xC4).

The **composite score** IASI (max potential 48) = IASI-E (max potential = 24) + IASI-S (max potential = 24).

Body region	Erythema (0-4)	Scaling (0-4)	Region score (0-6)	Multiplier	Score per body region
Head/neck	(+)		X	X 0.1	
Trunk	(+)		X	X 0.3	
Upper extremities	(+)		X	X 0.2	
Lower extremities	(+)		X	X 0.4	

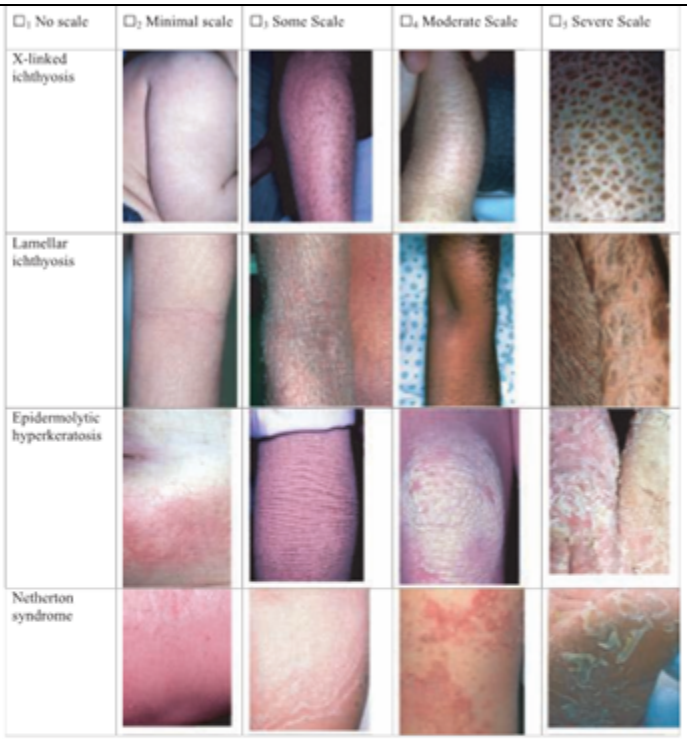
TOTAL(Sum Score per Region):

Product: Secukinumab
Protocol Number: CAIN457AUS05T
Date: 14 July 2018 44

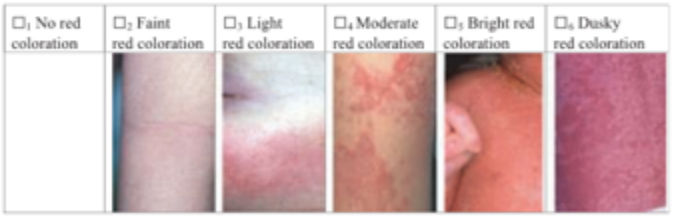
Appendix 3: Congenital Ichthyosis Severity Score (CISI): *To be performed by Investigators and by Subject

Ichthyosis Likert Scales for Grading of Clinical Severity

1. Please indicate your level of skin scale, as it appears today:



2. Please indicate your level of redness, as it appears today:



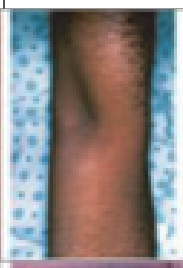
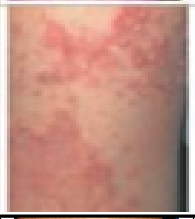
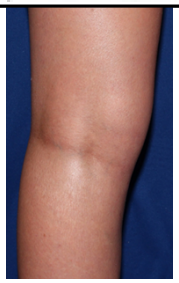
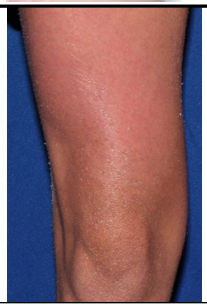
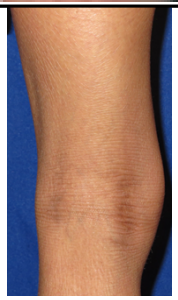
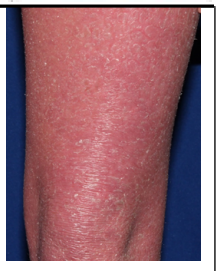
3. Please indicate your level of hair loss, as it appears today:

