A RANDOMIZED, BILATERAL COMPARISON, VEHICLE-CONTROLLED, SAFETY AND TOLERABILITY STUDY OF TOPICAL PAT-001 FOR THE TREATMENT OF CONGENITAL ICHTHYOSIS

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PROTOCOL APPROVAL

The following individuals approve version 3.0 of the 205-9051-201 protocol dated January 6, 2017. All changes to this version of the protocol must have prior written approval and require an amendment or administrative letter.

Patagonia Pharmaceuticals, LLC Representative(s):
Zachary Rome, B.S.
Executive Vice President

Signature: Zach Rome Date: 06 Jan 2017

Therapeutics, Inc. Representative(s):
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Anthony Andrasfay, B.S.
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Signature: Date: 06 Jan 2017

Sara Rhee, M.S.
Senior Lead Biostatistician

Signature: Sara Rhee Date: 09 Jan 2017

STUDY ACKNOWLEDGEMENT

I understand this protocol contains information that is confidential and proprietary to Patagonia Pharmaceuticals, LLC, the Sponsor.

I have read this protocol, agree that it contains all the details necessary to conduct the study as described, and will conduct this study following this protocol.

I will provide the contents of this protocol to study staff under my direct supervision that need to know the contents to conduct the study. I will discuss this information with the study staff to ensure they are fully informed about the study and the test articles. I will provide the contents of the protocol to the responsible Institutional Review Board(s). These disclosures may be made; providing the contents are not used in any other clinical study and they are not disclosed to any other person or entity without prior written consent from the Sponsor or designee. This condition does not apply to disclosure required by government regulations or laws; however, I agree to give prompt notice to the Sponsor or designee of any such disclosure.

I understand the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the interests of the study subjects.

Any additional information added to this protocol is also confidential and proprietary to the Sponsor and must be treated in the same manner as the contents of this protocol.

_____
Printed Name of Principal Investigator

_____ _____
Investigator Signature Date

Protocol number: 205-9051-201 Site number: _____

Version: 3.0

Date of original version (v1.0): July 19, 2016
Date of Amendment #1 (v2.0): September 30, 2016
Date of Amendment #2 (v3.0): January 6, 2017

PROTOCOL SYNOPSIS

Title	A Randomized, Bilateral Comparison, Vehicle-Controlled, Safety And Tolerability Study Of Topical PAT-001 For The Treatment Of Congenital Ichthyosis
Study Type	Phase 2
Test Articles	The blinded test articles to be used in this study include: • PAT-001 (isotretinoin) Ointment (0.1% and 0.2%) • Vehicle Ointment (Control)
Study Objectives	**Primary** • To investigate the safety and tolerability of topically applied PAT-001 as a treatment for congenital ichthyosis (CI) of either the Lamellar or X-Linked subtypes. **Secondary** • To explore evidence of a potential efficacy signal of the "active" test article(s) compared to vehicle. • To explore the plasma levels of isotretinoin and tretinoin from topically applied PAT-001 with comparison to background systemic retinoid levels pre- and post-treatment.
Study Design	Phase 2, proof-of-concept (POC), randomized, double-blind, vehicle-controlled, bilateral comparison study with active only treatment follow-up.
Treatment Groups	There will be two parts to this study. In Part 1, subjects will be randomized to two treatment groups and treated bilaterally with active and vehicle test articles (as described below) for eight weeks. In Part 2, subjects will enter an active only follow-up period of four weeks in which both Treatment Areas identified in Part 1 will be treated with the active test article of their assigned Treatment Group. After enrollment in the study, each subject will be randomized (1:1) to one of two Treatment Groups. Randomization will be stratified by CI subtype. Each subject will have two comparable Treatment Areas defined per protocol. One Treatment Area shall be randomly designated to be treated with one "active" test article with the contralateral Treatment Area assigned to the second test article (i.e., vehicle) within the assigned Treatment Group for Part 1. In Part 2, both Treatment Areas will be treated with the "active" test article within the assigned Treatment Group. Treatment Groups Blinded Test Articles: • Group 1: PAT-001, 0.1% vs vehicle • Group 2: PAT-001, 0.2% vs vehicle Treatments will be applied twice daily to all disease affected skin in the Treatment Area. Dosing may be adjusted by the investigator if there are concerns with tolerability as detailed in the protocol. Subjects will have the option of participating in the pharmacokinetic (PK)

	portion of the study per the Schedule of Events.
Duration of Treatment	Twice a day application for 12 weeks: eight weeks in Part 1 and an additional four weeks in Part 2.
Duration of Study	Each subject will participate in the study for approximately 18 weeks (including up to 45-day screening period).
Study Population	Male and/or female subjects, 12 years of age and older with confirmed diagnosis of protocol specified subtypes of CI.
Total Number of Subjects	Approximately 18 subjects will be enrolled in the study, with approximately nine subjects randomized to each Treatment Group.
Number of Sites	Approximately three sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is male or non-pregnant female, 12 years of age and older. Females must be post-menopausal[1], surgically sterile[2], or use two forms of birth control[3,4]. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[5] at Visit 1/Screening and Visit 2/Baseline. 2. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study the subject must provide written informed consent at that time to continue study participation. 3. Subject is willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study. 4. Subject has a clinical diagnosis of either Lamellar (e.g., transglutaminase 1-deficient) or X-Linked (e.g., deletion of steroid

[1] Defined as amenorrhea greater than 12 consecutive months in women 50 years of age and older.
[2] Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.
[3] Methods of acceptable contraception include A) total abstinence OR B) two forms of birth control including:
1) oral, patch, injected, or implanted hormonal methods of contraception, AND
2) a) partner vasectomy (performed at least six months prior to study entry) OR b) barrier methods of contraception [barrier methods include male condom with or without spermicide, diaphragm or cervical cap – both of which are to be used with spermicide] OR c) a vaginal contraceptive sponge containing a spermicide.

Subjects who become sexually active or begin to have relations with a partner during the study must agree to use two forms of birth control for 30 days prior to having relations and to continue such forms for the duration of the study.
[4] WOCBP taking hormonal therapy must be on treatment for (1) oral or patch: one complete cycle (e.g., four to eight weeks) or (2) injectable or implanted: at least one week prior to study entry, continued per label, and must not change their dosing regimen during the study.
[5] UPTs must have a minimum sensitivity of 25 mIU ß-hCG/mL.

	sulfatase gene) subtypes of CI and agrees to genetic testing[6] to confirm such clinical diagnosis during the study. 5. Subject must have two contralateral comparable Treatment Areas, as defined per protocol. Each Treatment Area must have a minimum of 150 cm^2 of affected diseased skin as identified by the investigator. [Note: each Treatment Area shall be contained within a discrete anatomic unit as defined in the protocol and shall not exceed 6% body surface area (BSA), excluding palms and soles.] 6. Both Treatment Area(s) must be of comparable size per protocol and have an identical Investigator's Global Assessment (IGA) score, with a score of either 3 (moderate) or 4 (severe) at Visit 2/Baseline. 7. Subject is either naïve to oral retinoid treatments; or, if subject is currently taking retinoids, has completed at least a 12-week washout of oral retinoids or a 2-week washout of topical retinoids prior to Visit 2/Baseline. 8. All protocol specified hematology, chemistry, and urinalysis assessments are considered not clinically significant with respect to the subject's participation in the study and typically are ≤2.5 times upper limit of normal (ULN) at Visit 1/Screening. 9. Subject has not donated blood within 30 days of Visit 2/Baseline and agrees to not donate blood during study drug treatment and for one month following discontinuation of treatment. 10. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of the Treatment Areas or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation.
Exclusion Criteria	A subject is ineligible to enter the study if he/she meets one or more of the following criteria: 1. Subject is pregnant, lactating, or is planning to become pregnant during the study. 2. Subject has inflammatory skin disease unrelated to ichthyosis. 3. Subject has previously failed on topical / oral retinoid therapy for treatment of CI. 4. Subject has used topical retinoid-containing therapies to treat Treatment Areas (except emollients) within two weeks prior to Visit 2/Baseline or topical corticosteroids within five days prior to Visit 2/Baseline. Non-Treatment Areas can be treated with topical therapies including emollients, keratolytics, or sunscreen. 5. Subject has used ultraviolet (UV) treatment for ichthyosis within four weeks prior to Visit 2/Baseline. 6. Subject has undergone systemic therapies using Vitamin A supplements or St. John's Wort within four weeks prior to Visit 2/Baseline. Note: Use of systemic retinoids is prohibited within 12 weeks of Visit 2/Baseline per inclusion criterion #7. 7. Subject is immunosuppressed (e.g., HIV, systemic malignancy, graft host disease, etc.). 8. Subject is currently taking concomitant immunosuppressive drugs,

[6] Fluorescence in situ hybridization (FISH) positive confirmation of steroid sulfatase gene deletion is also acceptable to diagnose X-Linked subtype of CI.

	including systemic corticosteroids, within two weeks of Visit 2/Baseline. 9. Subject has untreated secondary infections; however, subject may become eligible after successful treatment of his/her infections at the investigator's discretion. 10. Subject has clinically significant metabolic, pulmonary, cardiac, hematologic, renal, hepatic, immune, neurologic, psychiatric, infectious, neoplastic, or malignant disease (other than non-melanoma skin cancer) that would preclude his/her participation in the study. 11. [For PK Subjects Only] Subject has chronic gastrointestinal disease such as Crohn's disease, irritable bowel syndrome, colitis, inflammatory bowel disease, or chronic diarrhea. 12. Subject with a history of drug or alcohol abuse within the past six months. 13. Subject is currently enrolled in an investigational drug or device study. 14. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 2/Baseline. 15. Subject has a history of allergy to any of the ingredients in the test articles (see Section 6.1). 16. Subject has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the Treatment Areas (the contralateral treatment and control areas of CI). 17. Subject is unable to communicate or cooperate with the investigator due to language problems, impaired cerebral function, or physical limitations. 18. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.
Study Procedures	The study will consist of two parts. There will be one Screening Visit, five scheduled clinic visits, and two phone calls in Part 1 and one additional clinic visit in Part 2. Subjects will have the option to participate in the PK portion of the study. *Note: Subjects that elect to participate in the PK portion of the study should do so with the intent of completing all PK samplings required in the study, per protocol.* Visit 1: Screening (Day -45 to -7): At Visit 1, study staff will explain the study procedures and an informed consent/assent must be signed prior to the initiation of any study-related procedures. Demographics, inclusion/exclusion (I/E) criteria, medical/ichthyosis history, and prior/concomitant medications and therapies will be reviewed to determine subject eligibility. Subjects that require a "washout" period prior to enrollment into the treatment phase to meet I/E criteria requirements will be required to return to the clinic within 45 days to complete the remaining activities. Subjects who require "washout" for longer than 45 days will be re-consented. A brief physical examination including vital signs, UPT (if applicable), Fitzpatrick Skin Type assessment, and clinical laboratory testing will be performed at this visit. For those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected for genetic testing. **Qualified subjects must have two comparable in size (≥150 cm^2), contralateral Treatment Areas (per protocol) identified with equal IGA scores (i.e.,**

	IGA = 3 or 4) at Baseline, where an individual Treatment Area shall not exceed 6% BSA. Clinical evaluations (IGA) for both Treatment Areas will be performed. Prior to Visit 2/Baseline, after clinical laboratory results have been received and reviewed, and the investigator has confirmed the subject's eligibility, the site will contact the subject to confirm their willingness to participate in the study. Assuming the qualified subject is willing to participate, then the site will: • Make a randomization request to order test article for the subject to be delivered to the site prior to the subject's Baseline visit; • Schedule the subject's Baseline visit at a mutually convenient time when the designated subject's test article will be at the site; • NOTE: the ordered test article is specific to each subject and shall not be used for any other subject. In the event that the subject elects not to participate after receipt of their designated test article, the site should contact the monitor to discuss management of the test article received. Visit 2: Baseline (Day 1): At Visit 2, study staff will reaffirm informed consent/assent and re-review laboratory results prior to the initiation of any study-related procedures. Medical history, I/E criteria, and concomitant medications and therapies will be reviewed to confirm subject eligibility. A UPT (if applicable) will be performed. Treatment Areas will be defined as a region contained within a discrete anatomic unit (e.g., upper arm, forearm, upper leg, lower leg) with bilateral involvement and a minimum of 150 cm^2 in area of diseased skin. **Qualified subjects must have two contralateral Treatment Areas (per protocol) identified with equal IGA scores (i.e., IGA = 3 or 4) of comparable size where an individual Treatment Area shall not exceed 6% BSA.** Clinical evaluations (IGA, CI Signs/Symptoms, as well as Baseline local skin reactions [LSRs] pre-application) for both Treatment Areas and photographs will be performed at this visit; photographs will be taken of lesions only, without sharing subject identity. Copy(s) of the Baseline photos may be provided to the subject at the discretion of the investigator to help the subject consistently identify the two Treatment Areas. For those subjects participating in the PK portion of the study, prior to test article application, a PK blood sample will be taken. Subjects will be randomized using the designated test article specific for that subject that was ordered by the site after completion of Visit 1. Test article accountability will be documented and test article and Subject Diary will be dispensed. Subjects and parent/guardian (if applicable) will be instructed on how to apply the test articles and to record applications in the Subject Diary. The first dose will be applied at the site under supervision of the investigator. Adverse events (AEs) and LSRs post-application will be assessed. For those subjects participating in the PK portion of the study, the subject will have additional serial blood samples taken at 1, 2, 3, and 4 hours post-test article application. The subject will be scheduled for the first follow-up visit. Note: If the subject experiences issues with medication tolerability or other complications arise, ideally the subject will be seen by the investigator at one of the scheduled clinic visits or via an Unscheduled Visit to document the reactions and modifications to the dosing regimen prescribed by the

	investigator. In the event that a clinic visit is not possible or not warranted in the opinion of the investigator, the change in the subject's management will be clearly documented in the source documents and case report forms (CRFs) with corresponding changes noted in the Subject Diary regarding test article usage and/or concomitant medications/therapies (e.g., moisturizer use). Modifications to the dosing regimen and/or concomitant medication/therapy use may be prescribed by the investigator to manage intense LSRs and must be documented in the CRFs. **Any dosing modifications will be made bilaterally (e.g., if dosing is decreased to once a day given tolerability issues, both sides will be treated once daily, even if only one side is having the tolerability issue).** Frequency of dosing may be reduced to once per day (QD) or rest periods of up to several days may be allowed. Treatment per protocol should resume as soon as possible after any notable LSRs have materially subsided as determined by the investigator or designee (if possible via one of the scheduled clinic visits or via an Unscheduled Visit) such that dosing may resume. Additionally, use of provided bland emollient[7] in the Treatment Area as an aid to managing LSRs may be prescribed with the approval of the investigator and must be documented in the CRFs. In the event that additional moisturizer use is needed (i.e., greater than QD or BID or in lieu of the test articles) in the opinion of the investigator, such therapy may be used, must be documented in the CRFs, and the investigator must notify the Medical Monitor promptly. Note: Bland emollients should not be applied within four hours of application of the test articles. No other topical therapy within the Treatment Area or in the surrounding skin within one inch of the Treatment Area is permitted. Visits 3 and 7: Phone Call (Day 2 and Day 43±3): The site staff will contact the subject (or parent/guardian as applicable) by telephone to review the Subject Diary, test article compliance, changes in concomitant medications and therapies, query the subject about AEs, and confirm the next visit appointment. The site staff will remind the subject (and parent/legal guardian, if applicable) to continue to apply test article twice daily until the next clinic visit. Subjects with tolerability issues will ideally be scheduled for an in-office follow-up visit, but at the discretion of the investigator, as an Unscheduled Visit to stop/re-start/modify the dosing regimen. Visits 4 and 5 (Days 8+1 and 15±2): Subjects will return to the clinic and will be queried for any changes in health status and concomitant medications and therapies. Clinical evaluations (IGA, CI Signs/Symptoms, and LSRs) for both Treatment Areas will be performed and photographs (optional) may be taken. For those subjects participating in the PK portion of the study, a PK blood sample will be collected. Note: this sample will be collected 12 hours ± 30 minutes after the dose on the previous day. Test article accountability will be documented and compliance will be reviewed (based on review of Subject Diary and weights of test articles) with the subject and

[7] DML Lotion will be provided to subjects. Other bland emollients (e.g., Lubriderm [without alpha hydroxy acid], or other moisturizers that do not contain any "active" ingredients [e.g., salicylic acid, lactic acid, pyruvic acid, urea, or any other ingredient that could irritate or cause a keratolytic effect]) may be used with approval from the investigator, but must be documented as a concomitant medication/therapy.

	parent/guardian (if applicable). Test articles and Subject Diary will be dispensed/returned (as required). If possible, at each clinic visit, the subject will apply one of the daily doses in the clinic under staff supervision to reinforce proper use. The subject will be scheduled for the next follow-up visit. Visit 6 (Day 29±3): Subjects will return to the clinic and will be queried for any changes in health status and concomitant medications and therapies. A brief physical examination including vital signs, UPT (if applicable), and clinical laboratory testing will be performed at this visit. Prior to test article application, clinical evaluations (IGA, CI Signs/Symptoms, and LSRs) for both Treatment Areas will be performed and photographs will be taken. For those subjects participating in the PK portion of the study, a PK blood sample will be collected. Note: this sample will be collected 12 hours ± 30 minutes after the dose on the previous day. Test article accountability will be documented and compliance will be reviewed (based on review of Subject Diary and weights of test articles) with the subject and parent/guardian (if applicable). Test articles and Subject Diary will be dispensed/returned (as required). If possible, at each clinic visit, the subject will apply one of the daily doses in the clinic under staff supervision to reinforce proper use. The subject will be scheduled for Visit 8/End of Part 1. Visit 8: End of Part 1 (Day 57±4): Subjects will return to the clinic for the final visit in Part 1 and will be queried for any changes in health status and concomitant medications/procedures. A brief physical examination including vital signs, UPT (if applicable), and clinical laboratory testing will be performed at this visit. Prior to test article applications, clinical evaluations (IGA, CI Signs/Symptoms, and LSRs) for both Treatment Areas will be performed and photographs will be taken. For those subjects participating in the PK portion of the study, a PK blood sample will be collected. Note: this sample will be collected 12 hours ± 30 minutes after the dose on the previous day. Test article accountability will be documented and compliance will be reviewed (based on review of Subject Diary and weights of test articles) with the subject and parent/guardian (if applicable); all test articles from Part 1 will be collected and test articles will be dispensed for Part 2. Subjects and parent/guardian (if applicable) will be instructed to apply the assigned test article to both Treatment Areas twice per day until the next study visit and to record applications in the Subject Diary. Subject Diaries will be dispensed/returned (as required). Application of the test article will be performed under staff supervision in the clinic. AEs and LSRs post-application will be assessed. The subject will be scheduled for Visit 9/End of Treatment (EOT). Visit 9: EOT & Early Termination (Day 84±4): Subjects will return to the clinic for the final visit of the study and will be queried for any changes in health status and concomitant medications/procedures. A brief physical examination including vital signs, UPT (if applicable), and clinical laboratory testing will be performed at this visit. Clinical evaluations (IGA, CI Signs/Symptoms, and LSRs) for both Treatment Areas will be performed and photographs will be taken. For those subjects participating in the PK portion of the study, a PK blood sample will be collected. Note: this sample will be collected 12 hours ± 30 minutes after the dose on the previous day.

