STUDY TITLE: An Open-Label and Long-Term Extension Study to Evaluate the Efficacy and Safety of Ustekinumab in the Treatment of Patients with Ichthyoses.

Principal Investigator/Sponsor:
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

Date: 8 November 2022
Version 2.0

Drug and funding support provided by: Janssen Scientific Affairs, LLC

Table of Contents

INVESTIGATOR'S AGREEMENT

I have created and read the final version of the following protocol: An Open-Label and Long-Term Extension Study to Evaluate the Efficacy and Safety of Ustekinumab in the Treatment of Patients with Ichthyoses, dated 6 November 2020 where the COMPANY (Janssen Scientific Affairs, LLC) and SPONSOR (Dr. Amy Paller at Northwestern University) 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 STELARA® (ustekinumab) Prescribing Information (version November 2019).

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)
CDLQI	Children's Dermatology Life Quality Index
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
FDA	Food and Drug Administration
ISS	Ichthyosis Severity Score
ISS-E	Erythema subscore of Ichthyosis Severity Score
ISS-S	Scaling subscore of Ichthyosis Severity Score
IFTB	Ichthyosis Financial and Time Burden
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention-to-treat
LI	Lamellar Ichthyosis
NRS	Numerical Rating Scale
NS	Netherton Syndrome
PASI	Psoriasis Area Severity Index
SAE	Serious Adverse Event
TEWL	Transepidermal water loss

PROTOCOL SYNOPSIS

Title: An Open-Label and Long-Term Extension Study to Evaluate the Efficacy and Safety of Ustekinumab in the Treatment of Patients with Ichthyoses

Investigation Type: Drug

Study Type: Open Label

Purpose and Rationale: The ichthyoses are a group of lifelong genetic disorders that 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 more common "orphan" forms of ichthyosis are autosomal recessive congenital ichthyosis (ARCI; includes lamellar ichthyosis/LI and congenital ichthyosiform erythroderma/CIE), Netherton syndrome (NS) and epidermolytic ichthyosis (EI). However, there are dozens of other syndromic and non-syndromic ichthyotic disorders as well. 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 Th17/IL-23 pathway cytokines and chemokines in the skin of individuals with ichthyosis, most similar to the inflammatory pattern of psoriasis. While the significance of the high expression of Th17/IL-23 pathway genes across all forms of ichthyosis studied to date is unknown, the high expression of genes of the Th17/IL-23 pathway in psoriasis is thought to be causative for the disease manifestations. We propose that IL-12/IL-23 -targeting therapeutics will safely suppress the inflammation and possibly the other features of ichthyosis, improving quality of life. As a proof-of-concept study, we propose to treat children (6 years of age and higher) and adults with ichthyotic disorders with ustekinumab in an open-label trial to serially assess clinical response to and safety of ustekinumab for this group of disorders.

Co-primary objectives:

- To evaluate the efficacy of ustekinumab for ichthyosis, as measured by an at least 50% reduction in severity (using the Ichthyosis Severity Score (ISS) measure) at 7 months after initiation of study drug (Visit 6)
- To evaluate the safety of ustekinumab for ichthyosis, based on occurrence of bacterial and fungal infections

Secondary objectives:

- To evaluate reduction in ISS, and ISS subset measures for erythema and scaling (ISS-E, ISS-S) at months 7, 13, 19 and 25 after study drug initiation.
- To evaluate improvement in quality of life assessments at months 7, 13, 19, and 25 after study drug initiation (Dermatology Life Quality Index/DLQI for 16 years and older; Children's Dermatology Life Quality Index/CDLQI for children 6-15 years; specific questions about impact of scaling on daily life)
- To evaluate non-infectious AEs and all SAEs related to ustekinumab use, particularly injection reactions

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 over time.

Study Design: Patients will be screened for inclusion and exclusion criteria. If using a systemic retinoid or immunomodulatory agent, the patient will wait four weeks to initiate therapy. Washout for topical steroids will be one week. If the patient has not had testing for TB (QuantiFERON gold, given that the generalized skin scaling and erythema precludes PPDi) in the previous three months, testing will be performed at screening and must be negative before starting ustekinumab. All patients who have not had genetic testing (research or a CLIA-approved lab) will be required to have testing sent to Dr. Keith Choate at Yale University and will enroll in Dr. Paller's "Screening for the Genetic Basis of Dermatologic Disease" study IRB# 2009-13803. As long as the clinical diagnosis is ichthyosis / an ichthyotic disorder, having a known gene with mutation is not required before entry into this study, but is required before study end. Each subject will receive ustekinumab at Baseline (Day 0), month 1, and then every 8 weeks thereafter (months 3, 5, 7, 9, and 11). Subjects who do not achieve a 25% reduction in the Ichthyosis Severity Score (ISS) at month 7 (Visit 6) will be withdrawn from the study due to lack of efficacy. The final assessment of the open label period will be month 13. Those subjects who have evidence of improvement (per the subject) will have the option to continue in the Long Term Extension (LTE) portion of the study for an additional 12 months.

Month 13 may duplicate as a subject's baseline visit of the LTE, or a subject can return for an LTE baseline visit any time after completion of the open-label phase. During the LTE, subjects will have visits every 8 weeks (months 13, 15, 17, 19, 21, 23 and 25). Safety labs including hematology, chemistry and QuantiFERON gold will be repeated at months 13 and 25.

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
									OL end LTE start						End of LTE
	Screen (28 d-21 d of Day 0) Week -4	Baseline/ Day 0/ Week 0	Month 1/ Week 4	Month 3/ Week 12	Month 5/ Week 20	Month 7/ Week 28	Month 9/ Week 36	Month 11/ Week 44	Month 13/ Week 52	Month 15/ Week 60	Month 17/ Week 68	Month 19/ Week 76	Month 21/ Week 84	Month 23/ Week 92	Month 25/ Week 96
Drug supplied	0	1	1	1	1	1	1	1	1	1	1	1	1	1	0

Number of Centers: 1

Blinding: Not applicable—Open-label treatment

Study Duration: The clinical portion of the study will include 6 months for patient recruitment and up to 100 weeks (25 months plus at least 4 weeks for screening) of subject treatment, bringing the total maximum clinical study duration to 2.6 years.

Test Medication: Ustekinumab (STELARA®)

Study Population: 15 evaluable subjects

Subjects must be at least 6 years of age with a diagnosis of ichthyosis/ichthyotic disorder and must show at least moderate erythema. These subjects will primarily come from the Chicago/Midwest region, but the study is open to anyone meeting criteria, wishing to travel to Chicago to be in the study and able to comply with study requirements.

Inclusion Criteria

- Subject has provided informed consent; parental consent for patients under 18 years of age (plus assent for subjects age ≥ 12 and < 18).
- Subjects are at least 6 years of age or older at the time of screening.
- Before screening visit, females must be:
  - Postmenopausal, defined as
    ≥ 45 years of age with amenorrhea for at least 18 months,
    OR
  - ≥ 45 years of age with amenorrhea for at least 6 months and a serum FSH level > 40 IU/mL
    OR
  - Of childbearing potential, in which case she must satisfy at least one of the below:
    - Surgically sterile (has had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
    - If heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap, with spermicidal foam, cream, film, gel or suppository), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for a period of 16 weeks after the last administration of study agent,

    OR
    - Not heterosexually active. Abstinence is allowed as an acceptable form of contraception.
    - Note: If a woman participant's childbearing potential changes after start of the study (e.g., a premenarchal woman experiences menarche) or if women of childbearing potential who are not heterosexually active at screening become heterosexually active, they must agree to utilize a highly effective method of birth control, as described above.
    - Female participants of childbearing potential (menstrual and not surgically sterile), must have a negative serum beta-human chorionic gonadotropin ($_{\beta}$-hCG) pregnancy test at screening and a negative urine pregnancy test at Week 0 (prior to screening visit) and agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 16 weeks after the last administration of study agent.
  - Male participants who are not surgically sterilized and are heterosexually active with a woman of childbearing potential, must agree to use a barrier method of contraception (e.g.,

condom with spermicidal foam/gel/film/cream/suppository) and to not donate sperm during the study and for 16 weeks after last receiving study agent. Note that barrier methods must also be used in all male subjects sexually active with pregnant partners for at least 16 weeks after last study agent administration.

- Subjects must have a confirmed clinical diagnosis of ichthyosis/ichthyotic disorder, and either have completed genotype or be willing to be genotyped (genotype results will not be required for entry into the study).
- Subjects must have at least moderate erythema (ISS-erythema score ≥ 2) related to his/her ichthyosis/ichthyotic disorder.
- Subjects must be clinically judged to be immunocompetent based on baseline laboratory testing (chemistry and hematology), medical history and physical examination.
- Subjects will have baseline negative QuantiFERON®-TB gold, Hepatitis B, Hepatitis C, and HIV laboratory testing.

Exclusion criteria

- Subjects who are unable to provide informed consent or assent (or who do not have consent from a Legally Authorized Representative if < 18 years).
- Subjects with ichthyosis vulgaris or X-linked recessive ichthyosis.
- Subjects who have a known allergy to ustekinumab or its products.
- Female subjects who are pregnant or breastfeeding, or who are considering becoming pregnant.
- Subjects who have prior biologic use targeting IL-12/IL-23 monoclonal antibody.
- Subjects who have used a systemic retinoid or systemic anti-inflammatory agent within 4 weeks prior to baseline.
- Subjects who have used topical steroid in the previous week, retinoid or keratolytic agent in the previous 24 hours.
- Subjects with active infections or recent history of serious infections, malignancies or history of malignancies, recent immunizations with live vaccines, or any severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease, or signs or symptoms thereof
- Subjects who are under 6 years of age at the time of screening.