☐1 Normal hair ☐2 Mild <25% hair loss ☐3 Moderate (25–75%) hair loss ☐4 Severe (>75%) hair loss ☐5 No hair

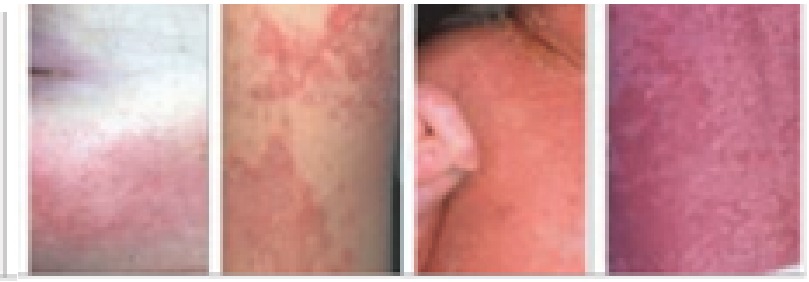
Product: Secukinumab
Protocol Number: CAIN457AUS05T
Date: 14 July 2018

Appendix 4: Modified CISI (m-CISI): *To be performed by Investigators and by Subject

1. Please indicate your level of skin scale, as it appears today:

0: No scale	1: Minimal Scale	2: Moderate Scale	3: Severe Scale	4: Very Severe Scale
Lamellar ichthyosis				
Epidermolytic hyperkeratosis				
Netherton syndrome				
CIE				

2. Please indicate your level of skin redness, as it appears today:

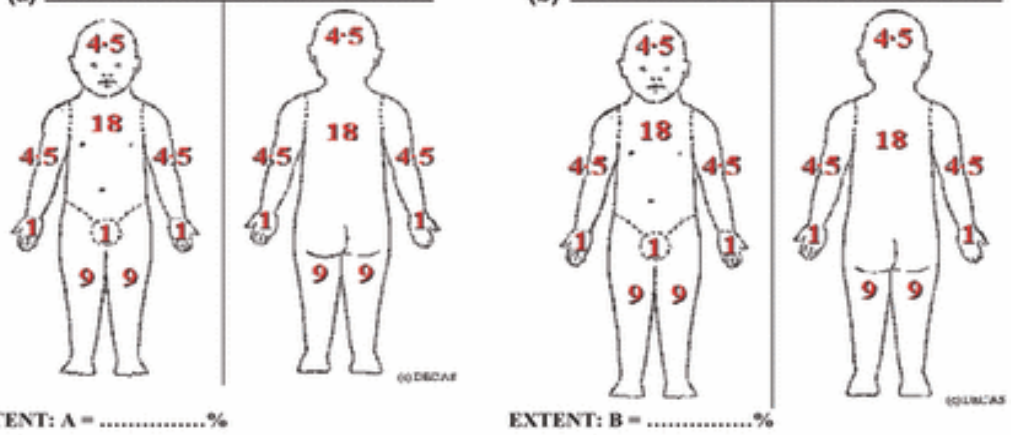


0: No red coloration	1: Light red coloration	2: Moderate red coloration	3: Bright red coloration	4: Dusky Red Coloration

TOTAL(scale +erythema scores):

Appendix 5: Bodemer Scale

(a) BODY SURFACE AREA WITH SCALES **(b) BODY SURFACE AREA WITH ERYTHEMA**



EXTENT: A = ...% **EXTENT: B = ...%**

(c) PRURITUS: **..... (C)** ***(Value in cm)***

PRURITUS (0 – 10) **0** _____ **10**
VISUAL ANALOGUE SCALE (average for the last 3 last days and nights)