	Test article accountability will be documented; all test articles and Subject Diaries will be returned. The subject will exit the study.
Study Measurements	The following assessments will be performed for each Treatment Area in a given subject. ***Efficacy*** Efficacy will be assessed by the investigator as follows for the Treatment Areas: • Investigator's Global Assessment: Overall severity of ichthyosis using a five-point scale from 0=clear to 4=severe will be conducted at each clinic visit. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. • Individual Clinical Signs/Symptoms: Overall severity of erythema, scaling, fissuring, and papulation/lichenification will be graded using a five-point scale from 0=clear to 4=severe at each clinic visit (except Screening). This is a static morphological scale that refers to a point in time and not a comparison to Baseline. ***Safety*** Physical examinations, vital signs, clinical laboratory tests, UPTs (if applicable), and AEs will be assessed by the investigator per the Schedule of Events. LSRs including burning/stinging, pain, and pruritus will be assessed in each Treatment Area using a four-point ordinal scale where 0=none, 1=mild, 2=moderate, and 3=severe at Visits 2, 4-6 , and 8-9 to allow a comparison between Treatment Groups and Test Articles. These LSRs will be collected independently of AEs. Only LSRs that require medical intervention (e.g., prescription medication) or require the withholding of the application of the test article will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs. ***Pharmacokinetics*** *Note: Subjects that elect to participate in the PK portion of the study should do so with the intent of completing all PK samplings required in the study, per protocol.* At Visit 2, for those subjects that have elected to participate in the optional PK portion of the study, serial PK blood samples will be collected pre-test article application (time 0) and at 1, 2, 3, and 4 hours post-test article application for the determination of isotretinoin and tretinoin levels. At Visits 4-6 and 8-9, a single PK blood sample will be collected pre-test article application (approximately 12 hours after the last dose on the previous day) for assessment of "trough" isotretinoin and tretinoin levels.
Study Endpoints	**Safety Endpoints:** • Incidence (severity and causality) of any local and systemic AEs. • Number of subjects with presence (and severity) of the following LSRs: stinging/burning, pain, and pruritus at each time point for each Treatment Area collected (summarized by Test Article). • Changes from Screening in vital signs at Days 29, 57, and 84 (or

EOT) (summarized by Treatment Group).
- Changes from Screening in clinical laboratory tests (hematology, chemistry, and urinalysis) at Days 29, 57, and 84 (or EOT) (summarized by Treatment Group).
- UPT results in all WOCBP at Screening, Baseline, Day 29, Day 57, and Day 84 (or EOT).

Efficacy Endpoints:
Part 1 (P1) and Part 2 (P2) efficacy data will be analyzed separately. For Part 1, efficacy endpoints will be summarized by Test Article (PAT-001, 0.1%; PAT-001, 0.2%; and Vehicle [pooled across Treatment Groups]) and/or by Part 1 Treatment Group (Group 1: PAT-001, 0.1%/Vehicle; and Group 2: PAT-001, 0.2%/Vehicle) as described below. For Part 2, efficacy endpoints will be summarized by Part 2 Summary Group, which consists of four groups:
- Group A: PAT-001, 0.1%-P2 Active/P1 Active;
- Group B: PAT-001, 0.1%-P2 Active/P1 Vehicle;
- Group C: PAT-001, 0.2%-P2 Active/P1 Active; and
- Group D: PAT-001, 0.2%-P2 Active/P1 Vehicle.

In Part 1, the following exploratory endpoints will be evaluated:
- Frequency distribution of IGA and CI Signs/Symptoms at Baseline, and Days 8, 15, 29, and 57 summarized by Test Article.
- Absolute change from Baseline in IGA and the CI Signs/Symptoms at Days 8, 15, 29, and 57 summarized by Test Article.
- Within-subject difference in IGA and the CI Signs/Symptoms at Baseline, Days 8, 15, 29, and 57 summarized by Part 1 Treatment Group.
- Within-subject difference in absolute change from Baseline in IGA and the CI Signs/Symptoms at Days 8, 15, 29, and 57 summarized by Part 1 Treatment Group.

In Part 2, the following exploratory endpoints will be evaluated:
- Frequency distribution of IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Summary Group (Group A-D).
- Absolute change from Baseline in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Summary Group (Group A-D).
- Absolute change from Day 57 in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Summary Group (Group A-D).
- Within subject difference in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Treatment Group (0.1% and 0.2%).
- Within-subject difference in absolute change from Baseline in IGA and the CI Signs/Symptoms at Day 84 summarized by Part 2 Treatment Group (0.1% and 0.2%).
- Within subject difference in absolute change from Day 57 in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Treatment Group (0.1% and 0.2%).

PK Endpoints:
- Concentration of isotretinoin and tretinoin pre-dose and at 1, 2, 3, and 4 hours after the first dose on Day 1.

	• Trough plasma concentrations of isotretinoin and tretinoin (C_{12h}) on Days 8, 15, 29, 57, and 84.
Sample Size Calculations	As a first-in-man POC study, no formal power calculations were used to determine the sample size.
Statistical Methods	Summary tables (descriptive statistics and/or frequency tables) will be provided for screening variables, baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data. **Study Populations:** The Safety population will include all randomized subjects who applied the test article. The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the test article. The PK population will include those subjects in the Safety population who participated in the PK portion of the study with no evidence of material dosing noncompliance. **Safety Analyses:** The analysis of safety will be conducted on the Safety population. <u>Extent of Exposure</u> Extent of exposure will be calculated separately for Part 1 and Part 2 and overall. The total amount of each test article used by each subject (difference between the weight of the tubes dispensed and weight of the tubes returned) and the mean daily amount of test article applied (total amount of test article used divided by the number of days dosed) will be calculated for each treatment group and test article. Descriptive statistics will be used to summarize the total amount and mean daily amount of test article applied. <u>Adverse Events</u> All AEs reported during the study will be listed, documenting onset, severity, whether therapy was required, any change in test article dosing, investigator assessment of the relationship to the test article, and outcome. AEs will be coded using MedDRA using preferred terms (PTs) and system organ class (SOC). The PTs and SOC will then be tabulated. All treatment emergent AEs (TEAEs) will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article. <u>Local Skin Reactions</u> Severity of LSRs (stinging/burning, pain, and pruritus) will be recorded for each Treatment Area (i.e., Test Article). LSRs will be summarized by frequency and severity of each individual LSR at each visit. <u>Physical Examinations</u> Findings from the brief physical examinations will be recorded in medical history (from assessment at Screening) or as AEs (from assessment at Days 29, 57, and 84). <u>Vital Signs</u>

Vital signs (heart rate, respiration rate, blood pressure (systolic and diastolic), and temperature) will be recorded at Screening, and Days 29, 57, and 84. Descriptive statistics will be used to summarize vital signs. Clinically significant changes from Screening in vital signs at Days 29, 57, and 84 will be summarized.

Clinical Laboratory Tests
Clinical laboratory data (hematology, chemistry, and urinalysis) will be tabulated at Screening and Days 29, 57, and 84. Changes from Screening in laboratory data at Days 29, 57, and 84 will also be summarized. All laboratory data will be listed and reported in the units received by the central laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Screening to Days 29, 57, and 84.

Urine Pregnancy Tests
UPT results (if applicable) at Screening, Baseline, and Days 29, 57, and 84 will be provided in a subject listing.

Concomitant Medications and Therapies
Concomitant medications and therapies will be provided in subject listings.

Efficacy Analyses:
The analysis of efficacy will be conducted on the ITT population. Given the small sample size, no formal hypothesis testing will be done.

Dosing Compliance
Dosing compliance will be evaluated separately for Part 1 and Part 2 and overall. Measures of test article compliance will include the duration of treatment (in number of days) and the total number of applications. Descriptive statistics will be used to summarize test article compliance. Subjects who applied at least 80% of the expected applications will be considered to be compliant with test article dosing.

Investigator's Global Assessment
Part 1. Frequency distributions of IGA score will be tabulated at Baseline, and Days 8, 15, 29, and 57 by Test Article. Absolute change from Baseline in IGA at Days 8, 15, 29, and 57 will also be summarized by Test Article. Within-subject difference (Active-Vehicle) in IGA score at Baseline, and Days 8, 15, 29, and 57 and absolute change from Baseline at Days 8, 15, 29, and 57 will be summarized by Part 1 Treatment Group.

Part 2. Frequency distributions of IGA score will be tabulated at Day 84 by Part 2 Summary Group. Absolute change from Baseline and absolute change from Day 57 in IGA at Day 84 will also be summarized by Part 2 Summary Group. Within-subject difference (Active-Vehicle) in IGA score, absolute change from Baseline, and absolute change from Day 57 at Day 84 will be summarized by Part 2 Treatment Group.

Individual Clinical Signs/Symptoms
Part 1. Frequency distributions of erythema, scaling, fissuring, and papulation/lichenification will be tabulated at Baseline, and Days 8, 15, 29, and 57 by Test Article. Absolute change from Baseline in each of the

	Signs/Symptoms at Days 8, 15, 29, and 57 will also be summarized by Test Article. Within-subject difference (Active-Vehicle) for each of the Signs/Symptoms scores at Baseline, and Days 8, 15, 29, and 57 and absolute change from Baseline at Days 8, 15, 29, and 57 will be summarized by Part 1 Treatment Group. *Part 2*. Frequency distributions for each of the Signs/Symptoms will be tabulated at Day 84 by Part 2 Summary Group. Absolute change from Baseline and absolute change from Day 57 for each of the Signs/Symptoms at Day 84 will also be summarized by Part 2 Summary Group. Within-subject difference (Active-Vehicle) for each of the Signs/Symptoms scores, absolute change from Baseline, and absolute change from Day 57 at Day 84 will be summarized by Part 2 Treatment Group. **Pharmacokinetic Analyses:** A PK analysis will be conducted on the PK population**.** <u>Concentrations After Single Dose</u> Concentrations of isotretinoin and tretinoin will be summarized pre-test article application (time 0) and 1, 2, 3, and 4 hours post-test article application for each subject and compared among Treatment Groups. <u>Trough Concentrations</u> Trough plasma concentrations of isotretinoin and tretinoin at Days 8, 15, 29, 57, and 84 will be compared between Treatment Groups.
Interim Analysis	No interim analysis is planned.

SCHEDULE OF EVENTS

	Screening[8]	Part 1							Part 2
Visit Number	**1**	**2**	**3[9]**	**4**	**5**	**6**	**7[9]**	**8**	**9**
Visit Type	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**
Day	**-45 to -7**	**1**	**2**	**8+1**	**15±2**	**29±3**	**43±3**	**57±4**	**84±4**
Informed Consent/Assent	X	X							
Demographics	X								
I/E Criteria	X	X[10]							
Medical/Ichthyosis History[11]	X	X							
Brief Physical Examination	X					X		X	X
Vital Signs[12]	X					X		X	X
UPT for WOCBP	X	X				X		X	X
Fitzpatrick Skin Type	X								
Clinical Laboratory Tests	X					X		X	X
Genetic Testing	X[13]								
Selection of Treatment Areas[14]		X							
IGA Scores	X	X		X	X	X		X	X
CI Sign / Symptoms		X		X	X	X		X	X

[8] Screening window at -7 days allows clinical lab tests to be finalized and test article to be shipped prior to Visit 2/Baseline.
[9] Unscheduled Visits may be performed in the clinic at the investigator's discretion, if there is a concern regarding tolerability or other AE.
[10] Subjects who do not meet the I/E criteria at Visit 2 will be classified as screen failures.
[11] Any change in Medical History from Visit 1/Screening to Visit 2/Baseline is not considered an AE, but will be captured as baseline Medical History. Ichthyosis history will only be captured at Visit 1/Screening.
[12] Vital signs will include weight and height at Visit 1/Screening.
[13] For those subjects who do not have genetic test confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected.
[14] Each contralateral Treatment Area must be comparable in size (≥150cm^2) and have the same IGA score of 3 (moderate) or 4 (severe) at Baseline and be contained within a discrete anatomic unit that shall not exceed 6% BSA. Location by body region and percent BSA of disease affected skin in each Treatment Area will be documented. Percent BSA will be estimated using the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together. [Note: Palms and soles are not eligible; the treatment of scalp and skin folds/intertriginous regions should be avoided]. Additionally, for treatment on the arms in subjects participating in the PK portion, the antecubital fossa (e.g., approximately 10-15 cm^2) will be excluded to minimize contamination of PK blood draws.

	Screening[8]	Part 1							Part 2
Visit Number	**1**	**2**	**3[9]**	**4**	**5**	**6**	**7[9]**	**8**	**9**
Visit Type	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**	**Clinic**	**Phone**	**Clinic**	**Clinic**
Day	**-45 to -7**	**1**	**2**	**8+1**	**15±2**	**29±3**	**43±3**	**57±4**	**84±4**
LSR		X[15] Pre&Post		X	X	X		X[15] Pre&Post	X
Photography		X		optional	optional	X		X	X
PK Blood Draws (optional)		X[16] Pre, 1, 2, 3, & 4 hr		X[17]	X[17]	X[17]		X[17]	X[17]
Randomization	X[18]	X							
Part 1: Dosing at the Clinic		X		X[19]	X[19]	X[19]			
Part 2 Dosing & Per Protocol Instructions								X[20]	
Test Articles Accountability: Dispense/Collect/Weigh –Part 1 Dosing		X		X	X	X		X	
Test Articles Accountability: Dispense/Collect/Weigh – Part 2 Dosing								X	X
Compliance / Diary Review[21]		X	X	X	X	X	X	X	X
Concomitant Medications and Therapies	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X

[15] LSRs will be evaluated pre- and post-test article application on Day 1 and Day 57.
[16] On Day 1, PK blood samples will be collected for isotretinoin and tretinoin pre-test article application (time 0) and at 1, 2, 3, and 4 hours post-application.
[17] On Days 8, 15, 29, 57, and 84, a PK blood sample will be collected for isotretinoin and tretinoin pre-test article application (approximately 12 hours ± 30 minutes after the last test article application on the previous day).
[18] Prior to Visit 2/Baseline, after laboratory results have been received and reviewed, a randomization request will be placed by the site in order for the test article to be provided to the site prior to baseline. Note: the ordered test article is specific to each subject and shall not be used for any other subject.
[19] If possible, the subject will apply one of the daily doses in the clinic under staff supervision to reinforce proper use.
[20] In Part 2, subjects will enter an active only treatment follow-up period of four weeks in which both Treatment Areas identified in Part 1 will be treated with the active test article of their assigned treatment group.
[21] Subject Diary will be reviewed; compliance will be discussed based on review of Subject Diary and Test Article Accountability, as applicable.

ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
β-HCG	Beta-Human Chorionic Gonadotropin
BID	Twice per day
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C_{12h}	Trough plasma concentrations
CFR	Code of Federal Regulations
CI	Congenital Ichthyosis
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOT	End of Treatment
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
GGT	Gamma-Glutamyl Transpeptidase
HIV	Human Immunodeficiency Virus
IB	Investigator Brochure
I/E	Inclusion/Exclusion
IGA	Investigator's Global Assessment
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
LDH	Lactate Dehydrogenase
LI	Lamellar Ichthyosis
LSR	Local Skin Reaction
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
OTC	Over-the-Counter
P1	Part 1
P2	Part 2
PEG	Polyethylene Glycol
PK	Pharmacokinetic
POC	Proof-of-Concept
PT	Preferred Term
QD	Once per day
RA	Retinoic Acid
RBC	Red Blood Cells
RDW	Red Blood Cell Distribution Width

SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Class
STS	Steroid Sulfatase
TA	Treatment Area
TEAE	Treatment Emergent Adverse Event
TGM1	Transglutaminase Type 1
TI	Therapeutics, Incorporated
ULN	Upper Limit of Normal
UPT	Urine Pregnancy Test
USP	United States Pharmacopeia
UV	Ultraviolet
WBC	White Blood Cells
WHO	World Health Organization
WOCBP	Women of Childbearing Potential
XRI	X-Linked Recessive Ichthyosis

TABLE OF CONTENTS

1. BACKGROUND

Congenital ichthyosis (CI) is a large, heterogeneous family of inherited skin disorders of cornification resulting from an abnormality of skin keratinization [1]. The classification of ichthyosis is complex and CI presents in a multitude of forms and phenotypes; however, the main features are scaling and often thickening of the skin. The presentation and severity of symptoms can differ greatly by patient and by the form of ichthyoses, but generally include skin inflammation and fragility, pruritus, fissuring and cracking of thickened skin, ectropion, anhidrosis, and in some severe cases, an increased susceptibility to infection. X-linked recessive ichthyosis (XRI), which occurs at a frequency of about one in/2500 (in males), shows no distinguishing features other than a thick horny layer [1] and diagnosis can be confirmed using genetic testing identifying a complete deletion of the gene encoding steroid sulfatase (*STS*) that is located at the terminus of the X chromosome [2]. Lamellar ichthyosis (LI), which occurs at a frequency of about one in 100,000-300,000, is a member of the nonsyndromic autosomal recessive CI group which manifests itself clinically as hyperkeratosis and dry, scaling skin across the entire body [3]; pathogenesis is related to a severely disturbed barrier function due either to abnormal corneocytes or to a defective deposition of stratum corneum lipids and is typically caused by truncation or missense mutations in the gene encoding keratinocyte transglutaminase type 1 (*TGM1*) [1, 3].