Ustekinumab is approved for Crohn's disease and has been tested/ found to be safe for psoriasis as young as 6 years of age with pK and safety validation to this age level. Although we would love to use in younger children with ichthyosis, we chose 6 years of age because of the extensive experience and safety testing to this age level.

We are focusing on inflammatory forms of ichthyosis with Th17 skewing in the skin and blood. Neither ichthyosis vulgaris nor recessive X-linked ichthyosis are inflammatory forms of ichthyosis and neither has been tested for Th17 skewing; both are easily amenable to available topical and OTC interventions and thus have little need for new interventions, especially using a systemic agent.

Duration of Treatment: 15 ichthyosis-affected subjects will be studied up to 25 months. The study will include an initial 13-month open-label phase, and a 12-month long-term extension to assure long-term safety.

Each subject will receive ustekinumab at Baseline (Day 0) and Months 1, 3, 5, 7, 9, and 11. During the LTE, subjects will receive injections every 8 weeks for one year: Month 13, Month 15, Month 17, Month 19, Month 21, and Month 23. Subjects will come back in for a follow-up visit at Month 25 for an end of study visit (no drug administration).

Efficacy Assessments

- ISS: Ichthyosis Severity Score and subscores (ISS-E, ISS-S)
- Ichthyosis Severity Self-Assessment
- DLQI: Dermatology Life Quality Index (for those 16 years and older)
- CDLQI: Children's Dermatology Life Quality Index (for those 6 - 16 years of age)
- IFTB: Ichthyosis Financial and Time Burden
- 8-item short form PROMIS itch and Stigma score for children 8 and above (parent proxy for under age 8)
- Itch and Pain NRS: Numerical Rating Systems (0-10) for pruritus and pain
- TEWL (transepidermal water loss): Functional assessment of barrier

Note the severity assessments will be performed by a trained study team member with PI supervision.

Safety Assessments

- Adverse events and serious adverse events monitoring
- Adverse events of special interest include all malignancies and all cases of active tuberculosis (TB).
- Laboratory assessments: QuantiFERON Gold, chemistry, hematology
- Vital signs, physical examination

Other Assessments

- Photography
- Serum samples for cytokine analysis or proteomics
- Microbiome samples
- Tape strips to evaluate mRNA expression and lipidomics
- Saliva for DNA analysis (stored; 2nd sample sent to Dr. Keith Choate at Yale University if gene unknown/untested and subject consents to IRB# 2009-13803). IRB 2009-13803 is separately supported only by the Department of Dermatology at Northwestern University.

Data Analysis

Statistical analysis will be performed by statisticians at Northwestern University.

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

Efficacy and other data will be summarized. Descriptive statistics of demographics and other baseline characteristics will be presented for all subjects. The primary efficacy variable is the ISS (composite) at 7

months after study drug initiation. The primary safety variable is t occurrence of bacterial and fungal mucocutaneous infections by 13 months after study drug initiation. Safety will be evaluated by tabulations of adverse events and will be presented with descriptive statistics at each visit. The number and percentage of subjects experiencing an AE/SAE will be stratified by organ system class, or a preferred term, and severity of the adverse event, and recorded and tabulated overall by each sub-strata.

Key Words: Ichthyosis, ustekinumab, IL-12, IL-23, biologic, monoclonal antibody

1. BACKGROUND AND RATIONALE

1.1 Disease

The ichthyoses are a group of lifelong genetic disorders that 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 >30 subtypes of ichthyosis are rare (<1:100,000 individuals). Among these rare subtypes are (i) epidermolytic ichthyosis (mutation in one of the genes encoding suprabasal keratins), (ii) Netherton syndrome (mutations in SPINK5, leading to excessive epidermal protease activity), (iii) autosomal recessive congenital ichthyosis or ARCI (associated with biallelic mutations in a dozen genes and ranges in appearance from darker, plate-like scaling as in lamellar ichthyosis or LI to intense erythema with fine scaling as in congenital ichthyosiform erythroderma or CIE, which includes harlequin ichthyosis, the most severe form), (iv) various forms of erythrokeratodermas (often defects in genes that encode connexins or desmosomal components), and (v) other ichthyosiform disorders, such as IFAP. 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 Clinical Hypotheses

We hypothesize that: a) intervention with ustekinumab will improve the severity of ichthyosis features; and b) the administration of ustekinumab will be well-tolerated.

1.3 Rationale for Ustekinumab Use

Ustekinumab is a fully human immunoglobulin G1 kappa monoclonal antibody (mAb) that binds both human interleukin (IL)-12 and IL-23 via a common IL-12/23p40 subunit. Ustekinumab neutralizes the activities of IL-12 and IL-23 by preventing these cytokines from binding to the IL-12 receptor beta-1 receptor protein, which is expressed on the surface of immune cells. Ustekinumab has been shown to be an effective treatment and has a favorable benefit risk profile for adult and pediatric psoriasis patients age 12 and older. Its use in psoriasis patients ages ≥ 6

and < 12 is currently being investigated (https://clinicaltrials.gov/ct2/show/NCT02698475?term=ustekinumab&cond=psoriasis&rank=1). We have recently found marked elevations in Th17/IL-23 pathway cytokines and chemokines in the skin of individuals with ichthyosis, most similar to the inflammatory pattern of psoriasis. While the significance of the high expression of Th17/IL-23 pathway genes across all forms of ichthyosis studied to date is unknown, the high expression of genes of the Th17/IL-23 pathway in psoriasis is thought to be causative for the disease manifestations. We had experience with initiation of ustekinumab in a 10 year old patient with erythrokeratoderma with cardiomyopathy; despite courses of numerous immunosuppressants and retinoids (and being on oral tacrolimus/rapamycin after cardiac transplant), her erythroderma was intense and her scaling was uncomfortable. We found high levels of Th17/IL-23 cytokines in her skin and blood. Within 4 months of ustekinumab use (and with continued improvement thereafter), her skin color had normalized, and her scaling was dramatically improved (Paller et al. The spectrum of manifestations in desmoplakin gene (DSP) spectrin repeat 6 domain mutations: immunophenotyping and response to ustekinumab. J Am Acad Dermatol. 2018;78:498-505). We propose that IL-12/IL-23 -targeting therapeutics will safely suppress the inflammation and possibly the other features of ichthyosis, improving quality of life.

1.4 Risks of Ustekinumab

Per the STELARA® (ustekinumab) Prescribing Information (version June 2018):

The most common (≥ 3%) adverse reactions associated with ustekinumab in patients being treated for psoriasis were nasopharyngitis, upper respiratory tract infection, headache, and fatigue. Sometimes serious infections have occurred in patients on ustekinumab. There is a theoretical risk for infections from mycobacteria, salmonella, and Bacillus Calmette-Guerin (BCG) vaccination in patients deficient in IL-12/IL-23. Patients will be evaluated for mycobacterium tuberculosis and treated for latent TB prior to administration of ustekinumab. Ustekinumab may increase the risk of malignancy; the safety of ustekinumab in patients with history of or a known malignancy has not been evaluated. Anaphylaxis or other clinically significant hypersensitivity reactions may occur. Cases of noninfectious pneumonia, including interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia have been reported during post-approval monitoring of ustekinumab. Allergic alveolitis has also been reported during the post-approval monitoring period. One case of Reversible Posterior Leukoencephalopathy Syndrome (RPLS) was also reported. The potential discomforts, side effects and risks associated with ustekinumab will be discussed with all subjects during the informed consent process.

2. STUDY ENDPOINTS

2.1 Primary Endpoints

Co-primary objectives:

- To evaluate the efficacy of ustekinumab for ichthyosis, as measured by an at least 50% reduction in severity (using the Ichthyosis Severity Score (ISS) measure) at 7 months after initiation of study drug (Visit 6)
- To evaluate the safety of ustekinumab for ichthyosis, based on occurrence of bacterial and fungal infections

2.2 Secondary Objectives:

- To evaluate reduction in ISS, and ISS subset measures for erythema and scaling (ISS-E, ISS-S) at months 7, 13, 19 and 25 after study drug initiation.
- To evaluate improvement in quality of life assessments at months 7, 13, 19, and 25 after study drug initiation (Dermatology Life Quality Index/DLQI for 16 years and older; Children's Dermatology Life Quality Index/CDLQI for children 6-15 years; specific questions about impact of scaling on daily life)
- To evaluate non-infectious AEs and all SAEs related to ustekinumab use, particularly injection reactions

Exploratory objectives:

- Skin and blood biomarkers will be stored. In the future, should ustekinumab prove effective, investigators will seek funding (ideally, through the NIH) to evaluate the reduction in stratum corneum and blood IL-12/IL-23 and Th17 marker expression, along with other involved biomarkers

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 over time.

3. INVESTIGATIONAL PLAN

3.1 Study Centers

This study will be performed at one site: the Department of Dermatology at Northwestern University Feinberg School of Medicine/Lurie Children's Hospital in Chicago. The entire clinical component will be performed and database housed at Northwestern University.

3.2 Study Organization

The Principal Investigator (PI) or the delegated sub-investigators of this project 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 IRB. Our 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 any reporting needed to Company.

The site project manager will also review consents, serious adverse events, and source verification on a quarterly basis throughout the study. The site project manager will work with the statisticians to complete any statistical analysis. Data will be entered by study coordinators in a central REDCap database based at Northwestern University. The Dermatology Clinical Trials Unit currently manages both international and national multisite REDCap databases.