(d) SKIN PAIN: **..... (D)** ***(Value in cm)***

SKIN PAIN (0 – 10) **0** _____ **10**
VISUAL ANALOGUE SCALE (average for the last 3 last days and nights)

(e) SEVERITY OF 10 SYMPTOMS: ..... (E) ***(Cumulated severity score for 10 symptoms: total value ranging from 0 to 60)***

SCORE = A/10 + B/10 + C + D + E = .../ 100

10 SYMPTOMS	
Scale grade: body **0**: absent **1**: light (thin scales) **3**: moderate (visible scales) **6**: severe (thick scales)	**Retraction: hand** **0**: absent **1**: at least two fingers of one hand **3**: all the fingers of one hand **6**: both hands
Scale grade: scalp **0**: absent **1**: light (thin scales) **3**: moderate (visible scales) **6**: severe (thick scales)	**Retraction: foot** **0**: absent **1**: at least two toes of one foot **3**: all the toes of one foot **6**: both feet
Palmoplantar keratoderma (PPK) **0**: absent **1**: light (not very pronounced) **3**: moderate (obvious) **6**: severe (with fissures)	**Functional impairment** **0**: absent **1**: neck (rotation, anteflexion) **3**: shoulders with 'winding' = 'inward' shoulders **6**: limb (s), whatever the location
Erythema (on the most representative area) **0**: absent **1**: light **3**: moderate **6**: severe	**Eyelids** **0**: no ectropion **1**: ectropion of one eyelid **3**: lack of eye occlusion: persistent slit opening **6**: lack of eye occlusion: persistent opening > slit
Fissures (apart from PPK) **0**: absent **1**: present, painless (one site only) **3**: present, painless (several sites) **6**: present, painful (one or several sites)	**Mouth (notwithstanding fissures at commissures)** **0**: no repercussion **1**: mild eclabium **3**: characterised eclabium **6**: limited opening of the mouth *(measurement of the maximal opening from upper lip to lower lip in cm)*

Appendix 6: YALE ICHTHYOSIS SEVERITY INDEX

There are two sets of scaliness standards, one (called lamellar scale and labeled L) for the typical flat scales that occur in most forms of ichthyosis and one (called keratoderma scale and labeled K) for the more columnar scales that are typical of epidermolytic ichthyosis and erythrokeratodermas. Severities range from 0-4 where 0 indicates no perceptible scale or surface hyperkeratosis and 4 represents very severe scale or surface hyperkeratosis. Each photographic standard has a written description of features characteristic of the severity score represented. We have also provided those written descriptions below.

To utilize the severity index, use either the lamellar or keratoderma standards for scale, and the single standard for erythema. First decide whether the K standard or the L standard is the best match for a particular patient, and then score scale for that patient with a number (0-4) and a letter (L if you used the lamellar standard or K if you used the keratoderma standard) for each site. Then use the single set of erythema standards to score erythema at all sites (0-4).

SCORING DESCRIPTORS

Definitions:

scale = visibly separated/fractured stratum corneum
smoothening = diminished fine skin markings; shininess; waxiness
surface accentuation = organized or geometric exaggeration of coarse skin markings, such as corrugation or follicular prominence
columnar hyperkeratosis = piles of scale with vertical fracturing

Guidelines for scoring:

Scoring for scaliness should be done for the entire region. That is, it should be more of an average than an indication of the worst score for that region. The score you give to a particular region should be representative of a rectangle that for the:
Upper back extends laterally from one posterior axillary fold to the other and from T1-T10. It excludes posterior arms and neck.
Upper arm extends from the acromial process to the lower humerus and includes the anterior axillary fold. It excludes antecubital fossa, elbow and any portion of the trunk that may be visible.
Lower leg extends from, and includes, the kneecap to the lower tibia. It excludes the ankle.
Dorsal foot extends from the tip of the toes to the ankle. It excludes glabrous skin.

By contrast, because erythema can be obscured by scale, *the erythema score for a particular region should be the worst score for that region*.