The management of the disease is a life-long endeavor, which remains largely symptomatic (i.e., emollients with or without keratolytics agents) and commonly focused on reducing scaling and/or skin lubrication with both systemic and topical treatments [1]. A first-line therapy includes hydration and lubrication accomplished by creams and ointments containing low concentrations of salt, urea, or glycerol, which increase the water-binding capacity of the horny layer. Addition of keratolytics agents are used to decrease corneocyte cohesiveness, to promote desquamation, and to dissolve keratins and lipids (e.g., α-hydroxy acids, salicylic acid, high dose urea, propylene glycol, N-acetylcysteine, and retinoids). Systemic retinoid treatment is reserved for those patients refractory to topical agents because of long-term adverse effects and teratogenicity [4].

Isotretinoin, a 'natural' retinoid (13-*cis* isomer of naturally occurring tretinoin [all-*trans*-retinoic acid]), was initially developed as a synthetic retinoid, but is also present in cells as a naturally occurring metabolite. Oral isotretinoin was first approved by the FDA as treatment for severe acne in 1982 [5]. Additionally, oral isotretinoin has demonstrated remarkable efficacy for the treatment of ichthyoses and other skin disorders associated with hyperkeratinization as one of isotretinoin mechanisms of action produces a significant reduction in comedogenesis by decreasing hyperkeratinization [6]. Teratogenicity is regarded as one of the most serious potential adverse effects, while common mucocutaneous side effects are dose dependent and can be managed by modification of the dose (e.g., reductions and/or drug holidays) and additional symptomatic therapy (e.g., moisturizers).

Patagonia Pharmaceuticals, LLC is developing a topical ointment (0.1% and 0.2%) formulation of isotretinoin, called PAT-001 (isotretinoin) Ointment, for the treatment of

CI (XRI and LI subtypes) in subjects 12 years of age and older. Development of a topical isotretinoin therapy for the treatment of ichthyosis would be advantageous as it would provide a product which encompasses the three main objectives of treatment: hydration, lubrication, and removal of thick scales (keratolysis) [4], while likely exhibiting a more favorable side effect profile than systemic retinoid treatment.

2. RATIONALE

Vitamin A, the parent molecule of the retinoid family, is important in maintaining general growth, in regulating proliferation and differentiation of epithelial tissues, and in maintaining visual and reproductive functions [7]; however, it is inactive and can be metabolized to its active form, all-*trans*-retinoic acid (RA) [8]. Retinoids cause a generalized keratolytic effect, which can abruptly lead to extensive shedding or peeling of scales [4]; thus making this class of molecules an attractive candidate to develop for the treatment of skin disorders associated with hyperkeratinization, such as CI. However, the side effects associated with systemic bioavailability constrain the use of the retinoid class of products.

Isotretinoin (13-*cis*-RA), a naturally occurring retinoid (derivative of Vitamin A), is an isomer of all-*trans*-RA [9] and offers several advantages over other synthetic retinoids and the naturally occurring tretinoin. The fact that isotretinoin can be considered a pro-drug, in which it converts into the naturally occurring tretinoin (or one of the other metabolites) as the intracellular moiety [6] suggests that isotretinoin could be used to selectively enhance the efficacy of pharmacologically active drug, while dampening any undesirable properties of the parent molecule. While some of isotretinoin's activity may be mediated by tretinoin, the isomerization of isotretinoin (13-*cis*-RA) into tretinoin (all-*trans*-RA) does not account for all the pharmacological effects observed upon use of this retinoid [9]; thus, isotretinoin's broader range of activity compared to other retinoids makes it advantageous for clinical development. Additionally, the shorter elimination half-life of isotretinoin (i.e., between 10 to 20 hours) compared to other synthetic retinoids (e.g., acitretin with an elimination half-life of two days [4]) provides practical considerations in clinical use simplifying dose changes, drug holidays, and family planning.

Nonclinical models can be used to evaluate the toxicity profile considering hypervitaminosis A and adverse effects on fertility and reproductive performance as metrics for comparison. In a mouse papilloma model, the substantially (5-fold) lower dose of tretinoin that causes hypervitaminosis A (80 mg/kg) compared to isotretinoin (400 mg/kg) suggests that the toxicity profile of tretinoin is more severe compared to isotretinoin. Additionally, isotretinoin may have a lower risk of teratogenicity given that adverse effects on fertility and reproductive performance in rats was observed at oral doses of 2 mg/kg/day of tretinoin [10] and no adverse effects were observed at oral doses of 32 mg/kg/day of isotretinoin [5]. Thus, these findings suggest that isotretinoin has a more favorable efficacy to toxicity ratio than tretinoin and supports its classification as a pro-drug.

For the treatment of CI, it would be desirable to have a topical formulation of isotretinoin as it would afford targeted delivery of the keratolytics agent at the disease tissue site, while minimizing systemic exposure compared to that of systemic retinoid treatment and also providing a topical formulation that would provide hydration and lubrication to the diseased skin.

3. OBJECTIVE

The primary objective is to investigate the safety and tolerability of topically applied PAT-001 as a treatment for CI of either the Lamellar or X-Linked subtypes.

The secondary objectives are (1) to explore evidence of a potential efficacy signal of the "active" test article (i.e., PAT-001, 0.1% and 0.2%) compared to vehicle and (2) to explore the plasma levels of isotretinoin and tretinoin from topically applied PAT-001 with comparison to background systemic retinoid levels pre- and post-treatment.

4. STUDY DESIGN

This is a two part, Phase 2, multicenter, proof-of-concept (POC) study of the safety and tolerability of PAT-001 for the treatment of CI in subjects 12 years of age and older. Part 1 will be a double-blind, randomized, vehicle controlled, bilateral comparison, and Part 2 will be a double-blind, active only treatment comparison of the two PAT-001 concentrations. Subjects will have the option to participate in the PK portion of the study. Approximately 18 subjects will be enrolled at three study sites.

Subjects will be randomized (1:1) to one of two Treatment Groups:

- Group 1: PAT-001, 0.1% vs. vehicle
- Group 2: PAT-001, 0.2% vs. vehicle

Subjects will have two comparable Treatment Areas defined per protocol. Each Treatment Area must be comparable in size, with a minimum of 150 cm^2 of affected diseased skin with an identical Investigator's Global Association (IGA) score, with a score of either 3 (moderate) or 4 (severe) at Baseline; each Treatment Area shall be contained within a discrete anatomic unit as defined in the protocol and shall not exceed 6% body surface area (BSA), excluding palms and soles. In Part 1, one Treatment Area (e.g., right side) will be randomly designated to be treated with one "active" test article (i.e., PAT-001, 0.1%, or 0.2%) and the other Treatment Area (e.g., left side) will be assigned the second test article (i.e., vehicle). Treatments will be applied twice daily for eight weeks to all disease affected skin in the Treatment Area. In Part 2, both Treatment Areas (i.e., right and left sides) will be treated with the "active" test article (i.e., PAT-001, 0.1% or 0.2%) of the assigned Treatment Group twice daily for an additional four weeks.

Subjects will have seven clinic visits and two phone calls. Safety, tolerability, and efficacy measures will be evaluated by Test Article, Treatment Group, within subjects, and by Summary Group as applicable (see Section 17). Pharmacokinetic (PK) measures of

isotretinoin and tretinoin will be compared to background systemic retinoid levels pre- and post-treatment for each Treatment Group in an optional PK portion of the study.

5. STUDY POPULATION

Approximately 18 male or female subjects, 12 years of age and older with confirmed diagnosis of Lamellar or X-Linked subtypes of CI will be enrolled in the study.

5.1 Subject Eligibility

To be included in the study, subjects must meet the following inclusion and none of the exclusion criteria.

5.1.1 Inclusion Criteria

1. Subject is male or non-pregnant female, 12 years of age and older. Females must be post-menopausal[22], surgically sterile[23], or use two forms of birth control[24,25]. Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[26] at Visit 1/Screening and Visit 2/Baseline.
2. Subject has provided written informed consent/assent. A subject under 18 years of age must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study the subject must provide written informed consent at that time to continue study participation.
3. Subject is willing and able to apply the test article(s) as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study.
4. Subject has a clinical diagnosis of either Lamellar (e.g., transglutaminase 1-deficient) or X-Linked (e.g., deletion of steroid sulfatase gene) subtypes of CI and agrees to

[22] Defined as amenorrhea greater than 12 consecutive months in women 50 years of age and older.
[23] Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.
[24] Methods of acceptable contraception include A) total abstinence OR B) two forms of birth control including:
1) oral, patch, injected, or implanted hormonal methods of contraception, AND
2) a) partner vasectomy (performed at least six months prior to study entry) OR b) barrier methods of contraception [barrier methods include male condom with or without spermicide, diaphragm or cervical cap – both of which are to be used with spermicide] OR c) a vaginal contraceptive sponge containing a spermicide.

Subjects who become sexually active or begin to have relations with a partner during the study must agree to use two forms of birth control for 30 days prior to having relations and to continue such forms for the duration of the study.
[25] WOCBP taking hormonal therapy must be on treatment for (1) oral or patch: one complete cycle (e.g., four to eight weeks) or (2) injectable or implanted: at least one week prior to study entry, continued per label, and must not change their dosing regimen during the study.
[26] UPTs must have a minimum sensitivity of 25 mIU ß-hCG/mL.

genetic[27] testing to confirm such diagnosis during the study.
5. Subject must have two contralateral comparable Treatment Areas, as defined per protocol. Each Treatment Area must have a minimum of 150 cm^2 of affected diseased skin as identified by the investigator. [Note: each Treatment Area shall be contained within a discrete anatomic unit as defined in the protocol and shall not exceed 6% BSA, excluding palms and soles.]
6. Both Treatment Area(s) must be of comparable size per protocol and have an identical IGA score, with a score of either 3 (moderate) or 4 (severe) at Visit 2/Baseline.
7. Subject is either naïve to oral retinoid treatments; or, if subject is currently taking retinoids, has completed at-least a 12-week washout of oral retinoids or a 2-week washout of topical retinoids prior to Visit 2/Baseline.
8. All protocol specified hematology, chemistry, and urinalysis assessments are considered not clinically significant with respect to the subject's participation in the study and typically are ≤2.5 times upper limit of normal (ULN) at Visit 1/Screening.
9. Subject has not donated blood within 30 days of Visit 2/Baseline and agrees to not donate blood during study drug treatment and for one month following discontinuation of treatment.
10. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of the Treatment Areas or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation.

5.1.2 Exclusion Criteria

1. Subject is pregnant, lactating, or is planning to become pregnant during the study.
2. Subject has inflammatory skin disease unrelated to ichthyosis.
3. Subject has previously failed on topical / oral retinoid therapy for treatment of CI.
4. Subject has used topical retinoid-containing therapies to treat Treatment Areas (except emollients) within two weeks prior to Visit 2/Baseline or topical corticosteroids within five days prior to Visit 2/Baseline. Non-Treatment Areas can be treated with topical therapies including emollients, keratolytics, or sunscreen.
5. Subject has used ultraviolet (UV) treatment for ichthyosis within four weeks prior to Visit 2/Baseline.
6. Subject has undergone systemic therapies using Vitamin A supplements or St. John's Wort within four weeks prior to Visit 2/Baseline. Note: Use of systemic retinoids is prohibited within 12 weeks of Visit 2/Baseline per inclusion criterion #7.
7. Subject is immunosuppressed (e.g., HIV, systemic malignancy, graft host disease, etc.).
8. Subject is currently taking concomitant immunosuppressive drugs, including systemic corticosteroids within two weeks of Visit 2/Baseline.
9. Subject has untreated secondary infections; however, subject may become eligible after successful treatment of his/her infections at the investigator's discretion.
10. Subject has clinically significant metabolic, pulmonary, cardiac, hematologic, renal, hepatic, immune, neurologic, psychiatric, infectious, neoplastic, or malignant disease

[27] Fluorescence in situ hybridization (FISH) positive confirmation of steroid sulfatase gene deletion is also acceptable to diagnose X-Linked subtype of CI.

(other than non-melanoma skin cancer) that would preclude his/her participation in the study.
11. [For PK Subjects Only] Subject has chronic gastrointestinal disease such as Crohn's disease, irritable bowel syndrome, colitis, inflammatory bowel disease, or chronic diarrhea.
12. Subject with a history of drug or alcohol abuse within the past six months.
13. Subject is currently enrolled in an investigational drug or device study.
14. Subject has used an investigational drug or investigational device treatment within 30 days prior to Visit 2/Baseline.
15. Subject has a history of allergy to any of the ingredients in the test articles (see Section 6.1).
16. Subject has lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the Treatment Areas (the contralateral treatment and control areas of CI).
17. Subject is unable to communicate or cooperate with the investigator due to language problems, impaired cerebral function, or physical limitations.
18. Subject is known to be noncompliant or is unlikely to comply with the requirements of the study protocol (e.g., due to alcoholism, drug dependency, mental incapacity) in the opinion of the investigator.

5.1.3 Subject Withdrawal Criteria

Procedures for handling subjects who are discontinued from the study are described in Section 13.2. Subjects who are discontinued will not be replaced.

6. TEST ARTICLES AND REGIMEN

6.1 Description

PAT-001 is a pale yellow, viscous ointment. Vehicle ointment is color matched to the active test article. In Part 1, each subject shall receive two test articles: a vehicle ointment and an active ointment product (either 0.1% or 0.2% PAT-001) for treatment to the left and right Treatment Areas. The test articles will be blinded using color coded labeling as detailed in Section 6.2 and Appendix 1 to facilitate proper use during the study period. In Part 2, each subject will receive the active ointment product assigned in Part 1 for both Treatment Areas.

Test Article Name:	PAT-001 (isotretinoin) Ointment, 0.1%
Active ingredient:	isotretinoin, USP
Other ingredients:	super refined polyethylene glycol (PEG) 400, PEG 1450, PEG 3350, methylparaben, butylated hydroxytoluene, and propyl 4-hydroxybenzoate, propylparaben

Test Article Name:	PAT-001 (isotretinoin) Ointment, 0.2%
Active ingredient:	isotretinoin, USP
Other ingredients:	super refined PEG 400, PEG 1450, PEG 3350, methylparaben, butylated hydroxytoluene, and propyl 4-hydroxybenzoate, propylparaben

Test Article Name:	Vehicle Ointment
Other ingredients:	super refined PEG 400, PEG 1450, PEG 3350, methylparaben, butylated hydroxytoluene, and propyl 4-hydroxybenzoate, propylparaben; color additive[28]

6.2 Instructions for Use and Application

At Visit 2/Baseline, the investigator will designate two comparable Treatment Areas. Each Treatment Area shall be contained within a discrete anatomic unit (e.g., upper arm, forearm, upper leg, lower leg) with bilateral involvement and a minimum of 150 cm^2 in area of diseased skin that shall not exceed 6% BSA; these Treatment Areas will be selected for treatment and designated by right and left sides. Both Treatment Areas must have comparable area of disease involvement and have the same IGA score of 3 (moderate) or 4 (severe) at Visit 2/Baseline. Note: Palms and soles are not eligible; the treatment of scalp and skin folds/intertriginous regions should be avoided. Additionally, for those subjects participating in the PK portion of the study, treatment on the arms, the antecubital fossa (e.g., approximately 10-15 cm^2) will be excluded to minimize contamination of PK blood draws. Location by body region and percent BSA[29] of disease affected skin in each Treatment Area at Baseline will be documented.

Subjects will be provided with an instruction sheet detailing how to apply the test articles (see Appendix 1) and a study staff member will demonstrate how to dispense and apply the test articles. If the subject is a minor, the parent/legal guardian will be given the Subject Instructions with their child and instructed to apply or supervise application on the subject; the level of involvement (i.e., application vs. supervision) by the parent/legal guardian will be determined by the investigator. Note: For Part 1, the test articles will be blinded using color coded labels to designate which test article to apply to each Treatment Area: **R**ED = **R**ight and **L**EMON YELLOW = **L**eft.

Subjects (and parent/legal guardians, if applicable) will be instructed to wash their hands before and after each test article application. Subjects (and parent/legal guardians, if applicable) will be instructed to wash the Treatment Areas with a mild non-medicated cleanser and water and then to dry the area gently. Subjects (with parent/legal guardian supervision, as required) will be instructed to apply a sufficient amount of the test article to provide a thin uniform film over the disease affected skin within the Treatment Area

[28] FD&C Yellow #3 and FD&C Blue #2.
[29] BSA will be estimated based on the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together.