3.3 Study Duration

The total clinical study duration will be 25 months. Patient recruitment and enrollment is expected to take approximately 6 months. The treatment period will include an initial 13-month open-label phase and a 12-month long-term extension phase. Complete data analysis and manuscript preparation will require approximately another 6 months.

3.4 Biomarker Analyses

Tape strips of the outer epidermis of the skin will be collected at Baseline, Month 7, Month 13, Month 19 and Month 25. A 15.0 mL blood sample will also be collected at Screening, Month 13, and Month 25. These samples will be labeled with the subject's study ID, study visit number, and visit date and stored at -80^{o}C at Northwestern University for possible future analysis of inflammatory biomarkers, including IL-12/23p40, IL-23p19 and Th17, as a function of clinical response. Such analysis will be conducted with future funding and will occur at Northwestern University only. Samples will not be shipped to outside individuals or institutions.

4. SUBJECT ELIGIBILITY

Subjects must be at least 6 years of age with a diagnosis of ichthyosis/ichthyotic disorder and must show at least moderate erythema (see specific inclusion criteria below). These subjects will primarily come from the Chicago/Midwest region, but the study is open to anyone meeting criteria, wishing to travel to Chicago to be in the study and able to comply with study requirements.

4.1 Inclusion Criteria

- Subject has provided informed consent; parental consent for patients under 18 years of age (plus assent for subjects age ≥ 12 and < 18).
- Subjects are at least 6 years of age or older at the time of screening.
- Before screening visit, females must be:
  - Postmenopausal, defined as
    ≥ 45 years of age with amenorrhea for at least 18 months,
    OR
  - ≥ 45 years of age with amenorrhea for at least 6 months and a serum FSH level > 40 IU/mL
    OR
  - Of childbearing potential, in which case she must satisfy at least one of the below:
    - Surgically sterile (has had a hysterectomy or bilateral oophorectomy, tubal ligation, or otherwise be incapable of pregnancy), or
    - If heterosexually active, practicing a highly effective method of birth control, including hormonal prescription oral contraceptives, contraceptive injections, contraceptive patch, intrauterine device, double-barrier method (e.g., condoms, diaphragm, or cervical cap, with spermicidal foam, cream, film, gel or suppository), or male partner sterilization, consistent with local regulations regarding use of birth control methods for subjects participating in clinical trials, for a period of 16 weeks after the last administration of study agent,

    OR

        - Not heterosexually active. Abstinence is allowed as an acceptable form of contraception.
        - Note: If a woman participant's childbearing potential changes after start of the study (e.g., a premenarchal woman experiences menarche) or if women of childbearing potential who are not heterosexually active at screening become heterosexually active, they must agree to utilize a highly effective method of birth control, as described above.
        - Female participants of childbearing potential (menstrual and not surgically sterile), must have a negative serum beta-human chorionic gonadotropin ($_{\beta}$-hCG) pregnancy test at screening and a negative urine pregnancy test at Week 0 (prior to screening visit) and agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the study and for a period of 16 weeks after the last administration of study agent.
    - Male participants who are not surgically sterilized and are heterosexually active with a woman of childbearing potential, must agree to use a barrier method of contraception (e.g., condom with spermicidal foam/gel/film/cream/suppository) and to not donate sperm during the study and for 16 weeks after last receiving study agent. Note that barrier methods must also be used in all male subjects sexually active with pregnant partners for at least 16 weeks after last study agent administration.
- Subjects must have a confirmed clinical diagnosis of ichthyosis/ichthyotic disorder, and either have completed genotype or be willing to be genotyped (genotype results will not be required for entry into the study).
- Subjects must have at least moderate erythema (ISS-erythema score ≥ 2) related to his/her ichthyosis/ichthyotic disorder.
- Subjects must be clinically judged to be immunocompetent based on baseline laboratory testing (chemistry and hematology), medical history and physical examination.
- Subjects will have baseline negative QuantiFERON®-TB gold, Hepatitis B, Hepatitis C, and HIV laboratory testing.

4.2 Exclusion criteria

- Subjects who are unable to provide informed consent or assent (or who do not have consent from a Legally Authorized Representative if < 18 years).
- Subjects with ichthyosis vulgaris or X-linked recessive ichthyosis.
- Subjects who have a known allergy to ustekinumab or its products.
- Female subjects who are pregnant or breastfeeding, or who are considering becoming pregnant.
- Subjects who have prior biologic use targeting IL-12/IL-23 monoclonal antibody.
- Subjects who have used a systemic retinoid or systemic anti-inflammatory agent within 4 weeks prior to baseline.
- Subjects who have used topical steroid in the previous week, retinoid or keratolytic agent in the previous 24 hours.
- Subjects with active infections or recent history of serious infections, malignancies or history of malignancies, recent immunizations with live vaccines, or any severe, progressive, or uncontrolled renal, hepatic, hematologic, endocrine, pulmonary, cardiac, neurologic, psychiatric, or cerebral disease, or signs or symptoms thereof

- Subjects who are under 6 years of age at the time of screening.

Ustekinumab is approved for Crohn's disease and has been tested/ found to be safe for psoriasis as young as 6 years of age with pK and safety validation to this age level. Although we would love to use in younger children with ichthyosis, we chose 6 years of age because of the extensive experience and safety testing to this age level.

We are focusing on inflammatory forms of ichthyosis with Th17 skewing in the skin and blood. Neither ichthyosis vulgaris nor recessive X-linked ichthyosis are inflammatory forms of ichthyosis and neither has been tested for Th17 skewing; both are easily amenable to available topical and OTC interventions and thus have little need for new interventions, especially using a systemic agent.

All screened subjects initially considered for this study will be documented. Study staff will create and maintain pre-screening logs and will contact potential subjects through IRB-approved recruitment methods. If the subject is excluded from the study, reasons for exclusion will be documented in the pre-screening log.

5. TREATMENT PROCEDURES

5.1 Investigational Treatment

The following study treatment will be used:

- Ustekinumab (STELARA®)

5.2 Dispense and Use of Investigational Treatment

5.2.1 Dispensing the Investigational Treatment

The research pharmacy at Lurie Children's Hospital will be supplied with ustekinumab (STELARA®) from the Company. Ustekinumab will be shipped to a designated, licensed pharmacist at the investigational pharmacy at Lurie Children's Hospital.

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. 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.

The ustekinumab for this study will be supplied as final vialed product (FVP), single-use 2 mL Schott Type I glass vial closed with a Daikyo D777-1 FluroTec®-coated stopper and a West 13 mm aluminum seal and plastic light green flip-off button. The FVP formulation is composed of 90 mg/mL ustekinumab

with excipient concentrations of 6.7 mM L-histidine, 7.6% (w/v) sucrose, and 0.004% (w/v) polysorbate 80, pH 6.0. There is 1 dose strength (i.e. 45 mg in 0.5 mL volume). No preservatives are present.

5.2.2 Instructions for prescribing and taking study treatment

Throughout the study, treatment will be via subcutaneous injection of ustekinumab, administered by a physician or nurse licensed in the state of Illinois. All subjects enrolled in the study will receive ustekinumab at Baseline (Day 0), Month 1, and then every 8 weeks thereafter (Months 3, 5, 7, 9, and 11). Dosing every 8 weeks is based on a case report of a pediatric patient with autosomal recessive congenital ichthyosis (ARCI) who had initial dramatic improvement with ustekinumab injection but subsequent worsening of skin symptoms prior to dosing every 12 weeks (Poulton, 2019). Improvements were sustained by dosing every 8 weeks. This patient did not experience any adverse events related to increased dosing frequency. While psoriasis patients treated with ustekinumab generally receive dosing every 12 weeks, patients with inflammatory bowel disease receive ustekinumab every 8 weeks The safety profile in clinical trials with dosing every 8 weeks (i.e. those for inflammatory bowel disease) has been consistent with the safety profile in clinical trials with dosing every 12 weeks (i.e. those for psoriasis and psoriatic arthritis) (Ghosh, 2019).

Subjects who have evidence of improvement (per the subject) will have the option to continue in the Long-Term Extension portion of the study for an additional 12 months and will receive ustekinumab every 8 weeks (Months 13, 15, 17, 19, 21, and 23). At each dosing visit, subject weight will be measured and the dose of ustekinumab will be adjusted accordingly. The weight-based dosing used will be the standard dosing used in clinical trials for pediatric patients receiving ustekinumab for psoriasis (Landells, 2015; Phillipp 2020). Subjects will receive one of the following dose levels depending on their weight:

- Weight < 60 kg: 0.75 mg/kg
- Weight ≥ 60 kg to ≤ 100 kg: 45 mg
- Weight > 100 kg: 90 mg

5.2.3 Prohibited treatment

If subjects are using a systemic retinoid or immunomodulatory agent, the patient will wait four weeks to initiate therapy with ustekinumab. Washout for topical steroids will be one week.

While enrolled in the study, subjects may not use any topical agent for the treatment of ichthyosis during the first 6 months other than bland emollients. After the 6-month time point, keratolytics, including but not limited to agents containing tazarotene, salicylic acid, alpha-hydroxyacids, and urea, can be added to the regimen as per investigator discretion. Subjects may not be on any systemic agents for the treatment of ichthyosis. Subjects who experience skin infection requiring antibiotics during the study may continue on study drug and stay in the study, unless per investigator discretion. These therapies will be noted by the investigator on the concomitant therapy form.

All concomitant therapies (including prescription medications, over-the-counter medications, vitamins, herbal supplements) will be recorded throughout the study.