Scaliness descriptors (for LI and CIE phenotypes)

0 = normal skin; no perceptible scale or smoothening

1 = areas of normal skin intermixed with areas showing smoothening (diminished fine skin markings;
shininess; waxiness) or small scales (visibly separated/fractured stratum corneum)
2 = confluent smoothening (diminished fine skin markings; shininess; waxiness)
or small scales (visibly separated/fractured stratum corneum)
3 = confluent scales (visibly separated/fractured stratum corneum) including some large (>1cm), thick scales
4 = confluent, primarily large, thick scales

Scaliness descriptors (for keratoderma phenotypes)

0 = normal skin; no perceptible scale or surface accentuation
1 = areas of normal skin intermixed with areas showing hyperkeratotic surface accentuation (organized or geometric exaggeration of coarse skin markings, such as corrugation or follicular prominence)
2 = confluent surface accentuation (organized or geometric exaggeration of coarse skin markings, such as corrugation or follicular prominence) and/or flat scale
3 = confluent surface accentuation (organized or geometric exaggeration of coarse skin markings, such as corrugation or follicular prominence), scales and some columnar hyperkeratosis (piles of scale with vertical fracturing)
4 = confluent, primarily columnar hyperkeratosis (piles of scale with vertical fracturing)

Erythema descriptors

0 = no perceptible redness
1 = barely perceptible pink
2 = pink
3 = red
4 = deep red-purple

Scoring:

	Upper Back	Upper Arm	Lower Leg	Dorsal Foot
Scale				
Erythema				
Sum by Region				

Total Score (Add Sum by Region, & phenotype scored):

Appendix 7

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Site No:
Date :
Visit Number:

Score:

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 **garden**?	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.

Appendix 8

IQoL-32

The following questions concern different periods of time. There are no right or wrong answers. Answer each one 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…

1. … Has your skin been red?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
2. … Has your skin been sensitive or painful (tense, uncomfortable)?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
3. … Have you had dry or thick skin, with a lot of scales (dead skin)?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
4. … Has your skin been itchy?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
5. … Does your skin hurt because of cracking?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
6. … Because of your ichthyosis, has your eyes bothered you (dryness, pain, watering, impaired vision, redness)?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
7. … Because of your ichthyosis, have your ears bothered you (earwax plug, impaired hearing, pain, itching)?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
8. … Did your skin have trouble adapting to temperature and/or weather changes?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable
9. … Have you been bothered by the smell of your skin?
   ☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

10. … Have you felt like your skin was unsightly because of your disease?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

11. … Does the disease make you feel dirty?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

12. … Have you felt uncomfortable performing certain everyday actions (such as writing, moving) because of the pains or stiffness caused by ichthyosis?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

13. … Have you felt “fatigue” in connection with your ichthyosis?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

14. … Does your scalp bothered you (combing, hair care, pain, or itching)?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

… have you performed all desired activities (sports and leisure) without fear that others might see your skin?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

15. … Have you changed your vacation plans or the places you go because the planning required by your ichthyosis was too complicated?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

16. … Have you felt that your ichthyosis was a handicap (aesthetic or physical), even if you do not consider yourself a handicapped person?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

17. … Have you experienced mood swings because of ichthyosis?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

18. … Have you felt sad, discouraged or powerless in the face of your disease?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

19. … have you felt lonely or withdrawn because of the disease?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

20. … Have you experienced a feeling of anger, being “fed up,” a sense of injustice because of your disease?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

21. … Have you felt afraid of the future (treatments losing their effectiveness, worsening, difficulty applying the creams with age)?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

22. … Have you felt afraid that the disease could restrain a romantic/sexual relationship?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

23. … Have you had the unpleasant feeling of being stared at or avoided by others?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

24. … Have you been afraid of being rejected or humiliated by others?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

25. … Have you felt afraid that others find your skin oily, sticky or rough?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

26. … Do you have bothersome side effects because of the medications?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

27. … Does the disease hampered you in performing your work or going about your studies?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

28. … Does ichthyosis influenced the way you dress?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

29. … Have you had a surplus of household chores because of your ichthyosis (skin flakes, oily clothes)?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

30. … Have you found caring for your skin difficult and unpleasant?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

31. … Has care taken too much of your time each day?
☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

32. … Has ichthyosis caused you significant expenses or inconvenient administrative procedures?