(Note: the volume of test article applied will vary with disease severity). For Part 1, the subject (and parent/legal guardians, if applicable) will be instructed to take great care to use the assigned test article to the right Treatment Area (on the subject's right side) and the other test article to the left Treatment Area (on the subject's left side). Subjects (with parental supervision, as required) will apply a thin uniform film of the assigned test article twice daily to the designated Treatment Area for eight weeks. Subjects (and parent/legal guardians, if applicable) will wash their hands after application with the first test article and prior to applying the second test article. For Part 2, the subject (and parent/legal guardians, if applicable) will be instructed to apply the assigned test article to both Treatment Areas by applying a thin uniform film twice daily for an additional four weeks. The test article will be applied at approximately the same time every day and at least eight hours apart. Note: for those subjects who are participating in the optional PK portion of the study, the application before a scheduled clinic visit with PK time point (i.e., on Days 7, 14, 28, 56, and 83) must be approximately 12 hours ± 30 minutes prior to the blood draw.

Subjects (with parent/legal guardian supervision, as required) will be instructed to record the date and time of each application in a Subject Diary (see Appendix 2). Subjects (and parent/legal guardians, if applicable) will be instructed to bring all containers of the test articles (used and unused) and the completed Subject Diary to each visit. If the subject is a minor, the parent/legal guardian will be given the Subject Diary and instructed to complete or supervise the completion of the Subject Diary; the level of involvement (i.e., completion vs. supervision) by the parent/legal guardian will be determined by the investigator.

At each visit, the study staff will review the application instructions with the subject and/or parent/legal guardian, if applicable (see Appendix 1) paying particular attention to proper use of the labeled test article for the Left and Right Treatment Areas (Part 1 only). If possible, at each clinic visit, the subject will apply one of the daily doses in the clinic under staff supervision to reinforce proper use.

Subjects (and parent/legal guardian, if applicable) will be instructed not to wash the treated area for at least four hours following test article application. Subject should not apply the test articles within four hours prior to clinic visits. For those subjects who are participating in the PK portion of the study, subjects must NOT apply the test articles prior to visits that require PK sample collection (i.e., Visit 4/Day 8, Visit 5/Day 15, Visit 6/Day 29, Visit 8/Day 57, and Visit 9/Day 84).

If the subject experiences issues with medication tolerability or other complications arise, ideally the subject will be seen by the investigator at one of the scheduled clinic visits or via an Unscheduled Visit to document the reactions and modifications to the dosing regimen prescribed by the investigator. In the event that a clinic visit is not possible or not warranted in the opinion of the investigator, the change in the subject's management will be clearly documented in the source documents and case report forms (CRFs) with corresponding changes noted in the Subject Diary regarding test article usage and/or concomitant medications/therapies (e.g., moisturizer use).

Modifications to the dosing regimen and/or concomitant medication/therapy use may be prescribed by the investigator to manage intense LSRs and must be documented in the CRFs. **Any dosing modifications or changes to concomitant medications/therapies will be made bilaterally (e.g., if dosing is decreased to once a day given tolerability issues, both sides will be treated once daily, even if only one side is having the tolerability issue).** Frequency of dosing may be reduced to once per day (QD) or rest periods of up to several days may be allowed. Treatment per protocol should resume as soon as possible after any notable LSRs have materially subsided as determined by the investigator or designee (if possible via one of the scheduled clinic visits or via an Unscheduled Visit) such that dosing may resume. Additionally, use of provided bland emollient[30] in the Treatment Areas as an aid to managing LSRs may be prescribed with the approval of the investigator and must be documented in the CRFs. In the event that additional moisturizer use is needed (i.e., greater than QD or twice a day (BID) or in lieu of the test articles) in the opinion of the investigator, such therapy may be used, must be documented in the CRFs, and the investigator must notify the Medical Monitor promptly. Note: Bland emollients should not be applied within four hours of application of the test articles. No other topical therapy within the Treatment Area or in the surrounding skin within one inch of the Treatment Area is permitted.

6.3 Warnings, Precautions and Contraindications

These test articles are for topical use only. Care should be taken to avoid contact with eyes and all mucous membranes. If contact with eyes occurs, rinse thoroughly with water.

Subjects with a known allergy to any of the ingredients in the test articles should not participate in this study.

Should severe skin irritation or rash develop, the subject should contact the investigator immediately to discuss the possibility of dose modifications or moisturizer use as detailed in Section 6.2).

In case of accidental ingestion, subjects should contact the investigator immediately.

The effects of the test article in nursing mothers, pregnant women and their unborn children are unknown. WOCBP must not be pregnant, lactating, or planning a pregnancy during the study period.

Exposure to sunlight, including UV sunlamps, may provoke additional irritation. Therefore, exposure should be avoided or minimized during the use of the test articles. In cases where significant exposure to sunlight cannot be avoided, use of sun protection

[30] DML Lotion will be provided to subjects. Other bland emollients (e.g., Lubriderm [without alpha hydroxy acid], or other moisturizers that do not contain any "active" ingredients [e.g., salicylic acid, lactic acid, pyruvic acid, urea, or any other ingredient that could irritate or cause a keratolytic effect]) may be used with approval from the investigator, but must be documented as a concomitant medication/therapy.

measures such as sunscreen products (for areas outside of the Treatment Area) and/or protective clothing over the Treatment Areas is recommended.

7. RANDOMIZATION ASSIGNMENT

Prior to Visit 2/Baseline, after laboratory results have been received and reviewed, a randomization request will be placed by the site in order for the test article to be provided to the site prior to baseline.

Subjects will be randomized to one of the two Treatment Groups on a 1:1 basis (PAT-001, 0.1%/Vehicle and PAT-001, 0.2%/Vehicle) using a central randomization scheme, which is stratified by disease subtype. Subjects with XRI and LI subtypes will be enrolled such that at least two thirds of the total number of subjects (i.e., 12 subjects) will be in the XRI subtype group and so that the proportion of subjects with XRI and LI subtypes will be similar across the two Treatment Groups.

8. PRIOR AND CONCOMITANT THERAPIES

Current medications and any medications taken within 30 days prior to the start of the study (Visit 1/Screening) will be recorded as prior/concomitant medications with the dose and corresponding indication. The medications to be recorded include prescription and over-the-counter (OTC) medications and vitamins, minerals, and dietary supplements. All medications taken on a regular basis should be recorded on the CRFs prior to commencing the use of the test article. All concomitant medications will be coded with the current version of the WHO Drug Dictionary.

Therapies (medication and non-medication therapies) not restricted by the protocol may be used during the study for the treatment or prevention of disease or to maintain good health. Vitamin and mineral supplements are permitted at dosages considered by the investigator as reasonable for maintaining good health. Non-prohibited chronic therapies being used at Visit 1/Screening may be continued, but must be recorded.

Any changes to concomitant medications or therapies during the study must be recorded. The reason for any change in concomitant medications and/or therapies will be evaluated and, if appropriate, reported as, or in conjunction with, an AE.

8.1 Prohibited Medications or Therapies

Prohibited medications or therapies during the study include:

- No topical therapy within the Treatment Area or in the surrounding skin within one inch of the Treatment Area other than the designated test article or provided bland emollient (e.g., DML Lotion)[31], if needed to manage LSRs (see Section 8.2);

[31] Other bland emollients (e.g., Lubriderm [without alpha hydroxy acid], or other moisturizers that do not contain any "active" ingredients [e.g., salicylic acid, lactic acid, pyruvic acid, urea, or any other ingredient

- Topical retinoid-containing therapies in the Treatment Areas or in the surrounding skin within one inch of the Treatment Area within two weeks of Visit 2/Baseline or any topical retinoid use during the study;
- Topical corticosteroids in the Treatment Areas or in the surrounding skin within one inch of the Treatment Area within five days of Visit 2/Baseline;
- UV treatment within four weeks of Visit 2/Baseline;
- Systemic retinoids within 12 weeks of Visit 2/Baseline;
- Other systemic therapies using vitamin A supplements or St. John's Wort within four weeks of Visit 2/Baseline;
- Immunosuppressive systemic drugs, including systemic corticosteroids, within two weeks of Visit 2/Baseline;
- Any other investigational drugs or devices within 30 days of Visit 2/Baseline.

8.2 Allowed Medications or Therapies

Allowed medication or therapies during the study must be documented and include:

- Bland emollients, keratolytics, or sunscreen to treat diseased areas that are NOT in the Treatment Area (but not in the surrounding skin within one inch of the Treatment Area);
- Topical steroids to treat cutaneous diseased areas that are NOT in the Treatment Area (but not in the surrounding skin within one inch of the Treatment Area);
- Inhaled, intranasal, and ophthalmic steroid dosage forms.

Additionally, use of provided bland emollients (e.g., DML Lotion)[32] in the Treatment Areas as an aid to managing LSRs may be prescribed by the investigator as detailed in Section 6.2 and must be documented in the CRFs. Application of such bland emollients should not be applied within four hours of application of the test articles.

9. STUDY PROCEDURES

The study will consist of seven clinic visits and two phone calls (see Schedule of Events). Specific activities for each study visit are listed below.

Note: If the subject experiences issues with medication tolerability or other complications arise, ideally the subject will be seen by the investigator at one of the scheduled clinic visits or via an Unscheduled Visit to document the reactions and modifications to the dosing regimen prescribed by the investigator. In the event that a clinic visit is not possible or not warranted in the opinion of the investigator, the change in the subject's management will

that could irritate or cause a keratolytic effect]) may be used with approval from the investigator, but must be documented as a concomitant medication/therapy.

[32] Other bland emollients (e.g., Lubriderm [without alpha hydroxy acid], or other moisturizers that do not contain any "active" ingredients [e.g., salicylic acid, lactic acid, pyruvic acid, urea, or any other ingredient that could irritate or cause a keratolytic effect]) may be used with approval from the investigator, but must be documented as a concomitant medication/therapy.

be clearly documented in the source documents and CRF with corresponding changes noted in the Subject Diary regarding test article usage and/or concomitant medications/therapies (e.g., moisturizer use).

Any dosing modifications and/or changes to concomitant medications/therapies will be made bilaterally (e.g., if dosing is decreased to once a day given tolerability issues, both sides will be treated once daily even if only one side is having the tolerability issue) (see Section 6.2). Treatment per protocol should resume as soon as possible after any notable LSRs have materially subsided as determined by the investigator or designee (if possible via one of the scheduled clinic visits or via an Unscheduled Visit) such that dosing may resume.

9.1 Visit 1 (Day -45 to -7): Screening

Subjects can be screened for the study up to 45 days before Visit 2. If applicable, qualified subjects can washout from prohibited medications or treatments prior to Visit 2 (after obtaining consent/assent). Subjects that require washout for longer than 45 days will be re-consented. Clinical laboratory tests will be performed after the subject has fasted (for approximately eight hours).

At Screening, the investigator or designee will:

- Obtain a signed, written informed consent (unless the subject signed a consent within the past 45 days). Note: Subjects under 18 years of age must provide written informed assent and be accompanied by the parent and legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study, the subject must provide written informed consent at the time to continue study participation.
- Record demographics.
- Confirm I/E criteria.
- Confirm the subject has qualified analogous right and left Treatment Areas, with adequate disease (≥150 cm^2) and identical IGA scores (≥ 3) consistent with the I/E criteria (see Section 5.1) that will likely meet protocol requirements and Baseline, in the opinion of the investigator.
- Record medical/ichthyosis history.
- For those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, collect blood or buccal samples for genetic testing (see Section 12.4).
- Record prior and/or concomitant medications and therapies.
- Perform brief physical exam. Record any findings in the medical history.
- Perform vital signs (heart rate, respiration rate, blood pressure, and temperature), and height/weight.
- Perform UPT for WOCBP. Results must be negative for the subject to be enrolled in the study.

- Perform Fitzpatrick Skin Type assessment.
- Collect urine and blood samples for clinical laboratory tests.

QUALIFIED SUBJECT DETERMINATION AND TEST ARTICLE REQUEST: Prior to Visit 2/Baseline, after clinical laboratory results have been received and reviewed, and the investigator has confirmed the subject's eligibility, the site will contact the subject to confirm their willingness to participate in the treatment phase of the study. Assuming the qualified subject is willing to participate, then the site will:

a) Make a randomization request to order test article for the subject to be delivered to the site prior to the subject's Baseline visit;
b) Schedule the subject's Baseline visit at a mutually convenient time when the designated subject's test article will be at the site;
c) **NOTE: the ordered test article is specific to each subject and shall not be used for any other subject.** In the event a subject elects not to participate after receipt of their designated test article, the site should contact your monitor to discuss management of the test article received.

9.2 Visit 2 (Day 1): Baseline

At Baseline, the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Re-confirm eligibility and re-review laboratory results. Patients who do not meet I/E criteria at Visit 2 will be classified as screen failures.
- Update medical history, as required. Any changes in health status from Visit 1 to Visit 2 are not considered an AE, and will be captured as baseline medical history.
- Perform UPT for WOCBP. Results must be negative for the subject to be enrolled in the study.
- Select the Treatment Areas (see Section 6.2); record location by body region and percent BSA of disease affected skin in each Treatment Area. Estimate BSA using the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together. Note: Palms and soles are not eligible; the treatment of skin scalp and folds/intertriginous regions should be avoided. Additionally for treatment on the arms in subjects participating in the PK portion of the study, the antecubital fossa (e.g., approximately 10-15 cm^2) will be excluded to minimize contamination of PK blood draws.
- Perform IGA for each Treatment Area.
- Assess CI Signs/Symptoms for each Treatment Area.
- Document LSRs for each Treatment Area PRIOR to test article application for each Treatment Area.
- Take Baseline photographs. Note: Copy(s) may be provided to the subject at the discretion of the investigator to help the subject consistently identify the two Treatment Areas.

- For those subjects participating in the PK portion of the study, collect PK blood sample pre-application. Note: Subjects that elect to participate in the PK portion of the study should do so with the intent of completing all PK samplings required in the study, per protocol.
- Randomize the subject using the designated test article specific for that subject that was ordered by the site after completion of Visit 1. **Note: the ordered test article is specific to each subject and shall not be used for any other subject.**
- Dispense the Subject Instruction Sheet to the subject (and parent/legal guardian, if applicable). Instruct the subject (and parent/legal guardian, if applicable) where and how to apply the test articles to the designated Treatment Areas.
- Document test article accountability; weigh the tubes and dispense the test articles to the subject.
- Dispense the Subject Diary to the subject (and parent/legal guardian, if applicable) and provide completion instructions.
- Supervise the first application of the test articles. The test article with the **R**ED label should be applied to the **R**IGHT Treatment Area and the test article with the **L**EMON YELLOW label should be applied to the **L**EFT Treatment Area.
- Record any AEs.
- Assess LSRs approximately 10 minutes post-application for each Treatment Area.
- For those subjects participating in the PK portion of the study, collect additional PK blood samples at 1, 2, 3, and 4 hours post-application.
- Instruct the subject (and parent/legal guardian, if applicable) to apply the test articles to the designated Treatment Areas twice per day, once in the morning and once in the evening with at least eight hours between applications, and to hold the application of the test articles on days of clinic visits. Note: For those subjects participating in the PK portion of the study, the application before a scheduled clinic visit with PK time point (i.e., on Days 7, 14, 28, 56, and 83) must be approximately 12 hours ± 30 minutes prior to the blood draw.
- Schedule Visit 3 (Phone Call) and Visit 4 (Clinic Visit).

9.3 Visit 3 (Day 2) and Visit 7 (Day 43±3): Phone Calls

The investigator or designee will contact the subject or parent/guardian (as appropriate) by telephone to:

- Review any change in health status since the previous visit, including concomitant medications and therapies to assure the subject is not using any prohibited medications, and document the findings. Note: concomitant mediations and therapies are not formally updated at these phone call visits in the CRF just in the subject's source documentation.
- Review compliance with the test articles.
- Emphasize the need to maintain the Subject Diary daily with each application.
- If there are any concerns regarding tolerability or other AE, schedule a clinic visit (i.e., Unscheduled Visit) at the discretion of the investigator.
- Confirm the next scheduled visit and remind the subject (and parent/legal guardian,

if applicable) to hold the morning application of the test articles on days of clinic visits. Note: For those subjects participating in the PK portion of the study, the application before a scheduled clinic visit with PK time point (i.e., on Day 56) must be approximately 12 hours ± 30 minutes prior to the blood draw.

9.4 Visit 4 (Day 8+1) and Visit 5 (Day 15±1): Follow-Up

At this visit the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings. Ensure any changes concomitant medications and therapies identified during phone visits are reviewed and documented in the CRFs.
- Perform IGA for each Treatment Area.
- Assess CI Signs/Symptoms for each Treatment Area.
- Document LSRs for each Treatment Area.
- Update Concomitant Medications and Therapies, as applicable.
- Take photographs (optional).
- For those subjects participating in the PK portion of the study, collect PK blood sample PRIOR to application of the test articles. Note: This sample will be collected 12 hours ± 30 minutes after the dose on the previous day.
- Document test article accountability; weigh the tubes and return/dispense the test articles, as applicable.
- Review compliance and collect/dispense Subject Diary, as applicable.
- **Review proper test article use and application guidelines with the subject (and parent/legal guardian, if applicable), stressing the importance that care should be taken so that the correct test article is applied to the two Treatment Area(s) on the subjects RIGHT and LEFT side.**
- If possible, supervise the application of the test articles. The test article with the **R**ED label should be applied to the **R**IGHT Treatment Area and the test article with the **L**EMON YELLOW label should be applied to the **L**EFT Treatment Area.
- Document any AEs.
- Remind the subject (and parent/legal guardian, if applicable) to hold the application of the test articles on days of clinic visits. Note: For those subjects participating in the PK portion of the study, the application before a scheduled clinic visit with PK time point (i.e., on Day 28) must be approximately 12 hours ± 30 minutes prior to the blood draw.
- Schedule follow-up visit.