5.3 Subject Withdrawal/Discontinuation

Subjects will be evaluable if they complete all required assessments and visits through and including Month 13. 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 withdrawal. Similarly, if subjects choose to discontinue their participation in the study, which can be done at any time per subject discretion, study staff will attempt to contact the subject to determine their reason for discontinuation.

Subjects who do not achieve a 25% reduction in the Ichthyosis Severity Score (ISS) at month 7 (Visit 6) will be withdrawn from the study due to lack of efficacy.

Treatment must be discontinued under the following circumstances due to concern for subject safety:

- The investigator believes that for safety reasons (e.g., AE or SAE) it is in the best interest of the subject to discontinue study treatment;
- An AE temporally associated with study drug injection, resulting in bronchospasm with wheezing and/or dyspnea requiring ventilatory support, or symptomatic hypotension with a greater than 40 mm Hg decrease in systolic blood pressure;
- A severe study drug injection-site reaction;
- The subject or their legally acceptable representative withdraws consent/assent for administration of study drug;
- Pregnancy, or pregnancy planned within the study period or within 6 months after the last study drug injection;
- Malignancy;
- An opportunistic infection;
- A recurrent or chronic serious infection;
- The subject is deemed ineligible according to the following TB screening criteria:
  - A diagnosis of active TB is made.
  - A subject has symptoms suggestive of active TB based on history or physical examination, or has had recent close contact with a person with active TB.
  - A subject undergoing evaluation has a positive QuantiFERON®-TB Gold test result and/or an indeterminate QuantiFERON®-TB Gold test result on repeat.

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.

5.4 Study Completion and Post-study Treatment

Study participation is completed for the subject at the conclusion of either their Month 13 study visit or, if participating in the long-term extension, their Month 25 study visit. Adverse events that occur within 30 days of the End of Study visit must be documented and reported by the PI.

The study in its entirety will be completed when 15 subjects have completed their treatment course as per the protocol and the complete data analysis 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" the visits at which each assessment will be 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).

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

6.1 Screening/Baseline Visit

The Screening and Baseline visit procedures may be combined on the same day if the subject meets all screening eligibility criteria. All patients who have not had genetic testing (research or a CLIA-approved lab) will enroll in Dr. Paller's "Screening for the Genetic Basis of Dermatologic Disease" IRB# 2009-13803 and have testing sent to Dr. Keith Choate at Yale University. If the clinical diagnosis is ichthyosis / ichthyotic disorder, having a known gene mutation is not required before entry into the study. The saliva sample for genetic testing will be obtained at the screening visit and before drug dosing/Baseline Visit. Urine pregnancy test (female subjects of childbearing potential only) will be completed prior to any baseline study procedures and ustekinumab injection. The saliva sample is part of study #2009-13803.

6.1.1 Consent

Consent will be obtained by the study investigator or by approved study team member at the screening visit (Visit 1) as indicated in Appendix 1 and before any study procedures take place. All participants will be given time to read the IRB-approved consent form and ask any questions they may have. The consenter will emphasize that the study is voluntary. Consent forms will be kept in subject source binders in a locked office in the Department of Dermatology.

6.1.2 Medical and Medication History

A PI or designated study team member will collect information regarding relevant medical history/current medical conditions 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 the patient's ichthyosis 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. 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/Weight

Vital signs, including blood pressure, pulse, respiratory rate, temperature, and weight will be collected at Screening, Baseline, and every visit at which there is study drug administration, as indicated in Appendix 1. Height will be recorded at the first visit, the end of the open label phase, and the end of the long-term extension, as indicated in Appendix 1.

6.1.4 Complete Physical Examination & Skin Examination

A complete physical examination will be performed by a physician at the screening and baseline visits, as well as the end of the open label phase and the end of the long-term extension. A full skin exam will occur at Baseline and then at every visit at which there is study drug administration, as indicated in Appendix 1. If the history and/or skin examination at interim visits suggests an additional issue, an unscheduled physical examination may be needed. 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 Safety Labs and Pregnancy Testing

Clinical lab evaluations at screening visit include QuantiFERON gold, Hepatitis B, Hepatitis C, HIV, chemistry and hematology testing to be resulted at local site hospitals. Blood will be drawn by a licensed phlebotomist or trained study team member per hospital requirements. QuantiFERON gold, chemistry and hematology testing will also be done at visits for Months 13 and 25.

All female study subjects of child-bearing potential (i.e. female subjects who have experienced menarche) will be tested for pregnancy at the screening and baseline 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 participation in this study. In addition, female subjects of child-bearing potential will have urine HCG testing prior to every administration of the study drug.

6.1.6 Severity Evaluations - ISS and Ichthyosis Severity Self-Assessment

Physician severity evaluations will be performed at every in-person study visit. Severity assessments will be performed by Ichthyosis Severity Score (ISS). ISS is a composite score that captures differences in severity in different body regions as a function of their body surface area. As in the EASI score for atopic dermatitis and the PASI score for psoriasis, ISS evaluates erythema and scaling as a 0-4+ scale and provides pictorial representations for comparisons. Severity is determined at each of four locations: head and neck (including scalp); arms (including palms); legs (including soles); and trunk, prorated based on body surface area. Separate scores are given for face, scalp, neck, groin, palms, soles, elbows and knees within their regions to allow for serial assessments of specific body regions that may cause special functional or psychosocial effects.

6.1.7 TEWL and Tape Strips

TEWL (transepidermal water loss) will be performed on the nondominant upper outer arm to assess the skin barrier at all in-person study visits. Tape strips will be also be obtained from subjects at Baseline, Month 7, Month 13, Month 19, and Month 25. TEWL will be performed at four different times during visits in combination with tape stripping: prior to applying tape strips, after application of the 6^{th} tape strip, after application of the 11^{th} tape strip, and after application of the 16^{th} tape strip. TEWL measurements at each time will be collected in triplicate. Tape strips are purchased from CuDerm. Tape stripping will be performed on the nondominant upper outer arm using circular 2x2 or 3x3 cm transparent tape strips at lesional skin sites. Equal pressure will be applied to affected areas for 10 seconds. Up to 16

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. Subjects will be asked not to apply emollient or moisturizer for at least 24 hours prior to tape stripping. The tape strips will be stored on site at the Paller Laboratory at Northwestern University. Depending on efficacy of ustekinumab for ichthyosis, in the future the study team may apply for additional funding to analyze the tape strips possible for detection of alterations of epidermal lipids and proteins in the outer stratum corneum of epidermis. Proteomics and lipidomics analysis will occur at Northwestern University only. Samples will not be shipped to outside individuals or institutions.

6.1.8 Microbiome Sampling

Microbiome sampling will be done at baseline, Month 7, Month 13, Month 19, and Month 25. This sampling will involve swabbing the lesional skin with three separate swabs in three different areas on the nondominant upper outer arm. Early skin microbiome studies have shown healthy skin has more microbial diversity. The contribution of alterations in the microbiome to skin disease pathology and severity is of growing interest. Subjects will be asked not to shower or apply emollient or moisturizer for at least 24 hours prior to sampling.

6.1.9 Photography

Photography will be done at Baseline, Month 7, Month 13, Month 19, and Month 25 as indicated in Appendix 1 and will be of assessment areas only. 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, research server maintained by Northwestern University within the Department of Dermatology and deleted from the camera memory card as soon as possible. Photos will be used to track visible skin changes that may occur throughout the duration of the study. Photographs may be taken of lesional skin at ad hoc times throughout the study if the subject experiences changes in their ichthyosis.

6.1.10 Blood Samples for Biomarkers

A 15.0ml blood sample will be collected at Screening, Month 13 and Month 25, as indicated in Appendix 1. Blood will be drawn by a licensed phlebotomist or trained study team member per hospital requirements. Samples will be centrifuged and serum separated within one hour of collection, labeled with the subject's study ID, study visit number, and visit date and stored at -80ºC at Northwestern University. Samples will stay at Northwestern University only. Samples will not be shipped to outside individuals or institutions.

6.1.11 DLQI / CDLQI and IFTB

Quality of life measures will be obtained at the baseline, Month 7, Month 13, Month 19, and Month 25 visit as indicated in Appendix 1. The Dermatology Life Quality Index (DLQI; Appendix 3) is the most commonly used and first dermatology-specific quality of life assessment tool (Basra et al 2008) used for ages 16 and older. It can be used to assess various dermatologic conditions and has been a reliable measure of quality of life (Finlay 1994). CDLQI (Appendix 4) is designated for use in children as young as four and has been validated (Lewis-Jones and Finlay, 1993). CDLQI will be used for ages 6-15 years. The Ichthyosis Financial and Time Burden (IFTB) is an ichthyosis-specific questionnaire with a scale that

aims to capture novel QoL data and better capture data specific to the time and financial burden of the disease. The IFTB is currently in development with plans for future validation. IFTB will be collected from all subject ages, with proxy assisting if the subject is 17 years or younger.

6.1.12 STIGMA Questionnaire

STIGMA Questionnaire (Appendix 7) is used to assess subjects' perceived social stigma in regard to their condition and will be administered at the Baseline, Month 7, Month 13, Month 19, and Month 25 visits (Appendix 1). All subjects will complete, and a proxy survey will also be collected if the subject is between the ages of 6yo-17yo.