☐tremendously ☐a lot ☐a little ☐not at all ☐not applicable

Appendix 9

5-D Pruritus Scale

1. **Duration:** During the last 2 weeks, how many hours a day have you been itching?

Less than 6hrs/day	6-12 hrs/day	12-18 hrs/day	18-23 hrs/day	All day
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. **Degree:** Please rate the intensity of your itching over the past 2 weeks

Not present	Mild	Moderate	Severe	Unbearable
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. **Direction:** Over the past 2 weeks has your itching gotten better or worse compared to the previous month?

Completely resolved	Much better, but still present	Little bit better, but still present	Unchanged	Getting worse
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. **Disability:** Rate the impact of your itching on the following activities over the last 2 weeks

	Never affects sleep	Occasionally delays falling asleep	Frequently delays falling asleep	Delays falling asleep and occasionally wakes me up at night	Delays falling asleep and frequently wakes me up at night
Sleep	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

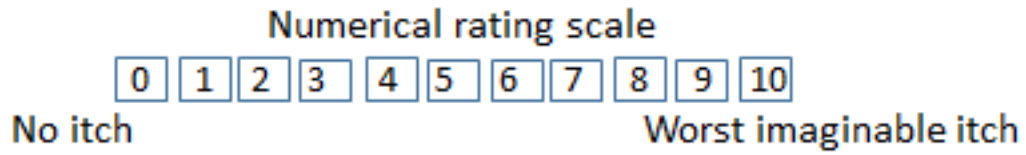
	N/A	Never affects this activity	Rarely affects this activity	Occasionally affects this activity	Frequently affects this activity	Always affects this activity
Leisure/Social	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Housework/ Errands	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Work/School	☐	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. **Distribution:** Mark whether itching has been present in the following parts of your body over the last 2 weeks. If a body part is not listed, choose the one that is closest anatomically.

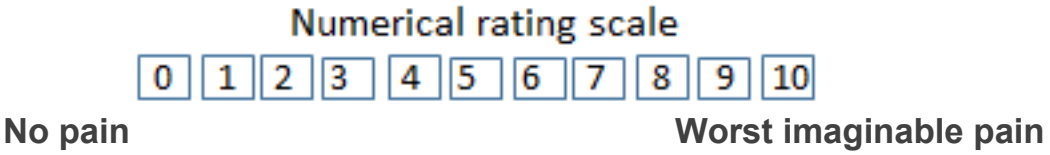
	Present		Present
Head/Scalp	☐	Soles	☐
Face	☐	Palms	☐
Chest	☐	Tops of Hands/Fingers	☐
Abdomen	☐	Forearms	☐
Back	☐	Upper Arms	☐
Buttocks	☐	Points of Contact w/ Clothing	
Thighs	☐	(e.g waistband, undergarment)	☐
Lower legs	☐	Groin	☐
Tops of Feet/Toes	☐		

Appendix 10

Numerical Rating Scale (NRS) for Pruritus (over past 3 days and nights)



Numerical Rating Scale (NRS) for Pain (over past 3 days and nights)



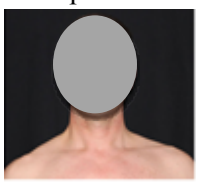
Appendix 11: Photography Protocol

Prior to photography: Have patient remove all wristbands and jewelry. Bras and underwear do not need to be removed. Photography should be performed on blue background.