9.5 Visit 6 (Day 29±3): Follow-Up

At this visit the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Perform brief physical exam. Record any new or worsening findings as AEs.

- Perform vital signs (heart rate, respiration rate, blood pressure, and temperature).
- Perform UPT for WOCBP. Results must be negative for the subject to continue in the study.
- Collect urine and blood samples for clinical laboratory tests. If possible, subject will have fasted for approximately eight hours or more prior to these laboratory tests.
- Perform IGA for each Treatment Area.
- Assess CI Signs/Symptoms for each Treatment Area.
- Document LSRs for each Treatment Area.
- Update Concomitant Medications and Therapies, as applicable.
- Take photographs.
- For those subjects participating in the PK portion of the study, collect PK blood sample PRIOR to application of the test articles. Note: This sample will be collected 12 hours ± 30 minutes after the dose on the previous day.
- Document test article accountability; weigh the tubes and return/dispense the test articles, as applicable.
- Review compliance and collect/dispense Subject Diary, as applicable.
- **Review proper test article use and application guidelines with the subject** (and parent/legal guardian, if applicable)**, stressing the importance that care should be taken that the correct test article is applied to the two Treatment Area(s) on the subjects RIGHT and LEFT side.**
- If possible, supervise the application of the test articles. The test article with the **R**ED label should be applied to the **R**IGHT Treatment Area and the test article with the **L**EMON YELLOW label should be applied to the **L**EFT Treatment Area.
- Document any AEs.
- Schedule Visit 7 (Phone Call; see Section 9.3) and Visit 8 (Clinic Visit).

9.6 Visit 8 (Day 57±4): End of Part 1

At this visit the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Perform brief physical exam. Record any new or worsening findings as AEs.
- Perform vital signs (heart rate, respiration rate, blood pressure, and temperature).
- Perform UPT for WOCBP. Results must be negative for the subject to continue in the study.
- Collect urine and blood samples for clinical laboratory tests. If possible, subject will have fasted for approximately eight hours or more prior to these laboratory tests.
- Perform IGA for each Treatment Area.
- Assess CI Signs/Symptoms for each Treatment Area.
- Document LSRs for each Treatment Area.
- Take photographs.

- For those subjects participating in the PK portion of the study, collect PK blood sample PRIOR to the application of the test articles. Note: This sample will be collected 12 hours ± 30 minutes after the dose on the previous day.
- Document test article accountability; weigh the tubes and return the test articles from Part 1. Dispense the test article for Part 2 to the subject.
- Re-educate the subject (and parent/legal guardian, if applicable) with respect to dosing and related activities for Part 2.
  - Review compliance and collect/dispense Subject Diary, as applicable.
  - Supervise the application of the test article to both Treatment Areas.
- Record any AEs.
- Assess LSRs approximately 10 minutes post-application for each Treatment Area.
- Schedule Visit 9.

9.7 Visit 9 (Day 84±4): End of Study and Early Termination

At this visit the investigator or designee will:

- Query the subject about any changes in health status since the previous visit, including concomitant medications and therapies, and document the findings.
- Perform brief physical exam. Record any new or worsening findings as AEs.
- Perform vital signs (heart rate, respiration rate, blood pressure, and temperature).
- Perform UPT for WOCBP.
- Collect urine and blood samples for clinical laboratory tests. If possible, subject will have fasted for approximately eight hours or more prior to these laboratory tests.
- Perform IGA for each Treatment Area.
- Assess CI Signs/Symptoms for each Treatment Area.
- Document LSRs for each Treatment Area.
- Take photographs.
- Document test article accountability; weigh the tubes and collect all test articles.
- Collect Subject Diary.
- Exit the subject from the study.

10. CLINICAL EVALUATIONS

The following clinical evaluations will be performed according to the schedules indicated during the study. The same investigator should complete the evaluations for a given subject throughout the study. If this becomes impossible a sub-investigator with overlapping experience with the subject and the study should complete the evaluations.

10.1 Investigator's Global Assessment

At each clinic visit, overall severity of ichthyosis will be assessed using a five-point IGA scale where 0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe. This is a static morphological scale that refers to a point in time and not a comparison to Baseline. Subjects

must have an IGA score of 3 (moderate) or 4 (severe) at Baseline AND the IGA score must be identical in each Treatment Area.

The investigator should NOT refer to any other assessments to assist with this evaluation. The following scale will be used to assess the "average" degree of severity within each Treatment Area (TA), taking into consideration the four lead individual characteristics of ichthyosis:

Clear (0)	
Erythema	No erythema (hyperpigmentation may be present).
Scaling	No evidence of scaling.
Fissuring	No evidence of fissuring.
Papulation, and/or lichenification	No evidence of papulation and/or lichenification.

Almost Clear (1)	
Erythema	No more than faint red coloration predominates over the TA.
Scaling	No more than a limited amount of very fine scales predominate, little of the TA is affected.
Fissuring	No or extremely rare fissuring predominates, little of the TA is affected.
Papulation, and/or lichenification	No more than a very slight papulation and/or lichenification predominates, often easier felt than seen, little of the TA is affected.

Mild (2)	
Erythema	No more than light red coloration predominates over the TA.
Scaling	No more than mainly fine scales predominate, with less than half of the TA is affected.
Fissuring	No more than mild fissuring, with less than half of the TA is affected.
Papulation, and/or lichenification	No more than a slight (≤ 1mm), but definite elevation of focal skin areas due to papulation and/or lichenification predominates, with less than half of the TA is affected.

Moderate (3)	
Erythema	No more than moderate red coloration predominates over the TA.
Scaling	No more than somewhat coarser scales predominate; greater than half the TA is affected.
Fissuring	No more than moderate fissuring; greater than half the TA is affected.
Papulation, and/or lichenification	No more than a moderate (1.1 to ≤ 2 mm) elevation of focal skin areas due to papulation and/or lichenification predominates; greater than half the TA is affected.

Severe (4)	
Erythema	Dusky to deep red coloration predominates over the TA.
Scaling	Coarse, thick tenacious scales predominate; virtually all of the TA is affected.
Fissuring	Severe fissuring predominates; virtually all of the TA is affected.
Papulation, and/or lichenification	Marked elevation (> 2mm) of papulation and/or lichenification predominates; virtually all of the TA is affected.

10.2 Individual Clinical Signs/Symptoms

At each clinic visit (except Visit 1/Screening), overall severity of erythema, scaling, fissuring, and papulation/lichenification will be graded for each TA using a five-point scale where 0=clear, 1=almost clear, 2=mild, 3=moderate, and 4=severe. This is a static morphological scale that refers to a point in time and not a comparison to Baseline.

ERYTHEMA		
0	Clear	No redness
1	Almost Clear	Faint red coloration predominates
2	Mild	Light red coloration predominates
3	Moderate	Moderate red coloration predominates
4	Severe	Dusky to deep red coloration predominates

SCALING		
0	Clear	No evidence of scaling
1	Almost Clear	Limited amount of very fine scales, little of the TA is affected
2	Mild	Mainly fine scales predominate, less than half of TA is affected
3	Moderate	Somewhat coarser scales predominate, greater than half of the TA is affected
4	Severe	Coarse, thick, tenacious scales predominate, virtually all of the TA is affected

FISSURING		
0	Clear	No evidence of fissuring
1	Almost Clear	No more than a very slight fissuring predominates, often easier felt than seen, little of the TA is affected
2	Mild	Mainly mild fissuring predominate, less than half of TA is affected
3	Moderate	Mainly moderate fissuring predominate, greater than half of the TA is affected
4	Severe	Mainly severe fissuring predominate, virtually all of the TA is affected

PAPULATION AND/OR LICHENIFICATION		
0	Clear	No evidence of plaque elevation above normal skin level.
1	Almost Clear	Very slight elevation above normal skin level predominates, easier felt than seen, little of the TA is affected.
2	Mild	No more than a slight (≤1 mm) but definite elevation of focal skin areas due to papulation and/or lichenification predominates; less than half of the TA is affected
3	Moderate	No more than a moderate (≤2 mm) elevation of focal skin areas due to papulation and/or lichenification predominates; greater than half the TA is affected
4	Severe	Marked elevation (>2 mm) of papulation and/or lichenification predominates; virtually all of the TA is affected.

10.3 Fitzpatrick Skin Type Assessment

At Visit 1, the investigator or designee will document the subject's skin phototype (I-VI) using the Fitzpatrick Skin Type Assessment.

Fitzpatrick Skin Type Assessment		
Phototype	**Typical Features**	**Tanning Ability**
I	Pale white skin, blue/hazel eyes,	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

10.4 Local Skin Reactions

At each clinic visit (except Visit 1/Screening), LSRs including burning/stinging, pain, and pruritus will be documented in each Treatment Area using a four-point ordinal scale where 0=none, 1=mild, 2=moderate, and 3=severe. These LSRs will be collected independently

of AEs. Only LSRs that require medical intervention (e.g., prescription medication) or require withholding or reduction in dosing frequency of the test articles will be documented as AEs. Any LSRs that are not listed above will be recorded as AEs.

11. PHOTOGRAPHY

Photography documentation is required in this study at Visit 2/Baseline/Day 1, Visit 6/Day 29, Visit 8/Day 57, and Visit 9/Day 84. Copy(s) of the Baseline photos may be provided to the subject, at the discretion of the investigator, to help the subject consistently identify the two Treatment Areas. Photographs may also be taken at other visits at the discretion of the investigator. Photographs taken as part of this study will be used to document the effects of treatment, AEs, or other findings during the study. The site will be provided with suggested guidelines to assist them in taking standardized photographs. Photographs will be taken of lesions only, without including subject identity (i.e., facial photos). All photographs taken as part of this study are for informational purposes only and are not to be used in grading or for any other assessment.

Note: Subjects may decline to have photographs taken during the conduct of the study. If a subject initially consents to photographs, then declines further photography, the Sponsor may use the photographs taken under consent for the purposes noted above.

12. LABORATORY TESTS

12.1 Blood Chemistries, Hematology and Urinalysis

Blood and urine specimens will be collected at Visit 1/Screening, Visit 6/Day 29, Visit 8/Day 57 (End of Part 1), and Visit 9/Day 84 (EOT or early termination) for chemistry, hematology, and urinalysis. Subjects must be fasting (approximately 8 hours) for screening laboratory tests and, if possible, for laboratory tests at Visit 6/Day 29, Visit 8/Day 57, and Visit 9/Day 84; however, if a subject arrives at the clinic for Visit 6, Visit 8, or Visit 9 without fasting for at least eight hours, laboratory specimens may be collected as non-fasting, at the discretion of the investigator, and with the appropriate fasting status documented on the lab requisition form.

The following tests will be performed

Chemistries	**Hematology**	**Urinalysis**
Albumin	Hemoglobin	Blood
Alkaline Phosphatase	Hematocrit	Glucose
ALT (SGPT)	MCV	Ketone
AST (SGOT)	MCH	pH
Bicarbonate	MCHC	Specific Gravity
Bilirubin, total	RBC (Erythrocytes)	Microscopic Analysis
Calcium	WBC (Leucocytes)	WBC
Chloride	RDW	RBC
Cholesterol	Differential count	Casts
Creatinine	Basophils	
GGT	Eosinophils	
Glucose (fasting)	Lymphocytes	
LDH	Monocytes	
Potassium	Neutrophils	
Phosphate	Platelets	
Protein, total		
Sodium		
Triglycerides		
Urea (BUN)		
Uric Acid		

Sample collection, handling, labeling, and shipping should be done following the instructions provided by the relevant certified laboratory and the applicable local regulations.

The investigator must review all the subject's laboratory reports in a timely manner. **NOTE:** The investigator will initial and date each laboratory report to indicate his/her review. The investigator will note, directly on the laboratory report, whether or not any abnormal test results are clinically significant. The investigator must complete an appropriate AE form for any new or worsening abnormal test results that are identified as clinically significant after Baseline.

AEs that may be associated with venipuncture and that must be included in the informed consent include:

- Pain
- Bruising
- Bleeding at the puncture site
- Fainting
- Inflammation of the vein

12.2 Urine Pregnancy Tests

UPTs must be performed on all WOCBP at Visit 1/Screening, Visit 2/Day 1 (prior to

randomization), Visit 6/Day 29, Visit 8/Day 57, and Visit 9/Day 84 (EOT or early termination); UPTs must be negative for the subject to be eligible for and to continue in the study. The UPTs will be performed at the study site, if the site is registered and conforms to CLIA regulations for such testing (possesses a current valid CLIA Certificate of Waiver), or at an appropriately registered reference laboratory. The investigator will report the UPT results on the CRFs, in the subject's medical records, and in independent records maintained at the study site. The UPT used must have a minimum sensitivity of 25 mIU of β-HCG/mL.

12.3 Pharmacokinetic Sample Collection, Storage, and Assay

At Visit 2/Day 1, PK blood samples will be collected for isotretinoin and tretinoin pre-test article application (time 0) and at 1, 2, 3, and 4 hours post-test article application. At Visit 4/Day 8, Visit 5/Day 15, Visit 6/Day 29, Visit 8/Day 57, and Visit 9/Day 84, a PK blood sample will be collected for isotretinoin and tretinoin pre-test article application (approximately 12 hours after the last test article application on the previous day). Sampling times will be recorded on the appropriate CRFs. Site (e.g., right versus left arm) of PK blood draws will be recorded.

The method of sample collection for PK analysis is detailed in the laboratory manual to be provided by the laboratory vendor. Each PK blood sample will be processed and stored as detailed in the laboratory manual. Samples will be prepared in duplicate; one of the samples will be shipped to the analytical laboratory using an authorized courier and the other sample will be stored at the site as back-up samples until confirmation that the initial shipment has been safely received by the analytical laboratory. Details and specific instructions on labeling and management of these specimens are provided in the laboratory manual.

Plasma will be analyzed for levels of isotretinoin and tretinoin and compared to background systemic retinoid levels pre- and post-treatment.

12.4 Genetic Testing

At Visit 1/Screening, for those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected for genetic testing. As/if required, this test may be repeated during the study as determined by the investigator (e.g., specimen quality, loss or handling concerns, indeterminate outcome). The subject may be enrolled based upon their clinical diagnosis only, with genetic testing to follow, such that the results are available at or before the conclusion of the study. Specifics regarding the testing options for these two ichthyosis subtypes, specimen handling, and related matters will be determined by the company used for genetic testing. In the event the genetic testing results do not concur with the clinical diagnosis the subject may complete the study as the inclusion criteria are based upon the clinical assessment of their skin disease by the Investigator at Baseline.

13. END OF STUDY CRITERIA

At the end of each subject's participation in the study, the investigator will complete an End of Study form for all completed and discontinued subjects.

13.1 Completion of the Study

Subjects who complete the 12 week course of treatment as specified in this protocol and all of the Visit 9/Day 84 evaluations will have completed the study.

13.2 Subject Discontinuation

A subject may be withdrawn from the study prior to completion for any of the following reasons:

- AE
- Death
- Lack of efficacy
- Lost to follow-up
- Noncompliance with study drug
- Physician decision
- Pregnancy
- Progressive disease
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject; Note: if the subject decides to withdraw from the study due to an AE then it should be classified as withdrawal due to an AE.
- Other (e.g., any other reason that may affect the outcome of the study or the safety of subjects)

If a subject withdraws from the study prematurely for any reason, the site should make every effort to have the subject return for the next scheduled visit to complete the final visit procedures. When a subject is withdrawn from the study for a test article related AE (i.e., possibly, probably or definitely related as defined in Section 14), when possible, the subject should be followed until resolution or stabilization of the AE. If the subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed.

Subjects who are prematurely withdrawn or discontinued from the study will not be replaced.

13.3 Study Termination

The study may be terminated by the investigator or the Sponsor. If, in the opinion of the investigator, clinical observations made during the study suggest that it may be unwise to continue, he or she may stop the study. A study termination by the investigator will be reported to the Sponsor.

In addition, a written statement fully documenting the reasons for this action will be submitted to the Sponsor by the investigator within five working days.

In the event that the Sponsor chooses to discontinue or terminate the study, appropriate notification will be given to the investigator.

14. ADVERSE EVENT REPORTING

An **adverse event** is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with any drug) and from any route of administration, formulation or dose, including an overdose.

Information on the medical condition of subjects should begin following the subject's written informed consent/assent to participate in the study and a medical history should be taken at screening. During any wash out and baseline periods, any changes in the health of subjects should be recorded as changes in medical history unless an event occurred as a result of a study-related procedure and is unanticipated; in such cases, the event should be recorded as an AE and reported to the Institutional Review Board (IRB) as an "unanticipated problem" in accordance with local procedures. Other changes in subject health information becomes AE data when the subject begins dosing with the test article; therefore AE data should be collected from the date of the first dose of test article until the date of the final study visit. These data are considered TEAEs.

Timely and complete reporting of all AEs assists the Sponsor or designee in identifying any untoward medical occurrence, thereby allowing:

1) protection of the safety of study subjects;
2) a greater understanding of the overall safety profile of the test article;
3) recognition of dose-related test article toxicity;
4) appropriate modification of study protocols;
5) improvements in study design or procedures; and
6) adherence to worldwide regulatory requirements.

Test article is defined as a pharmaceutical form of an active ingredient (or "primary operational component" for devices) or vehicle/placebo being tested or used as a reference in the study, whether blinded or unblinded. AEs may be either spontaneously reported or elicited during questioning and examination of a subject. All AEs must be completely recorded on the AE CRF. If known, the investigator should report the diagnosis of the underlying illness or disorder, rather than its individual symptoms. Subjects experiencing AEs that cause interruption or discontinuation of test article, or those experiencing AEs

that are present at the end of their participation in the study should receive follow-up as appropriate. If possible, report the outcome of any AE that caused permanent discontinuation or that was present at the end of the study particularly if the AE is considered by the investigator to be treatment-related (i.e., definitely, probably, or possibly related to test article).