6.1.13 Itch and Pain NRS/PROMIS Itch

A Numerical Rating Score (NRS) from 0-10 for both itch and pain will be administered to all subjects at every in-person study visit (Appendix 1). Parent proxy will be used for children 6 to 17 years of age. Patient-Reported Outcomes Measurement Information System (PROMIS) is a patient-centered measure that evaluates physical, mental and social health in adults and children with regards to impact of their itch. PROMIS Itch evaluation (Appendix 6) will be conducted at Month 0, Month 7, Month 13, Month 19, and Month 25 if the subject scores ≥ 2 on the Itch NRS (Appendix 6). All subjects will complete and a parent proxy will also be collected for children 6 to 17 years of age.

6.2 Open Label and Long Term Extension Rollover

Subjects will be examined at in-person study visits at Screening, Baseline, and Months 1, 3, 5, 7, 9, 11, and 13 for the open label phase. Specific study procedures conducted during each of these visits are outlined in Appendix 1. Should the subject find ustekinumab to be beneficial, they may have the option to continue to the Long-Term Extension with in-person study visits every 8 weeks (Months 15, 17, 19, 21, 23, and 25). The final in-person study visit will be at Month 25, with the final administration of study drug at Month 23 (Appendix 1).

6.2.1 Adverse Event Assessment

Adverse event assessments will occur at all study visits after Baseline. 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 be collected as specified in the Schedule of Assessments flowchart.

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 study files on a secure research server within the Department of Dermatology maintained by Northwestern University.

6.4.3 Transporting specimens

Specimens needing transport to outside collaborating laboratories will be done so using a competent courier (e.g. FedEx or World Courier). Samples will be retained in the Paller Lab at Northwestern University until shipment. The shipment will be traceable, and the chain of custody will be documented. The specimens will be delivered to a competent member of the study team at the collaborating laboratory, who will assure that the specimens have been properly de-identified and stored/transported in the proper environment.

6.4.4 Specimen management

Samples will be stored at Northwestern University following the date the analysis is complete and used solely for objectives outlined in this study. Patient confidentiality will be maintained. Results of all experiments will be reviewed by the PI 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 until data analysis is complete for this 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. AEs include any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. Lack of drug effect is not considered an AE because the purpose of the study is to establish drug effect.

All AEs, SAEs, pregnancies, adverse events of special interest, special reporting situations, and product quality complaints (PQCs) will be recorded and reported from the time the subject signs the informed consent form to 30 days after administration of the last dose of test article. Subjects will be instructed to report AEs and Serious AEs (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 team. Safety data will be reviewed by the investigators, study team, biostatisticians and project manager unrelated to the study approximately every 3 months, depending on the number of subjects enrolled.

In psoriasis trials, the most common adverse reactions per ustekinumab studies include nasopharyngitis, upper respiratory tract infection, headache and fatigue.

7.2 Follow-up of Subjects with Adverse Events

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. At study close, study staff will document any outstanding adverse events and communicate with each study subject's primary care physician for continuity of care and ongoing subject safety.

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
- is suspected transmission of any infectious agent via a medicinal product

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 of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused 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.

Death for any reason will be reported as a serious adverse event.

All AEs (serious and non-serious) are captured on the case report form; SAEs also require individual reporting to Company as per Section 7.3.2.

7.3.2. SAE, Adverse Events of Special Interest, and Special Reporting Situations

To ensure subject safety, every SAE, regardless of causality, adverse events of special interest and special reporting situations occurring after the subject has provided informed consent and until 30 days after the last study visit, will be reported to the IRB and Company within 24 hours of the study team becoming aware of the event. Any SAEs experienced after the 30-day period should be reported to Janssen Pharmaceutical Companies 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. 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 Company and IRB. 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, 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.

Deaths will be reported to the IRB and Company within 24 hours of becoming aware of the event. This information will be communicated by the PI via email. All serious adverse events will be reported to the IRB according to their policies, and these events will also be reported to the Company. Non-serious adverse events will be reported per their IRB policies and to the Company annually and at the end of the study. SAEs will be reported to PI immediately, and if the number of subjects experiencing AEs exceeds the pre-determined threshold, the PI will evaluate and determine if an early termination is needed.

7.4. Adverse Events of Special Interest

In addition to the usual expedited reporting of all "serious" adverse events (per ICH criteria), the following AEs of special interest must also be reported to the Company in an expedited fashion, i.e., per SAE reporting timelines, even when not serious (AE does not meet any of the ICH serious AE criteria):

- All malignancies
- All cases of active tuberculosis (TB)

Special consideration should be given to reporting adverse events that are opportunistic infections and clinically significant as serious adverse events based on the "otherwise medically significant" criteria for seriousness, when they do not meet other Serious AE ICH criteria (e.g., hospitalization).

7.5. Pregnancy Reporting

To ensure subject safety, each pregnancy occurring while the subject is on study treatment must be reported to the IRB and Company within 24 hours of learning of its occurrence using the Serious Adverse Event Form. 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.

Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Any subject who becomes pregnant during the study must discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported to the Company within 24 hours of learning of its occurrence using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

7.6. Special Reporting Situations

Safety events of interest for a Janssen medicinal product that require expediting reporting and/or safety evaluation include, but are not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events will be treated in the same manner as adverse events. Special situations will be recorded on the Adverse Event page of the CRF.

Any special situation that meets the criteria of a serious adverse event will be recorded on a Serious Adverse Event Report Form and be reported to the Company within 24 hours of becoming aware of the event.

Product Quality Complaint (PQC)
A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:
- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe
- Suspected Contamination
- Suspected Counterfeit

PQC Reporting
A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and the COMPANY, and are mandated by regulatory agencies worldwide. The COMPANY has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to the COMPANY by the PRINCIPAL INVESTIGATOR within 24 hours after being made aware of the event. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event, the PRINCIPAL INVESTIGATOR must report the PQC to the COMPANY according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by the COMPANY.

8. DATA REVIEW AND DATABASE MANAGEMENT

The project manager at Northwestern will be responsible for grant applications and yearly reports. 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. The statistician will meet with the project manager to discuss the progress of the study.

8.1. Site Monitoring

The Project Manager at Northwestern will monitor the site. The site will also be monitored internally by the IRB.

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 Coded Identifier List (CIL), on a secure research server maintained by Northwestern University.

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. Subjects' personal information collected from medical records and paper source documents will be maintained within study files that will be kept in a locked room in the Department of Dermatology. Any electronic documents will be saved on a secure research server within the Department of Dermatology and maintained by Northwestern University.

9. DATA ANALYSIS

Statistical analysis will be performed by statisticians at Northwestern University. Since this is a pilot study, data will be gathered to analyze efficacy to potentially develop a larger trial in the future.

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.

'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 patients who received at least one dose of the treatment. Because the loading dose is given at baseline, this should effectively include all enrolled 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. Due to the small subject population size, we will not adjust for demographics or baseline characteristics during analysis and assume that patients will be homogenous in these variables.

9.3. Efficacy Analyses

Primary and secondary endpoints will be analyzed at the time points specified in Section 2.0 (adjusting for baseline scores) using a paired T-test. The percent change from baseline will also be calculated. Data will be plotted across time to visually analyze for trends.

9.4 Safety Variables

Safety will be evaluated by tabulations of adverse events and will be presented with descriptive statistics at each visit. 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. The specific system organ classes and preferred terms analyzed will be those that are reported by at least five percent of the subjects.

9.5 Sample Size Justification

This is a pilot study and a power analysis is not needed.

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 presented 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) or parent/proxy and written assent from subjects 12-17 years of age (Lurie Children's Hospital IRB requires written assent for children over 12 years of age only). A copy of the subject's signed consent/assent form must be retained in the study file. Documentation of consent/assent 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.

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 Northwestern University. 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 the Company and approved by the IRB 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 Company.

12. REFERENCES

Ghosh S, Gensler LS, Yang Z, et al. Ustekinumab Safety in Psoriasis, Psoriatic Arthritis, and Crohn's Disease: An Integrated Analysis of Phase II/III Clinical Development Programs [published correction appears in Drug Saf. 2019 Apr 22;:]. *Drug Saf*. 2019;42(6):751-768. doi:10.1007/s40264-019-00797-3

Landells I, Marano C, Hsu MC, et al. Ustekinumab in adolescent patients age 12 to 17 years with moderate-to-severe plaque psoriasis: results of the randomized phase 3 CADMUS study. *J Am Acad Dermatol*. 2015;73(4):594-603. doi:10.1016/j.jaad.2015.07.002

Philipp S, Menter A, Nikkels AF, et al. Ustekinumab for the treatment of moderate-to-severe plaque psoriasis in paediatric patients (≥ 6 to < 12 years of age): efficacy, safety, pharmacokinetic and biomarker results from the open-label CADMUS Jr study [published online ahead of print, 2020 Mar 16]. *Br J Dermatol*. 2020;10.1111/bjd.19018. doi:10.1111/bjd.19018

Poulton, C., Gration, D., Murray, K., Baynam, G. and Halbert, A. (2019), Autosomal recessive congenital ichthyosis due to homozygous variants in *NIPAL4* with a dramatic response to ustekinumab. Pediatr Dermatol, 36: 1002-1003. doi:10.1111/pde.13995