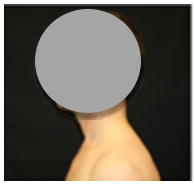
PHOTOGRAPHS

1. First, take a photograph of a card with subject ID, visit number, date of visit.

2. Take photo of face and shoulders with eyes open.

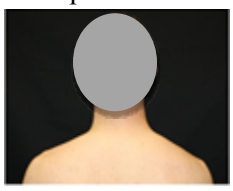


3. Take photo with body perpendicular to backdrop, left ear, eyes open.



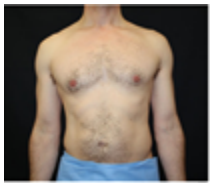
4. Take photo with body perpendicular to backdrop, right ear, eyes open.

5. Take photo of shoulders and back of head.

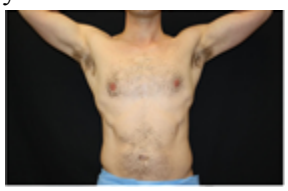


6. Take photo of scalp directly perpendicular to camera, capturing crown and tip of nose.

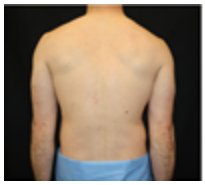
7. Take photo of abdomen to neck, capturing drape.



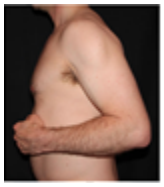
8. With patient's arms raised and hands behind head, take photo from elbows to drape.



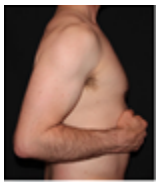
9. Take photo of back to neck, capturing drape.



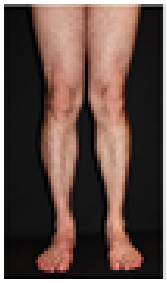
10. Have patient put arm parallel to floor, and bring arm back to expose flank. Rest closed fist on abdomen. Left side.



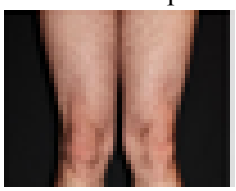
11. Have patient put arm parallel to floor, and bring arm back to expose flank. Rest closed fist on abdomen. Right side.



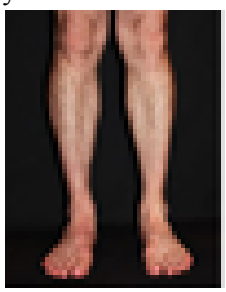
12. Raise drape as high as possible, take photo toes to drape.



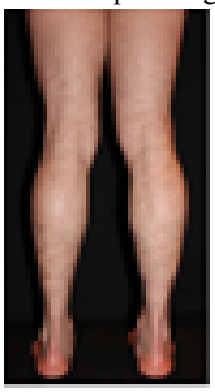
13. Zoom in to capture upper legs from knee to drape in more detail.



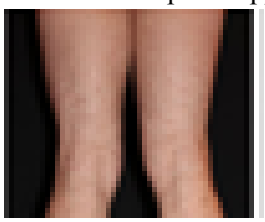
14. Zoom in to capture lower legs from knee to foot in more detail.



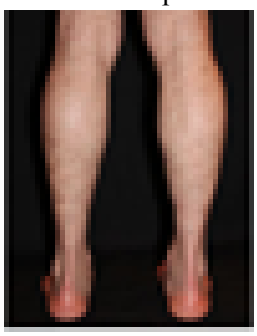
15. Raise drape as high as possible, take photo heels to drape.



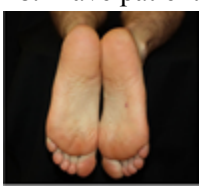
16. Zoom in to capture upper legs from posterior knee to drape in more detail.



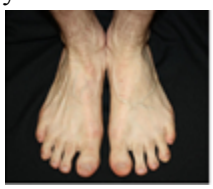
17. Zoom in to capture lower legs from posterior knee to foot in more detail.