14.1 Adverse Event

All AEs must be recorded on the AE CRF. AEs should be followed to resolution or stabilization (if possible), and reported as serious adverse events (SAEs) if they become serious.

No human studies have been conducted with PAT-001 (isotretinoin) Ointment. The most common adverse reactions associated with other topical retinoid formulations include application site erythema, skin exfoliation, pain of skin, application site pruritus, skin irritation, skin tenderness, skin burning sensation, application site stinging, dry skin/lips, skin hyperpigmentation, skin hypopigmentation, and photosensitivity. The most notable or common adverse reactions with oral isotretinoin are: dry lips , dry skin, back pain, dry eye, arthralgia, epistaxis, headache, nasopharyngitis, chapped lips, dermatitis, renal or hepatotoxicity, musculoskeletal discomfort, teratogenicity, and visual acuity reduced. Although systemic exposure is expected to be low given the route of topical administration and therefore many of these risks are unlikely, these, as well as other unknown risks, are considered potential risks pending clinical experience with this new dosage form.

The investigator will instruct the subject to report any AEs that may occur during the study. At each visit, the investigator should ask the subject, in non-directive fashion, about any change in the subject's overall condition since the previous visit.

The severity of each AE, as judged by the investigator, will be recorded on the appropriate AE CRF and will be graded according to the following scale:

Mild – The AE is transient and easily tolerated by the subject.

Moderate – The AE causes the subject discomfort and interrupts the subject's usual activities.

Severe – The AE causes considerable interference with the subject's usual activities, and may be incapacitating or life-threatening.

The investigator must determine the relationship of the AE to the test article according to the following categories:

Definite – An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing

the dosage, and reappearance of the event on repeated exposure (re-challenge).

Probable – An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; and that is confirmed by improvement on stopping or reducing the dosage of the test article; and that is unlikely to have been caused by concurrent/underlying illness or other drugs, procedures, or other causes.

Possible – An event that follows a reasonable temporal sequence from administration of the test article; that follows a known or expected response pattern to the test article; but may have been caused by concurrent/underlying illness, other drug, procedure, or other causes.

Unlikely – An event that does not follow a reasonable temporal sequence from administration of the test article; that does not follow a known or expected response pattern to the test article, or most likely was caused by concurrent/underlying illness, other drug, procedure, or other causes, because of their known effects.

Not Related – An event almost certainly caused by concurrent/underlying illness, other drug, procedure, or other causes.

The investigator should categorize the outcome of the AE according to the following categories:

Fatal – Termination of life as a result of an AE.

Not Recovered/Not Resolved – AE has not improved or the subject has not recuperated.

Recovered/Resolved – AE has improved or the subject has recuperated.

Recovered/Resolved with Sequelae – subject recuperated but retained the pathological conditions resulting from the prior disease or injury.

Recovering/Resolving – AE is improving or the subject is recuperating.

Unknown – Not known, not observed, not recorded or subject refused.

An **adverse reaction** is any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions for which there is reason to conclude that the drug caused the event. For the purposes of prescription drug labeling, the term adverse reaction means an undesirable effect, reasonably associated with the use of a drug that may occur as part of its pharmacological action or may be unpredictable in its occurrence.

A **suspected adverse reaction** is any AE for which there is a reasonable possibility that

the drug caused the event.

For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure (IB) or is not listed at the specificity or severity that has been observed; or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

14.2 Serious Adverse Event

An event that is serious must be recorded on the AE CRF and on the TI SAE Report Form, and requires expeditious handling to comply with regulatory requirements.

An AE or suspected adverse reaction is considered "serious" if, in the opinion of either the investigator or Sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening event.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Congenital anomaly/birth defect.
- Is an important medical event – defined as a medical event(s) that may not result in death, be life-threatening, or require hospitalization but, based upon appropriate medical judgment, may jeopardize the patient/subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- **Although not defined as an AE, pregnancy shall be considered as a serious event and must be immediately reported by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on**

the first page of the protocol.

Events NOT considered to be serious AEs are:

- Hospitalizations for the treatment, which was elective or pre-planned, of a pre-existing condition that did not worsen, and
- Treatment on an emergency, outpatient basis, for an event not fulfilling any of the definitions of "serious" given above and not resulting in hospital admission.

AEs classified as "serious" by either the investigator or the Sponsor require expeditious handling and reporting to TI to comply with regulatory requirements. **All SAEs, whether related or unrelated to test article, must be immediately reported by telephone to the Medical Monitor (619-889-7058) and, in the event that he/she is unavailable, to the Project Manager (858-571-1800, ext. 129) [additional contact information listed on the first page of the protocol].** Written notification of all SAEs should be sent to the Project Manager by email or confirmed facsimile transmission. These include those SAEs listed in the protocol or IB and must include an assessment of whether there is a reasonable possibility that the drug caused the event.

Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In this case, the investigator must immediately report the event to the Sponsor. In addition, such information should also be provided to the site's respective IRB per their governing guidelines for SAE reporting.

If only limited information is initially available, follow-up reports are required. Should the investigator become aware of a SAE (regardless of its relationship to test article) that occurs within 30 days after stopping the test article, the SAE must be reported in accordance with procedures specified in this protocol. In the event of death, if an autopsy is performed, a copy of the report should be sent to TI, if available.

As required, TI will notify participating investigators of all suspected adverse reactions that are serious and unexpected. This notification will be in the form of an IND safety report of potential serious risks as soon as possible but no later than 15 calendar days after the Sponsor determines that the information is "reportable" according to the criteria listed in 21 CFR Section 312.32. These are:

i) Serious and unexpected suspected adverse reactions,
ii) Findings from other studies including epidemiological studies, pooled analyses or other clinical studies that suggest a significant risk in humans exposed to the test articles,
iii) Findings from animal or in vitro tests that suggest a significant risk to humans exposed to the test articles, or reports of significant organ toxicity at or near the expected human exposure, and
iv) Clinically important increases in the rate of occurrence of serious suspected

adverse reactions.

v) Confirmed pregnancy at any time during the study or within one month from discontinuing from the study.

Upon receiving such notices, the investigator must review and retain the notice with the IB and immediately submit a copy of this information to the responsible IRB according to local regulations. The investigator and IRB will determine if the informed consent/assent requires revision. The investigator should also comply with the IRB procedures for reporting any other safety information. Where required, submission of safety updates by the investigator to Health Authorities should be handled according to local regulations.

14.3 Laboratory Test Abnormalities

In addition to being recorded on the appropriate laboratory test results CRF, or being electronically submitted from a central laboratory, any clinically significant laboratory test result that meets the criteria for an AE (see Section 14) or SAE (see Section 14.2) must also be recorded on the AE CRF. SAEs must be reported to the Sponsor and IRB as per Section 14.2. In these cases, TI will typically require additional information about the clinically significant abnormality, including information regarding relationship to test article or other causes, any action taken, and resolution. Other laboratory test abnormalities will be addressed by the investigator on the actual laboratory test reports, and on the associated laboratory test results CRF.

14.4 Pregnancy

WOCBP include any female who has experienced menarche or is 10 years of age or older and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea >12 consecutive months in women 50 years of age and older]. Even women who are using hormonal methods of contraception and/or barrier methods to prevent pregnancy, practicing abstinence, or who have a monogamous partner that is sterile (e.g., vasectomy) should be considered to be of childbearing potential. Surgical means of sterilization (e.g., vasectomy, tubal ligation) must be a minimum of six months post-procedure to be considered effective birth control.

WOCBP must have a negative pregnancy test prior to study enrollment and must use the methods of contraception outlined in the protocol during the course of the study, in a manner such that risk of failure is minimized. Methods of acceptable contraception include A) total abstinence OR B) two forms of birth control including:

- Oral, patch, injected, or implanted hormonal methods of contraception[33] AND
- Partner vasectomy (performed at least six months prior to study entry) OR barrier

[33] WOCBP taking hormonal therapy must be on treatment for (1) oral or patch: one complete cycle (e.g., four to eight weeks) or (2) injectable or implanted: at least one week prior to study entry, continued per label, and must not change their dosing regimen during the study.

methods of contraception (barrier methods include male condom with or without spermicide, diaphragm with spermicide, or cervical cap with spermicide) OR vaginal contraceptive sponge containing a spermicide.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent/assent form documenting this discussion.

WOCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period). If a subject or investigator suspects that a subject may be pregnant at any time during the study the test article must be withheld until the results of laboratory pregnancy testing are available. If pregnancy is confirmed, the subject must not receive or apply further test article and must be discontinued from the study. The investigator must immediately notify the Medical Monitor of the pregnancy and record the pregnancy on the appropriate pregnancy surveillance form.

If following initiation of study treatment, it is subsequently discovered that a study subject was pregnant or may have been pregnant at the time of test article exposure, the investigator must immediately notify the Medical Monitor of this event, and record the pregnancy on the appropriate pregnancy surveillance form. The form will be sent to TI. The investigator must notify the IRB of any pregnancy associated with the study therapy and keep careful source documentation of the event.

Protocol-required procedures for those subjects that are discontinued from the study must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated, including counseling of the subject by the investigator and her managing physician or health care provider (e.g., obstetrician). In addition, the investigator must report to TI, on the appropriate TI pregnancy surveillance form(s), any follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Although pregnancy itself is not an AE, any complications during pregnancy should be recorded as AEs (or SAEs, if they fulfill the SAE criteria). Offspring should be followed for a minimum of eight weeks. Any congenital anomaly/birth defect in a child born to a subject exposed to the test article(s) should be recorded as a SAE and details documented in the pregnancy surveillance form. Abortion, whether accidental, therapeutic or spontaneous should be reported as a SAE.

15. BLINDING/UNBLINDING

Blinding is important for the integrity of this clinical study. However, the blind may be broken in the event of a medical emergency in a subject, in which knowledge of the test article identity is critical to the subject's management. Before breaking the blind for a subject, the investigator should determine that the information is necessary (i.e., that it will

alter the subject's immediate management). In many cases, particularly when the emergency is clearly not test article related, the problem may be effectively managed by assuming that the subject is receiving active product without the need for unblinding. The need to break the blind should first be discussed with the responsible Medical Monitor and the best method to do this will be determined.

In Part 1, the test articles will be blinded using color coded labels to designate which test article to apply to each Treatment Area.

16. CLINICAL SUPPLIES

16.1 Test Article Information

Test articles will be packaged and labeled by the Sponsor or designee. Detailed information on the packaging/labeling, blinding/unblinding, storage and preparation, dispensing, accountability etc. is included in Appendix 3.

16.2 Supplies Provided by Therapeutics, Inc.

- CRFs
- Source document draft templates
- Site regulatory binder
- UPT kits
- Digital camera
- Bland emollient (e.g., DML Lotion)

16.3 Supplies Provided by Investigator

- Personal computer to store and view study images
- Urine collection containers for UPTs
- Centrifuge to process blood samples per specifications in laboratory manual (if participating in PK portion of the study)
- Ultra-low freezer for storage of PK blood samples (if participating in PK portion of the study)

16.4 Supplies Provided by the Clinical Laboratory

- Supplies to collect and transport urine and blood samples to the clinical laboratory
- Tubes and labels for plasma aliquots for PK analysis (for sites participating in the PK portion of the study)
- Urine collection containers for urinalysis

17. STATISTICAL CONSIDERATIONS

17.1 Sample Size

As a first-in-man POC study, no formal power calculations were used to determine the sample size.

17.2 Endpoints

17.2.1 Safety Endpoints

Safety endpoints will include:

- Incidence (severity and causality) of any local and systemic AEs
- Number of subjects with presence (and severity) of the following LSRs: stinging/burning, pain, and pruritus at each time point for each Treatment Area collected (summarized by Test Article).
- Changes from Screening in vital signs at Days 29, 57, and 84 (or EOT) (summarized by Treatment Group).
- Changes from Screening in clinical laboratory tests (hematology, chemistry, and urinalysis) at Days 29, 57, and 84 (or EOT) (summarized by Treatment Group).
- UPT results in all WOCBP at Screening, Baseline, Day 29, Day 57, and Day 84 (or EOT).

17.2.2 Pharmacokinetic Endpoints

PK endpoints with include:

- Concentration of isotretinoin and tretinoin pre-dose and at 1, 2, 3, and 4 hours after the first dose on Day 1.
- Trough plasma concentrations (C_{12h}) on Days 8, 15, 29, 57, and 84.

17.2.3 Efficacy Endpoints

Part 1 (P1) and Part 2 (P2) efficacy data will be analyzed separately. For Part 1, efficacy endpoints will be summarized by Test Article (PAT-001, 1%; PAT-001, 0.2%; and Vehicle [pooled across Treatment Groups]) and/or by Part 1 Treatment Group (Group 1: PAT-001, 0.1%/Vehicle; and Group 2: PAT-001, 0.2%/Vehicle) as described below. For Part 2, efficacy endpoints will be summarized by Part 2 Summary Group, which consists of four groups:

- Group A: PAT-001, 0.1%-P2 Active/P1 Active
- Group B: PAT-001, 0.1%-P2 Active/P1 Vehicle;
- Group C: PAT-001, 0.2%-P2 Active/P1 Active; and
- Group D: PAT-001, 0.2%-P2 Active/P1 Vehicle.

In Part 1, the following exploratory endpoints will be evaluated:

- Frequency distribution of IGA and CI Signs/Symptoms at Baseline, and Days 8,

15, 29, and 57 summarized by Test Article.
- Absolute change from Baseline in IGA and the CI Signs/Symptoms at Days 8, 15, 29, and 57 summarized by Test Article.
- Within subject difference in IGA and CI Signs/Symptoms at Baseline and Days 8, 15, 29, and 57 summarized by Part 1 Treatment Group.
- Within subject difference in change from Baseline in IGA and CI Signs/Symptoms at Baseline and Days 8, 15, 29, and 57 summarized by Part 1 Treatment Group.

In Part 2, the following exploratory endpoints will be evaluated:
- Frequency distribution of IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Summary Group (Group A-D).
- Absolute change from Baseline in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Summary Group (Group A-D).
- Absolute change from Day 57 in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Summary Group (Group A-D).
- Within subject difference in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Treatment Group (0.1% and 0.2%).
- Within subject difference in absolute change from Baseline in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Treatment Group (0.1% and 0.2%).
- Within subject difference in absolute change from Day 57 in IGA and CI Signs/Symptoms at Day 84 summarized by Part 2 Treatment Group (0.1% and 0.2%).

17.3 Statistical Methods

Summary tables (descriptive statistics and/or frequency tables) will be provided for screening variables, baseline variables, efficacy variables, and safety variables. Continuous variables will be described by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum). Frequency counts and percentage of subjects within each category will be provided for categorical data.

Study Populations:
The Safety population will include all enrolled subjects who applied the test article. The intent-to-treat (ITT) population will include all randomized subjects who were dispensed the test article. The PK population will include those subjects in the Safety population who participated in the PK portion of the study with no evidence of material dosing noncompliance.

17.3.1 Safety Analyses

The analysis of safety will be conducted on the Safety population.

Extent of Exposure

Extent of exposure will be calculated separately for Part 1 and Part 2 and overall. The total amount of each test article used by each subject (difference between the weight of the tubes dispensed and weight of the tubes returned) and the mean daily amount of test article applied (total amount of test article used divided by the number of days dosed) will be calculated for each Treatment Group and Test Article. Descriptive statistics will be used to summarize the total amount and mean daily amount of test article applied.

Adverse Events

All AEs reported during the study will be listed, documenting onset, severity, whether therapy was required, any change in test article dosing, investigator assessment of the relationship to the test article, and outcome. AEs will be coded using MedDRA using preferred terms (PTs) and system organ class (SOC). The PTs and SOC will then be tabulated. All treatment emergent AEs (TEAEs) will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article.

Local Skin Reactions

Severity of LSRs (stinging/burning, pain, and pruritus) will be recorded for each Treatment Area (i.e., Test Article). LSRs will be summarized by frequency and severity of each individual LSR at each visit.

Physical Examinations

Findings from the brief physical examinations will be recorded in medical history (from assessment at Screening) or as AEs (from assessment at Days 29, 57, and 84).

Vital Signs

Vital signs (heart rate, respiration rate, blood pressure (systolic and diastolic), and temperature) will be recorded at Screening, and Days 29, 57, and 84. Descriptive statistics will be used to summarize vital signs. Clinically significant changes from Screening in vital signs at Days 29, 57, and 84 will be summarized.

Clinical Laboratory Tests

Clinical laboratory data (hematology, chemistry, and urinalysis) will be tabulated at Screening and Days 29, 57, and 84. Changes from Screening in laboratory data at Days 29, 57, and 84 will also be summarized. All laboratory data will be listed and reported in the units received by the central laboratory. Shift tables by analyte and by out of range flag will be presented to facilitate the evaluation of change from Screening to Days 29, 57, and 84.

Urine Pregnancy Tests

UPT results (if applicable) at Screening, Baseline, and Days 29, 57, and 84 will be provided in a subject listing.

Concomitant Medications and Therapies

Concomitant medications and therapies will be provided in subject listings.

17.3.2 Efficacy Analyses

The analysis of efficacy will be conducted on the ITT population. Given the small sample size, no formal hypothesis testing will be done.

Dosing Compliance
Dosing compliance will be evaluated separately for Part 1 and Part 2 and overall. Measures of test article compliance will include the duration of treatment (in number of days) and the total number of applications. Descriptive statistics will be used to summarize test article compliance. Subjects who applied at least 80% of the expected applications will be considered to be compliant with test article dosing.