Additional references are available upon request

Appendix 1: Schedule of Assessments Flowchart

	Screening	Baseline	Month 1	Month 3	Month 5	Month 7	Month 9	Month 11	Month 13
	Week -4	Week 0	Week 4	Week 12	Week 20	Week 28	Week 36	Week 44	Week 52/ OL end
Procedures	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**	**Visit 7**	**Visit 8**	**Visit 9**
Consent	X								
Demographics	X								
Inclusion/Exclusion	X	X							
Medical History (baseline or interim)	X	X	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X	X
Full physical exam, including skin	X	X							X
Full Skin Examination			X	X	X	X	X	X	
Vital Signs (incl. weight)	X	X	X	X	X	X	X	X	X
Height	X								X
Severity evaluations	X	X	X	X	X	X	X	X	X
Venipuncture	X								X
Saliva collection and DNA extraction	X								
Collection of PAX RNA and protein	X								X
Tape Strip collection		X				X			X
Microbiome collection		X				X			X
TEWL		X	X	X	X	X	X	X	X
NRS Pain and Itch		X	X	X	X	X	X	X	X
PROMIS Itch (if ≥2 on NRS, otherwise subject does not need to complete)		X				X			X
DLQI/CDLQI and IFTB		X				X			X
STIGMA questionnaire		X				X			X
Subject severity self-assessment		X	X	X	X	X	X	X	X
Photography		X				X			X
QuantiFERON®-TB gold	X								X
Hep B/C, HIV testing	X								
Chemistry, hematology testing	X								X
Urine HCG (if applicable)	X	X	X	X	X	X	X	X	X
Injection		X	X	X	X	X	X	X	

	Month 13	Month 15	Month 17	Month 19	Month 21	Month 23	Month 25
	Week 52/LTE Start**	Week 60	Week 68	Week 76	Week 84	Week 92	Week 96/End of LTE
Procedures	Visit 9	Visit 10	Visit 11	Visit 12	Visit 13	Visit 14	Visit 15
Consent							
Demographics							
Inclusion/Exclusion							
Medical History (baseline or interim)	X	X	X	X	X	X	X
Concomitant Meds	X	X	X	X	X	X	X
Adverse Event Assessment	X	X	X	X	X	X	X
Full physical examination, including skin	X						X
Full Skin Examination		X	X	X	X	X	
Vital Signs (incl. weight)	X	X	X	X	X	X	X
Height	X						X
Severity evaluations	X	X	X	X	X	X	X
Venipuncture	X			X			X
Saliva collection and DNA extraction							
Collection of PAX RNA and protein	X						X
Tape Strip collection	X			X			X
Microbiome collection	X			X			X
TEWL	X	X	X	X	X	X	X
NRS Pain and Itch	X	X	X	X	X	X	X
PROMIS Itch (if ≥2 on NRS, otherwise subject does not need to complete)	X			X			X
DLQI/CDLQI and IFTB	X			X			X
STIGMA questionnaire	X			X			X
Subject severity self-assessment	X	X	X	X	X	X	X
Photography	X			X			X
QuantiFERON®-TB gold	X						X
Hep B/C, HIV testing							
Chemistry, hematology testing	X						X
Urine HCG (if applicable)	X	X	X	X	X	X	X
Injection	X	X	X	X	X	X	

**If subject continues to LTE, procedures above will be followed which include injection of study drug. If not continuing to LTE, then subject will follow procedures for OL End in the table preceding.

Appendix 2: Ichthyosis Severity Score (ISS)

What is the ichthyosis scoring system (ISS)?

The ISS is a comprehensive and user-friendly instrument for assessing the **extent** and clinical **severity** of ichthyosis. It aims to be a validated tool that will be adopted by the FDA. We addressed several of the FDA's concerns and specifications through developing new descriptors for severity and developing two separate scoring systems for patients under 8 years of age and patients older than 8 years in order to take into account differences in relative body proportions.

Scores will grade: 1) **scale severity and** 2) **erythema**.

Scoring overview

Scoring for scale (0-4) should be done for the entire region. It should be an **average** of affected areas, not the worst score for that region.

Half-points are allowed. 2 limbs=one body region.

Erythema score (0-4) for a particular region should be the **worst** score for that region because erythema can be obscured by scale.

Body regions scored for each patient:

Each region will be scored separately

1. **Head and neck:** Scalp, face, neck
2. **Trunk:** Groin and chest/abdomen/back
3. **Upper extremities:** Elbow and palms
4. **Lower Extremities:** Knees and soles

Anatomical definitions of body parts:

Head and neck

- Head
    - Face: extends from the forehead to the chin and includes the mouth, nose, cheeks, eyes, and ears. It excludes the neck. (1/3)
    - Scalp: extends from the junction of forehead skin to the occiput (back of head). It excludes the face. (1/3)
- Neck: extends from the mandible to the attachment of the sternocleidomastoid at the clavicle. It also includes the back of the neck, which extends from the C1 vertebrae to the trapezius muscle. (1/3)

Torso – Includes back, chest, abdomen, and groin

- Chest, abdomen, groin: extends from one anterior axillary fold to the other and from the clavicles to the anterior iliac spine
- Back: extends laterally from one posterior axillary fold to the other and from T1-S1. It excludes posterior arms and neck.

Upper extremities: extends from the acromial process to the fingers and includes the anterior axillary fold and antecubital fossa. *(It excludes the elbow and any portion of the trunk that may be visible.)*

Lower extremities: extends from the superior iliac spine to the toes and includes the buttocks.

Elbows and knees

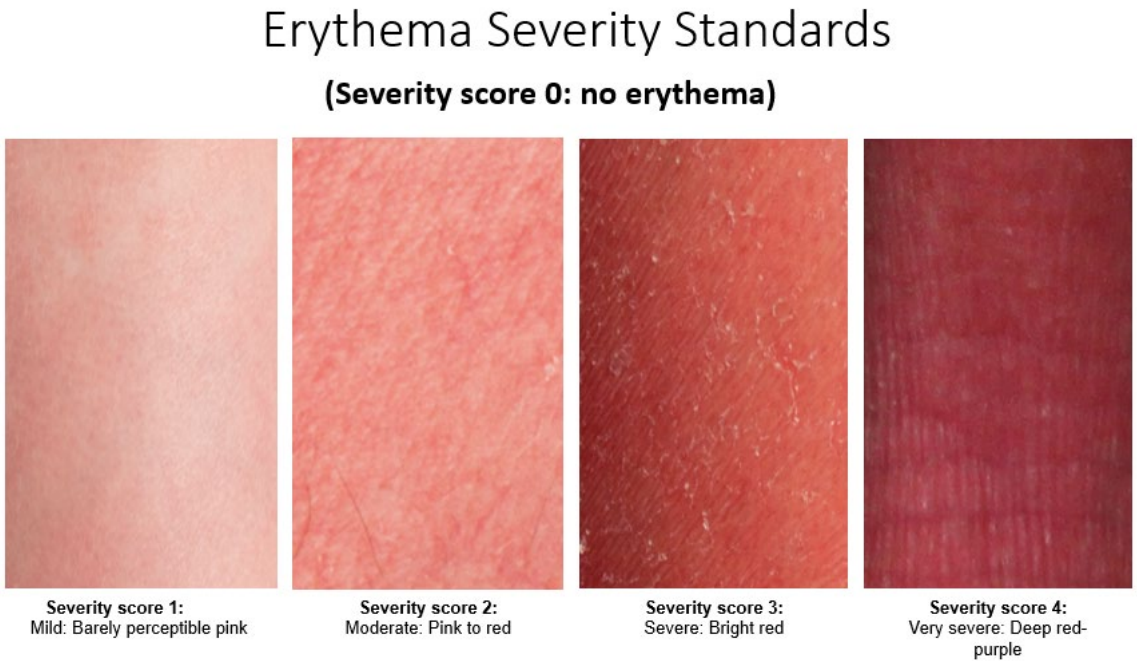
- Elbows: Includes attachment of the humerus to the proximal radius and ulna. It excludes antecubital fossa.
- Knees: Includes attachment of the femur to the tibia and patella. It excludes the popliteal fossa.

Palms: extends from the tip of the phalanges to the carpal bones (wrist joint) and includes the area between the five phalanges. It includes glabrous skin.

Soles: extends from the tip of the toes to the calcaneus (heel). It includes 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.

Scale descriptors for all sites but the palms and soles	
0	Normal skin; no perceptible scale, and no loss of normal skin markings
1	Normal skin intermixed with small scales or areas of minimally shiny/waxy/thickened skin and/or partial loss of normal skin markings
2	Several areas of scaling upon a background of mildly thickened skin often with some loss of normal skin markings
3	Confluent scales with or without focal areas of thick, piled scales and moderately thickened skin
4	Extensive areas of confluent, primarily thick, piled scale and severely thickened skin

Scale descriptors for the palms and soles	
0	Normal skin; no perceptible scale or accentuated skin markings
1	Minimal, confluent or focal thickening with continued visibility of normal skin lines. May have minimal desquamative scale.
2	Mild, confluent or focal thickening that at least partially obscures skin lines. May have mild desquamative scale, some accentuation of coarse skin lines and/or mild fissuring.
3	Moderate, confluent or focal piled or desquamative scale or yellow thickening. Often with accentuated coarse skin lines with or without fissures.
4	Thick, confluent or focal yellow piled scale and/or severe desquamative scale with or without fissures.