18. Have patient kneel on block or chair draped with blue cloth, take photo of soles.



19. Have patient stand on blue cloth, take photo of dorsal feet.



20. Take photo of palms with fingers flat, forearms together and fingers evenly spaced.

21. Flip hands over, take photo of dorsal hands with thumbs touching and fingers evenly spaced.

22. Bring finders together take photo capturing nails and fingertips. Pose is relaxed, not tightly clenched.

Appendix 12: Microbiome Survey and Swabs—(Scalp, Upper outer arm, Upper buttock)

1. Have patient fill out lifestyle questionnaire (next page)
2. **Make sure to take skin swabs before any disinfection to area (for blood or biopsy)!**
3. Explain the procedure to the participant
4. Put on a surgical mask and gloves
5. Start with swabbing scalp, proceed with upper arm and upper buttock
6. Unpack the first swab. To avoid contamination each swab should be unpacked only immediately before sampling.
7. The swab is performed on an area of 2-4 cm2 by rubbing gently back and forth (20 times in 15 seconds).
8. Insert the swab into the tube (with 500 µl Stabilizer solution/Zirkonia) without touching its edge. Break off the swab shaft to leave the swab within the solution and close it tightly. Shake down the swab tip to the bottom of the tube by tapping the tube to the working surface in order to cover the entire tip with buffer.
9. Label tube with collection date, subject ID, visit number, location and procedure. Dispose of swab.
10. Collect tissue scraping from an adjacent site immediately after swabbing
11. Take sterile weighing spatulas and use to vertically scrape scale into a sterile small Petri dish
12. Transfer to a 1.5 ml sterile Eppendorf to freeze.
13. Label tube with collection date, subject ID, visit number, location and procedure.
14. Repeat process for next areas to be swabbed (upper outer arm near biopsy site, upper buttock)
15. Place tubes for subject into a ziplock bag (label with date, subject ID, visit number).

Microbiome Survey (to be filled out by patient)

City, State of Residence:

Ethnicity: Non-Hispanic Caucasian Hispanic/Latino African American Asian
Other:_____

Skin Type Check all that apply: ☐ Dry ☐ Oily ☐ Mixed ☐ Sensitive

Which skin conditions do you have in addition to ichthyosis? Check all that apply: ☐ Acne ☐ Atopic Dermatitis ☐ Psoriasis ☐ Ezcema ☐ Rosacea ☐ Dandruff ☐ Other:_____

How happy are you with your skin on a scale of 1 to 10? : 1 2 3 4 5 6 7 8 9 10

Please indicate: Bath or Shower

Frequency of Bath/ Shower

Duration of Bath/Shower

Please list the products (brand) you are currently using on your skin, and how often:

Cleanser:

Face moisturizer:

Body Wash/Soap:

Body Moisturizer:

Topical medications:

Oral Medications:

Makeup/Sunscreen products:

Shampoo/Conditioner:

Bleach Baths (or use of vinegar, baking soda, other additives):

Topical antibiotics:

Exfoliation:

Other:

Did you use products to swabbed areas within 24 hours of sample collection?

In the past year, have you used any antibacterial products (soap, topical cream/ointment, or oral antibiotics?):

If Yes, What and When?

How many hours of sleep on average per night?:_____hours
Hours of sun exposure on average in the past week?:_____hours

Which Best Describes Your Diet ? (circle): Balanced Paleo Flexitarian (occasional meat) Pescetarian (Fish but not other meat) Vegetarian Vegan *Elimination Diet
Other_____
*WHAT DO YOU ELIMINATE: _____
Do you avoid white bread, sugar and pasta?: Y N
Do you eat a diet high in dairy products?: Y N
Do you drink skim milk?: Y N
Do you select organic, hormone free meats and dairy products? Y N

_____

WOMEN ONLY: Circle your current menstrual cycle stage: menstruating in menopause post menopause irregular menstruation
Pill?_____ Are you on hormone therapy?
_____
Allergies:
_____
List Medications, Vitamins, Supplements [include brand name]:
_____
_____
Do you take probiotics?: Y N [Brand name]: _____
Smoker: Y
Pets: Y Type_____ No
How many times do you exercise per week?: _____
Exercise Intensity: Light Moderate Vigorous Exercise Type: Aerobic Strength Training Mixed
Any Exercise in past 3-4 hours? Y N