Investigator's Global Assessment
Part 1. Frequency distributions of IGA score will be tabulated at Baseline and Days 8, 15, 29, and 57 by Test Article. Absolute change from Baseline in IGA at Days 8, 15, 29, and 57 will also be summarized by Test Article. Within-subject difference (Active-Vehicle) in IGA score at Baseline, and Days 8, 15, 29, and 57 and absolute change from Baseline at Days 8, 15, 29, and 57 will be summarized by Part 1 Treatment Group.

Part 2. Frequency distributions of IGA score will be tabulated at Day 84 by Part 2 Summary Group. Absolute change from Baseline and absolute change from Day 57 in IGA at Day 84 will also be summarized by Part 2 Summary Group. Within-subject difference (Active-Vehicle) in IGA score, absolute change from Baseline, and absolute change from Day 57 at Day 84 will be summarized by Part 2 Treatment Group.

Individual Clinical Signs/Symptoms
Part 1. Frequency distributions of erythema, scaling, fissuring, and papulation/lichenification will be tabulated at Baseline, and Days 8, 15, 29, and 57 by Test Article. Absolute change from Baseline in each of the Signs/Symptoms at Days 8, 15, 29, and 57 will also be summarized by Test Article. Within-subject difference (Active-Vehicle) for each of the Signs/Symptoms scores at Baseline, and Days 8, 15, 29, and 57 and absolute change from Baseline at Days 8, 15, 29, and 57 will be summarized by Part 1 Treatment Group.

Part 2. Frequency distributions for each of the Signs/Symptoms will be tabulated at Day 84 by Part 2 Summary Group. Absolute change from Baseline and absolute change from Day 57 for each of the Signs/Symptoms at Day 84 will also be summarized by Part 2 Summary Group. Within-subject difference (Active-Vehicle) for each of the Signs/Symptoms scores, absolute change from Baseline, and absolute change from Day 57 at Day 84 will be summarized by Part 2 Treatment Group.

17.3.3 Pharmacokinetics Analyses

A PK analysis will be conducted on the PK population.

Concentrations After Single Dose
Concentrations of isotretinoin and tretinoin will be summarized pre-test article application (time 0) and 1, 2, 3, and 4 hours post-test article application for each subject and compared among Treatment Groups.

Trough Concentrations
Trough plasma concentrations of isotretinoin and tretinoin at Days 8, 15, 29, 57, and 84 will be compared between Treatment Groups.

17.4 Subgroup Analyses

No formal subgroup analyses are planned; however, potential differences between the two types of CI may be evaluated depending on the availability of subjects in both groups.

17.5 Interim Analyses

No interim analyses are planned.

18. ETHICAL AND REGULATORY CONSIDERATIONS

18.1 Compliance with Good Clinical Practice

This study will be conducted in compliance with the principles of the Declaration of Helsinki, with the current Good Clinical Practice guidelines and with other applicable regulations. The investigator and all study staff will conduct the study in compliance with this protocol. The protocol, informed consent/assent documents, recruitment advertisements and any amendments to these items will have IRB approval prior to study initiation. Voluntary informed consent/assent will be given by every subject prior to the initiation of any study-related procedures. The rights, safety and well-being of the study subjects are the most important considerations and prevail over the interests of science and society. All personnel involved in the conduct of this study must be qualified by education, training, and experience to perform their assigned responsibilities.

18.2 Institutional Review Board and Informed Consent/Assent

Before study initiation, the investigator must have written and dated approval from the IRB for the protocol, consent/assent form, subject recruitment materials/process (e.g., advertisements), and any other written information to be provided to subjects and parent/guardian (if applicable). The investigator should also provide the IRB with a copy of the product labeling, information to be provided to subjects and parent/guardian (if applicable) and any updates. The investigator will submit documentation of the IRB approval to TI.

The IRB approved consent/assent form must include all elements required by FDA, state, and local regulations, and may include appropriate additional elements.

The investigator/designee will explain the study to each potential subject and parent/guardian (if applicable) and the subject must indicate voluntary consent/assent by signing and dating the approved informed consent/assent form. The investigator must provide the subject with a copy of the consent form, in a language the subject understands. If the subject is under 18 years of age, the subject must provide written informed assent and be accompanied by the parent or legal guardian at the time of assent/consent signing. The parent or legal guardian must provide informed consent for the subject. If a subject becomes 18 years of age during the study the subject must provide written informed consent at that time to continue study participation.

The investigator will maintain documentation that informed consent/assent was obtained prior to the initiation of any study-specific procedures.

18.3 Protocol Compliance

The IRB approved protocol must be followed except in the case of a change that is intended to eliminate an immediate risk to subjects. All protocol deviations must be documented.

18.4 Protocol Revisions

TI must prepare all protocol revisions. All protocol amendments must receive IRB approval prior to implementation. All administrative letters must be submitted to the IRB for their information. Copies of all correspondence with the IRB regarding this study must be sent to TI.

New or altered consent/assent forms required by the IRB due to a protocol change must be signed by all subjects and parent/guardian (if applicable) currently enrolled in the study and must be used for any subsequent subject enrollment.

18.5 Study Monitoring

Representatives of TI and/or the Sponsor must be allowed to visit all study sites, to review study records and to directly compare them with source documents (including, but not limited to patient and hospital records), to discuss the study conduct with the investigator and study staff and to verify that the investigator, study staff and facilities remain acceptable for the conduct of the study.

Representatives of government regulatory authorities may also evaluate the study records, source documents, investigator, study staff and facilities.

The investigator should immediately notify TI of any audits of this study by any regulatory agency, and must promptly provide copies of any audit reports.

18.6 Case Report Form Requirements

The study will utilize electronic CRFs (eCRFs) with a validated 21CFR Part 11 compliant

electronic data capture (EDC) software to collect data. All requested information must be entered on the eCRFs in the areas provided in a timely manner. When changes or corrections are made in the eCRF, the EDC system will maintain a complete audit trail of the person making the changes, the date and time of the change and the reason for the change. Only individuals listed on the Delegation of Responsibilities Log with responsibility for eCRF completion may make entries on the eCRFs. Usernames and passwords will be provided to each authorized user after completion of EDC training.

The investigator or physician sub-investigator must electronically sign and date each subject's eCRF. Individuals who will be providing electronic signatures must first submit documentation with a handwritten signature acknowledging that their electronic signature is a legally binding equivalent to their handwritten signature.

18.7 Reports to Institutional Review Board

The investigator should provide the IRB with reports, updates, and other information (e.g., safety updates, protocol amendments, and administrative letters) according to regulatory requirements or Institution procedures.

18.8 Quality Assurance Audits

Representatives from TI and/or the Sponsor or a third party selected by the Sponsor may conduct a quality assurance audit of this study. During the audit, the investigator must provide the auditor with direct access to all relevant documents and discuss any findings with the auditor.

In the event of an inspection by the FDA or other regulatory authorities, the investigator must give the inspector direct access to relevant documents and to discuss any findings with the inspector. The investigator must notify TI in the event of a FDA site audit.

18.9 Records Retention

The investigator must maintain all study records (including test article disposition, informed consents/assents, eCRFs, source documents, correspondence, regulatory documents, contracts etc.) for the maximum period required by TI or the institution where the study is conducted, whichever is longer. The original Test Article Accountability Logs will be kept at the sites. Copies of the Test Article Accountability Logs will be returned to the Sponsor.

The investigator must contact TI or the Sponsor prior to destroying any records associated with this study.

If the investigator withdraws from the study, the records shall be transferred to a mutually agreed upon designee. Written notification of such a transfer must be given to TI.

18.10 Record Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the subject or the subject's guardian (if appropriate), except as necessary for monitoring by TI or the Sponsor, the FDA or other regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study shall not disclose or use for any purpose other than performance of the study, any data, records, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from TI or the Sponsor must be obtained for the disclosure of any said confidential information to other parties.

19. REFERENCES

1. Vahlquist A, Ganemo A, Virtanen M. Congenital ichthyosis: an overview of current and emerging therapies. Acta Derm Venereol. 2008;88:4-14.

2. Nomura K, Nakano H, Umeki K, Harada K, Kon A, Tamai K, et al. A study of the steroid sulfatase gene in families with X-linked ichthyosis using polymerase chain reaction. Acta Derm Venereol. 1995;75:340-2.

3. Vahlquist A, Blockhuys S, Steijlen P, van Rossem K, Didona B, Blanco D, et al. Oral liarozole in the treatment of patients with moderate/severe lamellar ichthyosis: results of a randomized, double-blind, multinational, placebo-controlled phase II/III trial. Br J Dermatol. 2014;170:173-81.

4. Digiovanna JJ, Mauro T, Milstone LM, Schmuth M, Toro JR. Systemic retinoids in the management of ichthyoses and related skin types. Dermatol Ther. 2013;26:26-38.

5. ACCUTANE® (isotretinoin) capsules, 10-mg, 20-mg, 40-mg (US Package Insert). Nutley, NJ: Roche Laboratories Inc.; 1982.

6. Layton A. The use of isotretinoin in acne. Dermatoendocrinol. 2009;1:162-9.

7. Lucek RW, Colburn WA. Clinical pharmacokinetics of the retinoids. Clin Pharmacokinet. 1985;10:38-62.

8. Napoli JL. Retinoic acid biosynthesis and metabolism. FASEB J. 1996;10:993-1001.

9. Blaner WS. Cellular metabolism and actions of 13-cis-retinoic acid. J Am Acad Dermatol. 2001;45:S129-35.

10. RETIN-A® (tretinoin) Liquid, 0.05% (US Package Insert). Skillman, NJ: Ortho Dermatological; 2002.

APPENDIX 1 SAMPLE SUBJECT AND PARENT/GUARDIAN INSTRUCTION SHEET

A copy of the Subject and Parent/Guardian Instruction Sheet will be provided to each site.

The investigator or designee should provide a copy of the Part 1 Subject and Parent/Guardian Instruction Sheet to each subject and parent/guardian (if applicable) at Visit 2 prior to dispensing containers of the test articles and a copy of the Part 2 Subject and Parent/Guardian Instructions Sheet at Visit 8.

A body diagram will be given to the subject by the study staff to remind the subject where to apply the test articles. A sample body diagram is included on the back of the Subject Instruction Sheet.

SAMPLE SUBJECT AND PARENT/GUARDIAN INSTRUCTION SHEET FOR PROTOCOL 205-9051-201

Please follow these instructions carefully. Parents/guardians should apply or supervise each application on their child, as determined by the study doctor. Contact the study staff at the telephone number below, if you have any questions or concerns about the study.

Subject Number:_____ Initials: _____ Phone: _____

PART 1

You will be instructed how to apply the study medication. If you need help, ask your parent/guardian. Apply EACH study medication to the designated RIGHT and LEFT Treatment Areas twice daily, once in the morning and once in the evening at approximately the same time every day with at least 8 hours between doses. **TAKE SPECIAL CARE TO USE THE CORRECT STUDY MEDICATION ON THE RIGHT AND LEFT TREATMENT AREAS.**

1. Wash and dry your hands before and after applying each of the study medications.
2. Wash the Treatment Areas with mild cleanser and water and gently dry the areas.
3. Refer to the diagram on the back of this form for the Treatment Areas. In addition, if the study doctor instructs you to, you can refer to the photos that the study staff has taken to help you identify the two Treatment Areas.
4. Dispense a sufficient amount of study medication #1 with the **R**ED label and marked **R**IGHT to provide a thin uniform film over the diseased skin in the Treatment Area.
5. Using your fingertip, gently apply the **RED label study medication #1** to the diseased skin within the designated **Treatment Area ON YOUR RIGHT SIDE** and spread the study medication evenly in a thin even coat over the entire area.
6. Wash your hands after applying study medication #1. Then, repeat Steps #3 and #4 for study medication #2 with the **L**EMON YELLOW label and marked **L**EFT, applying the study medication to the **Treatment Area ON YOUR LEFT SIDE**.
7. Record the date and time of study medication application in your Subject Diary.
8. Do not wash the treated area for at least 4 hours after application.
9. Do not apply the study medication within 4 hours of clinic visits.

If you are participating in the PK portion of the study, apply the study medication between

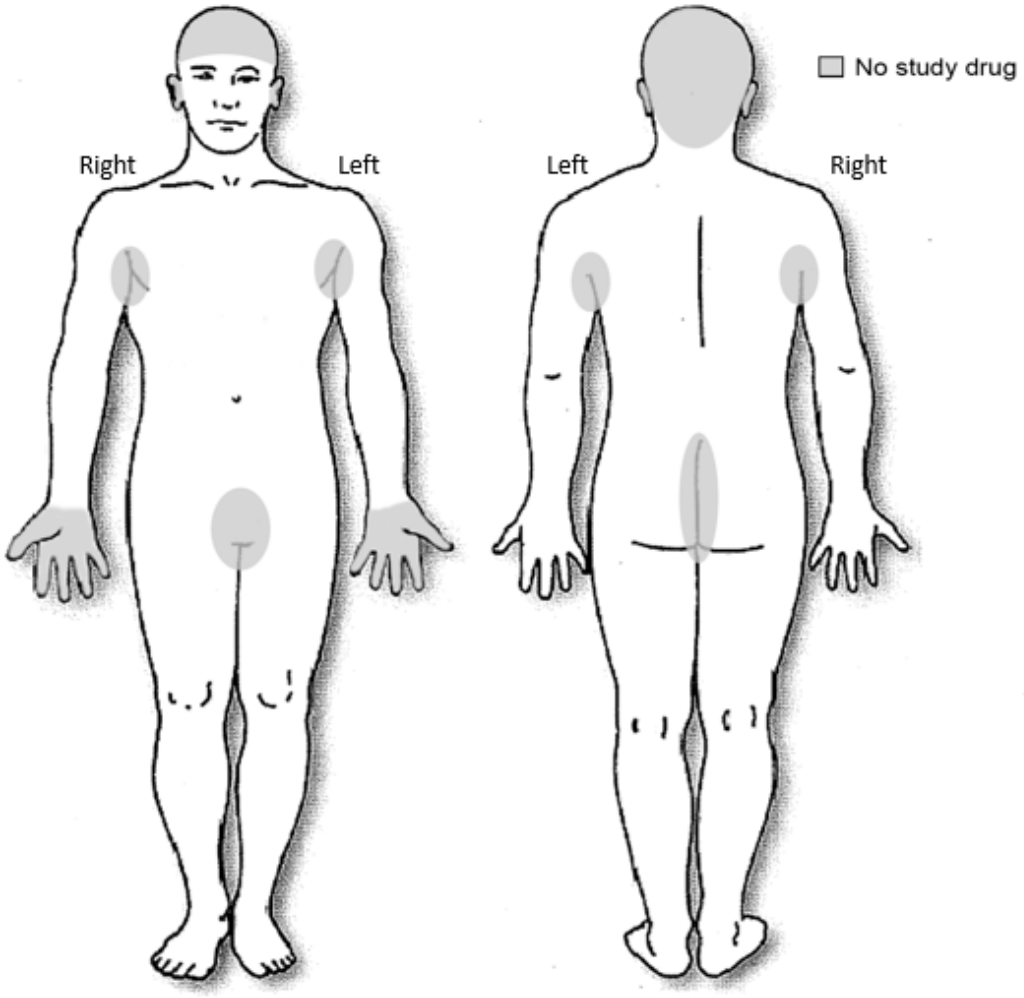
_____ (time) and _____ (time) on _____ (date).

STUDY VISIT SCHEDULE

V4: Date:	Time:	**V5:** Date:	Time:
V6: Date:	Time:	**V8:** Date:	Time:

Your Treatment Areas are:
(1) _____ and (2) _____

The study doctor or designee will indicate which areas are to be treated on the diagram below.



ADDITIONAL REMINDERS

- Store the study medication according to the instructions on the label.
- Bring this sheet, the Subject Diary, and ALL containers (used and unused) of study medication with you to every study visit.
- Do not allow anyone else to use the study medications, only apply the study medication to the designated Treatment Area, and keep the containers of study medication away from children/pets.
- Discontinue use if severe skin irritation or rash develop and contact the study site.
- Avoid significant sun exposure; use appropriate sun protection measures such as sunscreen (for areas outside of the Treatment Areas) and/or protective clothing over the Treatment Area is recommended.
- Be extra careful not to use other topical products on the Treatment Area(s), no topical products should be applied within one inch of either Treatment Areas.

SAMPLE SUBJECT AND PARENT/GUARDIAN INSTRUCTION SHEET FOR PROTOCOL 205-9051-201

Please follow these instructions carefully. Parents/guardians should apply or supervise each application on their child, as determined by the study doctor. Contact the study staff at the telephone number below, if you have any questions or concerns about the study.

Subject Number:_____ Initials: _____ Phone: _____

PART 2

You will be instructed how to apply the study medication. If you need help, ask your parent/guardian. Apply the study medication to BOTH Treatment Areas twice daily, once in the morning and once in the evening at approximately the same time every day with at least 8 hours between doses.

1. Wash and dry your hands before and after applying the study medications.
2. Wash the Treatment Areas with mild cleanser and water and gently dry the areas.
3. Refer to the diagram on the back of this form for the Treatment Areas. In addition, if the study doctor instructs you to, you can refer to the photos that the study staff has taken to help you identify the two Treatment Areas.
4. Dispense a sufficient amount of the study medication to provide a thin uniform film over the diseased skin in one of the Treatment Areas.
5. Using your fingertip, gently apply the study medication to the diseased skin within that Treatment Area and spread it evenly in a thin even coat over the entire area.
6. Repeat Steps #3 and #4 for the second Treatment Area.
7. Record the date and time of study medication application in your Subject Diary.
8. Do not wash the treated area for at least 4 hours after application.
9. Do not apply the study medication within 4 hours prior to Visit 9.