UNDER 8 YEARS OLD

Body region	Scale (0-4)	Multiplier		Erythema (0-4)	Multiplier	Score per region
Head						
Scalp		X 0.067	+		X 0.067	
Face		X 0.067	+		X 0.067	
Neck		X 0.067	+		X 0.067	
Trunk						
Chest/back/ abdomen		X 0.297	+		X 0.297	
Groin		X 0.003	+		X 0.003	
Upper extremities						
Palms		X 0.004	+		X 0.004	
Elbows		X 0.004	+		X 0.004	
Arms (including dorsal hands)		X 0.192	+		X 0.192	
Lower extremities						
Knees		X 0.012	+		X 0.012	
Soles		X 0.009	+		X 0.009	
Legs (including dorsal feet/buttocks)		X 0.279	+		X 0.279	
Final Score:						_____ (0-8)

8 YEARS AND OLDER

Body region	Scale (0-4)	Multiplier		Erythema (0-4)	Multiplier	Score per region
Head:						
Scalp		X 0.033	+		X 0.033	
Face		X 0.033	+		X 0.033	
Neck		X 0.033	+		X 0.033	
Trunk:						
Chest/back/ abdomen		X 0.297	+		X 0.297	
Groin		X 0.003	+		X 0.003	
Upper extremities:						
Palms		X 0.004	+		X 0.004	
Elbows		X 0.004	+		X 0.004	
Arms (including dorsal hands)		X 0.192	+		X 0.192	
Lower extremities:						
Knees		X 0.016	+		X 0.016	
Soles		X 0.012	+		X 0.012	
Legs (including dorsal feet/buttocks)		X 0.372	+		X 0.372	
Final Score:						_____ (0-8)

Appendix 3: 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 4: CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX (CDLQI)

Name: Diagnosis: CDLQI
Age: SCORE:
Address: Date:

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

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

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

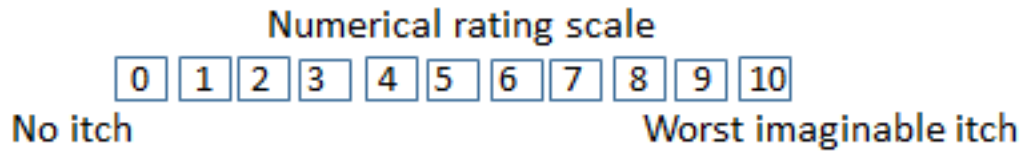
Please check that you have answered EVERY question. Thank you.

Appendix 5: CHILDREN'S DERMATOLOGY LIFE QUALITY INDEX (CDLQI) Cartoon

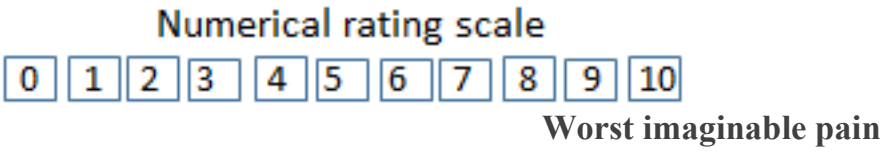
Separate worksheet for subjects of a young age who would prefer to complete the cartoon version of the questionnaire.

Appendix 6: NRS Itch/Pain and PROMIS Itch Scores

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



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



No pain **Worst imaginable pain**

PROMIS Itch Scores

Pediatric Itch - Short Form 1 (2 + 6)

Please respond to each item by marking one box per row.

		No itch	Mild	Moderate	Severe	Very Severe
QPIQC38	What is your level of itch right now?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days . . .					
QPIQC37	How bad was your itch on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days . . .

		Never	Rarely	Sometimes	Often	Almost Always
QPIQC20	Because of itch, I could not do some physical activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC42	Because of itch, it was hard to sit still	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC47	Because of itch, I could not focus my thinking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC49	Because of itch, I felt frustrated	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC50	Because of itch, I avoided being around people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC54	I scratched myself until I bled	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Parent Proxy Itch - Short Form 1 (2 + 6)

Please respond to each item by marking one box per row.

		No itch	Mild	Moderate	Severe	Very Severe
QPIQC38	What is your child's level of itch right now?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days . . .

QPIQC37	How bad was your child's itch on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

In the past 7 days . . .

		Never	Rarely	Sometimes	Often	Almost Always
QPIQC20	Because of itch, my child could not do some physical activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC42	Because of itch, it was hard for my child to sit still	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC47	Because of itch, my child couldn't focus his/her thinking	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC49	Because of itch, my child was frustrated	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC50	Because of itch, my child avoided being around people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
QPIQC54	My child scratched until s/he bled	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 7: Stigma Questionnaire

STIGMA-Child Questionnaire

NQSTGped03c	Lately (in the last 1-2 months)	Because of my condition, others my age avoided me.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped04c	Lately (in the last 1-2 months)	Because of my condition, I felt left out of things.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped06c	Lately (in the last 1-2 months)	Because of my condition, others my age made fun of me.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped07c	Lately (in the last 1-2 months)	Because of my condition, I felt embarrassed when I was in front of others my age	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped10c	Lately (in the last 1-2 months)	Because of my condition, I was treated unfairly by others my age.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGped07	Lately (in the last 1-2 months)	Because of my condition, others my age didn't see the good things about me.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped17c	Lately (in the last 1-2 months)	Because of my condition, I felt different from others my age.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped19c	Lately (in the last 1-2 months)	I avoided making new friends to avoid talking about my condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped01c	Lately (in the last 1-2 months)	Because of my condition, others my age bullied me.	1 = Never 2 = Rarely 3 = Sometimes

			4 = Often 5 = Always
NQSTGped02c	Lately (in the last 1-2 months)	Because of my condition, others my age seemed uncomfortable with me	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped05c	Lately (in the last 1-2 months)	Because of my condition, others my age were mean to me.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped08c	Lately (in the last 1-2 months)	Because of my condition, others my age tended to stare at me.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped09c	Lately (in the last 1-2 months)	Because of my condition, I worried about what others my age thought about me.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped11c	Lately (in the last 1-2 months)	I was unhappy about how my condition affected my appearance.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped14c	Lately (in the last 1-2 months)	Because of my condition, I worried that I made life harder for my parents or guardians.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped15c	Lately (in the last 1-2 months)	I felt embarrassed about my condition	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGped20c	Lately (in the last 1-2 months)	I lost friends by telling them that I have this condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGped01	Lately (in the last 1-2 months)	Because of my condition, people thought I wasn't clean.	1 = Never 2 = Rarely 3 = Sometimes

			4 = Often 5 = Always
DermSTGped02	Lately (in the last 1-2 months)	Because of my condition, others avoided touching me (ex: holding my hand).	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGped03	Lately (in the last 1-2 months)	I wished my condition wasn't visible to other people.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGped04	Lately (in the last 1-2 months)	I felt embarrassed when others my age asked about my condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGped08	Lately (in the last 1-2 months)	Because of my condition, I couldn't wear the clothing/shoes I wanted to wear.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always

STIGMA-Proxy QuestionnaireNQSTGprox03	Lately (in the last 1-2 months)	Other children avoided my child because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox04	Lately (in the last 1-2 months)	My child felt left out of things because of his/her condition	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox06	Lately (in the last 1-2 months)	Other children made fun of my child because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always

NQSTGprox07	Lately (in the last 1-2 months)	My child felt embarrassed in front of other children because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox10	Lately (in the last 1-2 months)	My child was treated unfairly by other children because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGprox07	Lately (in the last 1-2 months)	Other children didn't see the good things about my child because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox17	Lately (in the last 1-2 months)	My child felt different from other children because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox19	Lately (in the last 1-2 months)	My child avoided making new friends to avoid talking about his/her condition	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox01	Lately (in the last 1-2 months)	Other children bullied my child because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox02	Lately (in the last 1-2 months)	Other children seemed uncomfortable with my child because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always

NQSTGprox05	Lately (in the last 1-2 months)	Other children were mean to my child because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox08	Lately (in the last 1-2 months)	Other children tend to stare at my child because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox09	Lately (in the last 1-2 months)	My child worried what other children thought of him/her because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox11	Lately (in the last 1-2 months)	My child was unhappy about how this condition affected his/her appearance.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox14	Lately (in the last 1-2 months)	My child worried that he/she made life harder for us (parents or guardians) because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox15	Lately (in the last 1-2 months)	My child felt embarrassed about his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
NQSTGprox20	Lately (in the last 1-2 months)	My child lost friends by telling them that he/she has this condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always

DermSTGprox01	Lately (in the last 1-2 months)	Others thought my child wasn't clean because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGprox02	Lately (in the last 1-2 months)	Others avoided touching my child (ex: holding his/her hand) because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGprox03	Lately (in the last 1-2 months)	My child wished his/her condition wasn't visible to other people my age.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGprox04	Lately (in the last 1-2 months)	My child felt embarrassed when other children asked about his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always
DermSTGprox08	Lately (in the last 1-2 months)	My child couldn't wear the clothing/shoes he/she wanted to wear because of his/her condition.	1 = Never 2 = Rarely 3 = Sometimes 4 = Often 5 = Always

Appendix 8: Photography Protocol

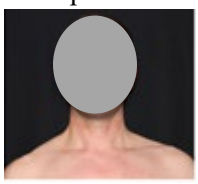
Prior to photography: Have patient remove all wristbands and jewelry. Bras and underwear do not need to be removed. Photography should be performed on blue background.

This protocol is a general outline to follow to capture each body area. Per this protocol, only assessment area/target lesions should be photographed.

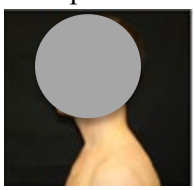
PHOTOGRAPHS

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.

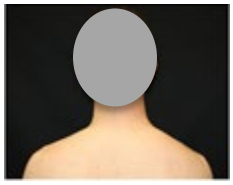


3. Take photo with body perpendicular to backdrop, left ear, eyes open.

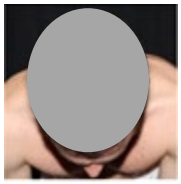


4. Take photo with body perpendicular to backdrop, right ear, eyes open.

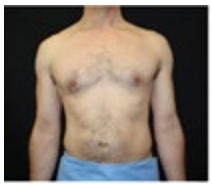
5. Take photo of shoulders and back of head.



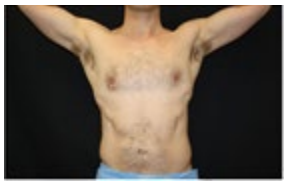
6. Take photo of scalp directly perpendicular to camera, capturing crown and tip of nose.



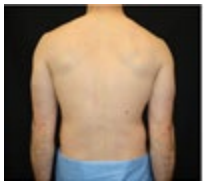
7. Take photo of abdomen to neck, capturing drape.



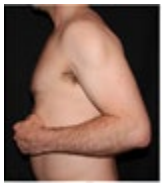
8. With patient's arms raised and hands behind head, take photo from elbows to drape.



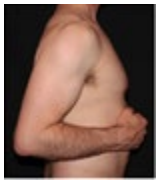
9. Take photo of back to neck, capturing drape.



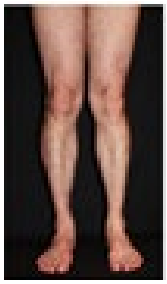
10. Have patient put arm parallel to floor, and bring arm back to expose flank. Rest closed fist on abdomen. Left side.



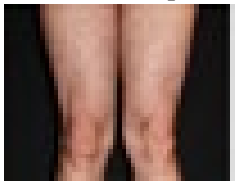
11. Have patient put arm parallel to floor, and bring arm back to expose flank. Rest closed fist on abdomen. Right side.



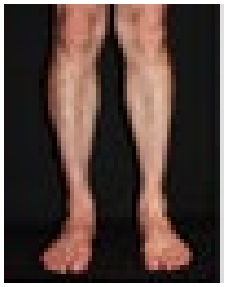
12. Raise drape as high as possible, take photo toes to drape.



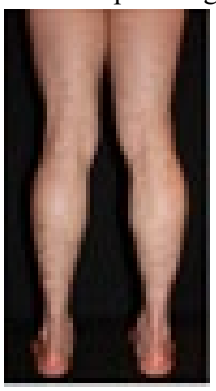
13. Zoom in to capture upper legs from knee to drape in more detail.



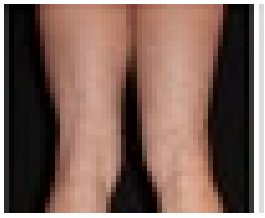
14. Zoom in to capture lower legs from knee to foot in more detail.



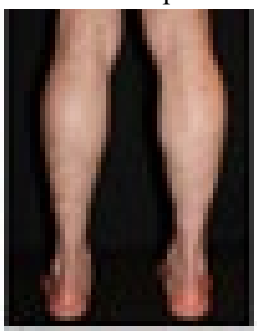
15. Raise drape as high as possible, take photo heels to drape.



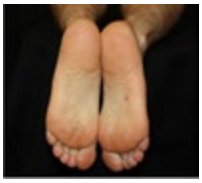
16. Zoom in to capture upper legs from posterior knee to drape in more detail.



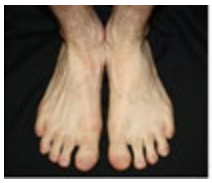
17. Zoom in to capture lower legs from posterior knee to foot in more detail.



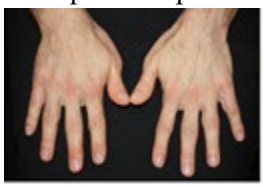
18. Have patient kneel on block or chair draped with blue cloth, take photo of soles.



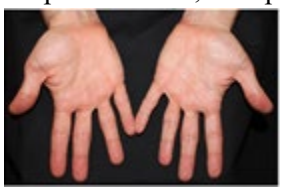
19. Have patient stand on blue cloth, take photo of dorsal feet.



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



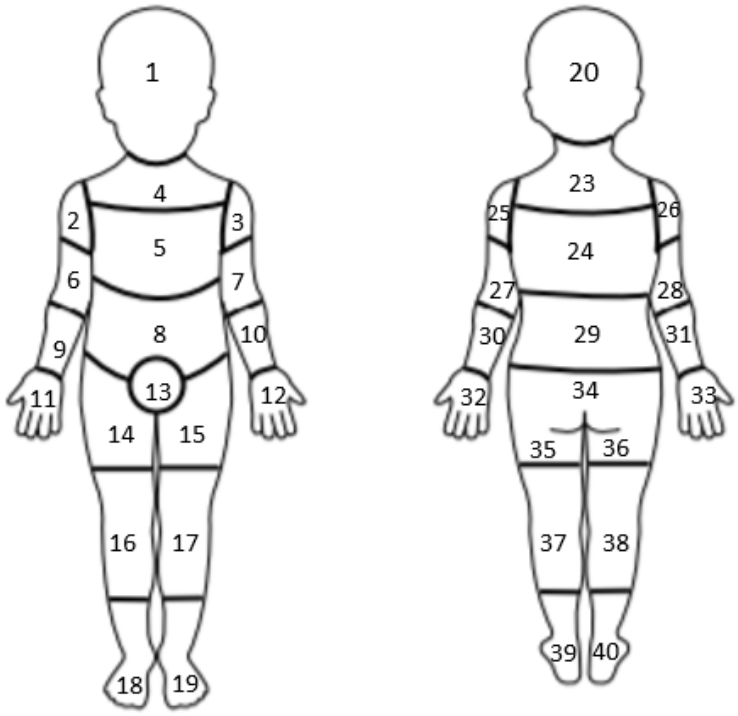
21. Flip hands over, take photo of dorsal hands with thumbs touching and fingers evenly spaced.



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

Appendix 9: Ichthyosis Severity Self-Assessment

Surface Area Affected by Ichthyosis:
Using the drawing below, please list the numbers that correspond to which areas of your skin are affected.



Intensity of Symptoms:
Please rate your skin symptoms according to the following scale

0 = none
1 = mild
2 = moderate
3 = severe

Symptom	Intensity (0-3)
Scaling / Flaking	
Redness	
Tightness	
Pain	
Itch	

Appendix 10: Ichthyosis Financial and Time Burden

The following questions ask about different periods of time. Please think about the past 4 weeks when answering. There are no right or wrong answers. Please answer each question as spontaneously as possible by checking the box with the answer that is closest to your opinion.

1. Does your ichthyosis cause you to lose sleep (because of itching, pain, lack of time due to caring for ichthyosis, etc.)?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐	☐	☐	☐	☐

2. Over a typical week, on how many nights have you lost sleep because of your ichthyosis?

Not applicable	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

3. Because of your ichthyosis, do you feel fatigue during the day?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐	☐	☐	☐	☐

4. Over a typical week, on how many days do you feel fatigue because of your ichthyosis?

Not applicable	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

5. Over a typical week, on how many days was housework performed specifically for your ichthyosis (vacuuming around the house, etc.)?

Not applicable	1-2 days	3-4 days	5-6 days	Every day
☐	☐	☐	☐	☐

6. Because of your ichthyosis, do you feel that you have to do extra steps or feel that there is extra work involved when you do housework?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐	☐	☐	☐	☐

7. Over a typical week, on how many days did you or others do your laundry because of your ichthyosis?

Not applicable ☐ 1-2 days ☐ 3-4 days ☐ 5-6 days ☐ Every day ☐

8. Because of your ichthyosis, do you feel that you have to do extra steps or feel that there is extra work involved when you do laundry?

Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐

9. Does your ichthyosis affect your choice of clothing to wear (cannot wear black clothing, certain colors or fabrics, etc.)?

Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐

10. Because of your ichthyosis, do you have to throw away or replace clothing (socks, underwear, etc.) due to factors (moisturizers, excess washing, etc.) related to your ichthyosis?

Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐

11. How often do you have to throw away or replace clothing (socks, underwear, etc.) due to factors (moisturizers, excess washing, etc.) related to your ichthyosis?

Not applicable ☐ Every year ☐ Every 2-3 months ☐ Every month ☐ Every week ☐

12. Are your daily activities or work impacted by hot weather due to factors relating to your ichthyosis?

Not at all ☐ A little bit ☐ Somewhat ☐ Quite a bit ☐ Very much ☐

13a. On a typical day, how much time did you spend bathing/showering and scrubbing skin because of your ichthyosis?

$\leq$30 minutes ☐ 1 hour ☐ 1.5 hours ☐ 2 hours ☐ $\geq$2 hours ☐

13b. On a typical day, how much time did you spend caring for your skin (moisturizing, trimming skin, etc.) because of your ichthyosis?

≤15 minutes	30 minutes.	45 minutes	1 hour	75 minutes
☐	☐	☐	☐	☐

13c. Overall, on a typical day, how much time do you spend caring for your skin (include bathing/showering, scrubbing skin, moisturizers, etc.) because of your ichthyosis?

≤30 minutes	1 hour	1.5 hours	2 hours	≥2 hours
☐	☐	☐	☐	☐

14. Based on how severe your ichthyosis is now, if you had enough time, how many times a day would you apply moisturizer over your whole body?

0	1	2	3	≥ 4
☐	☐	☐	☐	☐

15. In a typical week, how often do you or others have to clean your bed (brushing/shaking off skin, etc.) or change your sheets due to your ichthyosis?

0	1	2	3	≥ 4
☐	☐	☐	☐	☐

16. Does your ichthyosis interfere with your performance in work/school?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐	☐	☐	☐	☐

17. Do you feel that because of your ichthyosis, you spend too much money or are burdened financially?

Not at all	A little bit	Somewhat	Quite a bit	Very much
☐	☐	☐	☐	☐