If you are participating in the PK portion of the study, apply the study medication between

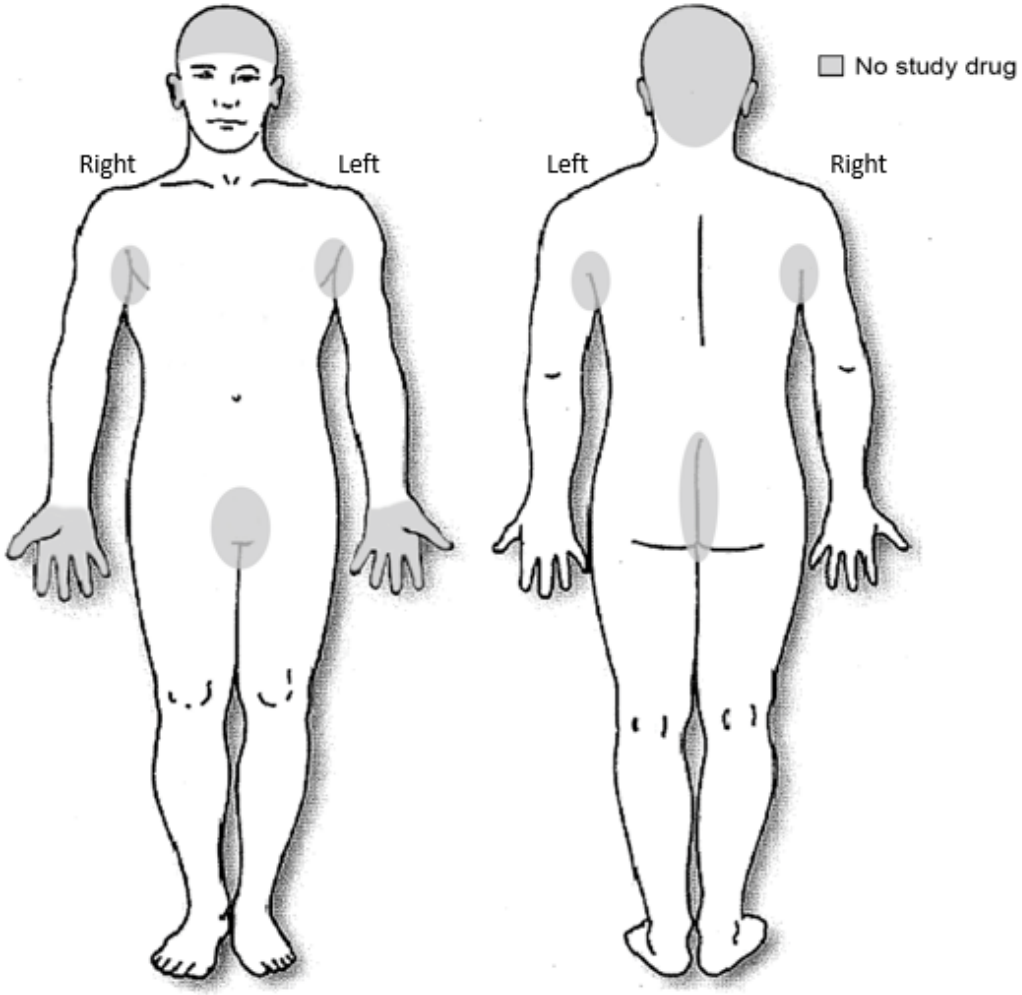
_____ (time) and _____ (time) on _____ (date).

STUDY VISIT SCHEDULE

V9: Date: Time:

Your Treatment Areas are:
(1) _____ and (2) _____

Please refer to the body diagram below, which indicates which areas are to be treated.



ADDITIONAL REMINDERS

- Store the study medication according to the instructions on the label.
- Bring this sheet, the Subject Diary, and ALL containers (used and unused) of study medication with you to every study visit.
- Do not allow anyone else to use the study medications, only apply the study medication to the designated Treatment Area, and keep the containers of study medication away from children/pets.
- Discontinue use if severe skin irritation or rash develop and contact the study site.
- Avoid significant sun exposure; use appropriate sun protection measures such as sunscreen (for areas outside of the Treatment Areas) and/or protective clothing over the Treatment Area is recommended.
- Be extra careful not to use other topical products on the Treatment Area(s), no topical products should be applied within one inch of either Treatment Area.

APPENDIX 2 SAMPLE SUBJECT DIARY

A copy of the Subject Diary will be provided to each site.

The investigator or designee should provide a copy of the Subject Diary to each subject and parent/guardian (if applicable) at Visit 2 and all follow-up visits as necessary.

SAMPLE SUBJECT DIARY FOR PROTOCOL 205-9051-201

Parents/legal guardians should complete or supervise the diary entry for their child, as determined by the study doctor. Apply the study medications as prescribed by the study doctor. After dosing, record the date and time of the dose applied. If you miss a dose, write MISSED where the time is recorded. **Return this diary and all study medications (used and unused) at each visit.**

Next Appointment: ________________________________ at _______________ am/pm

DATE (dd-MMM-yyyy)	DOSE 1 TIME (HH:MM)	AREAS DOSED	DOSE 2 TIME (HH:MM)	AREAS DOSED
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left
_____ / ________ / __________	____ : ____ am	☐ Right ☐ Left	____ : ____ pm	☐ Right ☐ Left

If you have any questions, call:
Name: ___________________________

Telephone: ________________________

Date Diary Dispensed:	Date Diary Returned:
Visit Dispensed: ☐ Visit 2 ☐ Visit 4 ☐ Visit 5 ☐ Visit 6 (x 2) ☐ Visit 8 (x 2)	

APPENDIX 3 TEST ARTICLE INFORMATION

A 3.1 Test Article Packaging and Labeling

The test articles will be packaged and labeled by the Sponsor or designee. PAT-001 Ointment will be packaged in laminate tubes. Each subject will be assigned a subject number sequentially at Visit 1/Screening. At Visit 2/Baseline, the subject will be dispensed the necessary amount of each test article for the designated treatment period during the study based on the size of the Treatment Area; dispensing/return of all test articles will be documented in a Test Article Accountability Log, which is to be kept at the investigational site.

Subject Kits, Cartons, and Labels
Each Subject Kit will consist of two or more Subject Cartons for Part 1 and one or more Subject Cartons for Part 2. The number of Subject Cartons to be provided will be based on the BSA to be treated by each subject. Tubes of the test articles will be contained within Subject Cartons. Each Subject Carton label will, at a minimum, contain the following information: protocol number, subject identifiers (subject number and subject initials, to be filled in), the contents, the carton number, an investigational test article disclaimer (e.g., Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions. In the event of an emergency, the contents of the carton can be unblinded using the proper procedures as outlined in the protocol and by instructions provided to the site.

Tube Labels
Each tube will contain, at a minimum, the following information: the protocol number, subject identifiers (subject number), the contents, the tube number, an investigational test article disclaimer (e.g., Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions.

Note: In Part 1, the test articles will be blinded using color coded labels to designate each test article to the correct Treatment Area. The **R**ED label should be identified as **R**IGHT and the **L**EMON YELLOW label should be identified as **L**EFT.

A 3.2 Test Article Storage and Preparation

Test articles will be stored under secure conditions until they are dispensed to the subjects. Test articles should be stored in accordance with the temperature specified on the label.

A 3.3 Dispensing Test Article

Sites will receive shipments of Subject Cartons after a randomization request has been placed. At Visit 1/Screening, subjects will be assigned a three digit subject number by the study staff in ascending order beginning with the lowest available number. Prior to

Visit 2/Baseline, after laboratory results have been received and reviewed, a randomization request will be placed by the site in order for the Subject Carton to be provided to the site prior to Baseline, on a subject-by-subject basis. The test article will only be dispensed to the subjects who qualify for enrollment at Visit 2/Baseline.

The test article must be dispensed only to study subjects and only at study sites specified on the form FDA 1572 by authorized personnel as required by applicable regulations and guidelines.

The subject will be dispensed the necessary amount of each test article for the designated treatment period during the study. The subject will be instructed to bring all tubes (used and unused) to each clinic visit. All test articles will be weighed prior to dispensing to the subject and at return. At each post-Baseline visit, all tubes should be collected and accounted for; additional tubes may be dispensed to the subject to ensure each subject has sufficient test article for the designated treatment period. Test Article Accountability logs will be used to record dispensing information. Every effort should be made to obtain the return of all dispensed tubes of the test article. If these efforts fail, a detailed note of the reason for failure should be made in the source documents.

A 3.4 Test Article Supply Records at Study Sites

It is the responsibility of the investigator to ensure that a current record of test article disposition is maintained. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received placed in storage area.
- Amount currently in storage area.
- Label ID number or batch number.
- Dates and initials of the person responsible for each product inventory entry/movement.
- Amount dispensed to and returned by each subject, including unique subject identifiers.
- Amount transferred to another area for dispensing or storage.
- Non-study disposition (e.g., lost, wasted, broken).
- Amount returned to Sponsor.
- Amount destroyed at study site, if applicable.

TI will provide forms to facilitate inventory control if the staff at the study site does not have an established system that meets these requirements.

A 3.5 Dose Modifications

The subject should not modify the treatment regimen without consultation with the investigator. See Section 6.2 for details on managing intense LSRs. If skin irritation or rash develops, the subject should contact the study site immediately. All dose modifications

must be reported on the appropriate CRF.

A 3.6 Documentation of Application and Compliance

The date of the first and last application of the test articles will be recorded on the appropriate CRF for Part 1 and Part 2. A CRF will also be used to record any changes in Test article dosing from the application as specified in the protocol. A Subject Diary will be dispensed to the subjects and parent/guardian (if applicable) to record all dates and times of application doses and to record any missed doses of the test articles (Appendix 2). Subjects will be instructed to bring the Subject Diary with them to each study visit.

A 3.7 Return and Destruction of Test Article Supplies

Upon completion or termination of the study, all test articles must be accounted for and any missing tubes of the test articles must be explained on the completed Test Article Accountability Log. All returned test articles will be weighed to the nearest tenth gram (0.1 grams) in order to document extent of exposure. Unless instructed otherwise by the Sponsor, the study site will keep the original Test Article Accountability Log in the study file and a copy will be returned to the Sponsor. All tubes of the test articles will then either be a) returned to the study Sponsor or b) emptied and provided to a sponsor-identified third party vendor for appropriate destruction, according to applicable regulations with the provision of a certificate of destruction.

APPENDIX 4 PROTOCOL AMENDMENTS

A 4.1 Protocol Amendment #1: v2.0

Summary:

1. Each treatment area was limited to 6% BSA based on feedback from the FDA.
2. Operational procedures were updated concerning randomization processes and test article dispensing.
3. Section 12.4 was added to include genetic testing, for subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis prior to enrollment.

SPECIFIC CHANGES: Added text has been **bolded** and deleted text has been ~~redlined~~.

Section # / Name	Revised Text
Title Page	Amendment 1, Date of Amendment 1 and updated name of file
Page Headers	Updated to include protocol date and version number.
Protocol Approval	The following individuals approve version ~~1~~**2**.0 of the 205-9051-201 protocol dated **September 30**~~July 19~~, 2016 … Garet Heintz, RAC ~~Associate~~ Director of Regulatory Affairs
Study Acknowledgement	Version: ~~1~~**2**.0 Date of original version **(v1.0)**: July 19, 2016 **Date of Amendment #1 (v2.0): September 30, 2016**
Protocol Synopsis & Section 5.1, Inclusion Criteria	4. Subject has a clinically and genetically[6] confirmed diagnosis of either Lamellar (e.g., transglutaminase 1-deficient) or X-Linked (e.g., deletion of steroid sulfatase gene) subtypes of CI. Footnote #6/26: Fluorescence in situ hybridization (FISH) positive confirmation of steroid sulfatase gene deletion is also acceptable to diagnose X-Linked subtype of CI. If the investigator is highly confident in the clinical diagnosis of X-Linked or Lamellar CI without confirmatory genetic testing, the subject may be enrolled in the study ~~pending the results of genetic testing a~~**s detailed in Section 12.4**~~fter discussion with AND written permission from the Medical Monitor~~ with the genetic testing being performed at Baseline. 5. Subject must have two contralateral comparable Treatment Areas, as defined per protocol. ~~The~~**Each** Treatment Area must

	have a minimum of 150 cm^2 of affected disease as identified by the investigator. [Note: ~~the~~**each** Treatment Area shall be **contained within** a discrete anatomic unit as defined in the protocol ~~that~~**and shall not exceed 6% body surface area (BSA)**, excluding palms and soles.]
Protocol Synopsis & Section 5.2, Exclusion Criteria	10. Subject has clinically significant metabolic, pulmonary, cardiac, hematological, renal, hepatic, immune, neurological, psychiatric, infectious, neoplastic, or malignant disease (other than non-melanoma skin cancer) **that would preclude their participation in the study.** 11. **[For PK Subjects Only]** Subject has chronic gastrointestinal disease such as Crohn's disease, irritable bowel syndrome, colitis, inflammatory bowel disease, or chronic diarrhea.
Protocol Synopsis, Study Procedures	Visit 1: Screening (Day -45 to -~~73~~): … Qualified subjects must have two comparable in size (≥150 cm2), contralateral Treatment Areas (per protocol) identified with equal IGA scores (i.e., IGA = 3 or 4) at Baseline**, where an individual Treatment Area shall not exceed 6% BSA**. Clinical evaluations (IGA) for both Treatment Areas will be performed. ~~The subject will be scheduled for Visit 2/Baseline.~~ **Prior to Visit 2/Baseline, after laboratory results have been received and reviewed, and the investigator has confirmed the subject's eligibility, the site will contact the subject to confirm their willingness to participate in the study. Assuming the qualified subject is willing to participate, then the site will:** • **Make a randomization request to order test article for the subject to be delivered to the site prior to the subject's Baseline visit;** • **Schedule the subject's Baseline visit at a mutually convenient time when the designated subject's test article will be at the site;** • **NOTE: the ordered test article is specific to each subject and shall not be used for any other subject. In the event that the subject elects not to participate after receipt of their designated test article, the site should contact the monitor to discuss management of the test article received.** Visit 2: Baseline (Day 1): At Visit 2, study staff will reaffirm informed consent/assent and **re-**review laboratory results prior to the initiation of any study-related procedures. Medical

	history, I/E criteria, and concomitant medications and therapies will be reviewed to confirm subject eligibility. A UPT (if applicable) will be performed. **For those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected for genetic testing.** Treatment Areas will be defined **as a region contained within a discrete anatomic unit (e.g., upper arm, forearm, upper leg, lower leg) with bilateral involvement and a minimum of 150 cm^2 in area of diseased skin**. Qualified subjects must have two contralateral Treatment Areas (per protocol) identified with equal IGA scores (i.e., IGA = 3 or 4) **of comparable size where an individual Treatment Area shall not exceed 6% BSA**. Clinical evaluations (IGA, CI Signs/Symptoms, as well as Baseline local skin reactions [LSRs] pre-application) for both Treatment Areas and photographs will be performed at this visit; photographs will be taken of lesions only, without sharing subject identity. **Copy(s) of the Baseline photos may be provided to the subject at the discretion of the investigator to help the subject consistently identify the two Treatment Areas.** For those subjects that do not have documented prior confirmatory genetic testing, blood samples will be collected for genetic testing. For those subjects participating in the PK portion of the study, prior to test article application, a PK blood sample will be taken. Subjects will be randomized **using the designated test article specific for that subject that was ordered by the site after completion of Visit 1**~~and assigned to the next available (lowest) subject number in ascending order~~. Test article accountability will be documented and **test article** and Subject Diary will be dispensed. Subjects and parent/guardian (if applicable) will be instructed on how to apply the test articles and to record applications in the Subject Diary. … **Modifications to the dosing regimen and/or concomitant medication/therapy use may be prescribed by the investigator to manage intense LSRs and must be documented in the CRFs. Any dosing modifications will be made bilaterally (e.g., if dosing is decreased to once a day given tolerability issues, both sides will be treated once daily, even if only one side is having the tolerability issue). Frequency of dosing may be reduced to once per day (QD) or rest periods of up to several days may be allowed. Treatment per protocol should resume as soon as possible**

	after any notable LSRs have materially subsided as determined by the investigator or designee (if possible via one of the scheduled clinic visits or via an Unscheduled Visit) such that dosing may resume. Additionally, use of provided bland emollient[7] in the Treatment Area as an aid to managing LSRs may be prescribed with the approval of the investigator and must be documented in the CRFs. In the event that additional moisturizer use is needed (i.e., greater than QD or BID or in lieu of the test articles) in the opinion of the investigator, such therapy may be used, must be documented in the CRFs, and the investigator must notify the Medical Monitor promptly. Note: Bland emollients should not be applied within four hours of application of the test articles. No other topical therapy within the Treatment Area or in the surrounding skin within one inch of the Treatment Area is permitted. **Footnote #7: DML Lotion will be provided to subjects. Other bland emollients (e.g., Lubriderm [without alpha hydroxy acid], or other moisturizers that do not contain any "active" ingredients [e.g., salicylic acid, lactic acid, pyruvic acid, urea, or any other ingredient that could irritate or cause a keratolytic effect]) may be used with approval from the investigator, but must be documented as a concomitant medication/therapy.**
Schedule of Events	Visit 1; Days -45 to -**7**~~3~~, added **X[16]** under Randomization Visit 2; Day 1, added **X[12]** in a row for **Genetic Testing** Footnote #**8**~~7~~: Screening window at -**7**~~3~~ days allows clinical lab tests to be finalized **and test article to be shipped** prior to Visit 2/Baseline. **Footnote #13: For those subjects who do not have genetic test confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected.** Footnote #1**4**~~2~~: Each contralateral Treatment Area must be comparable in size (>150cm2) and have the same IGA score of 3 (moderate) or 4 (severe) at Baseline **and be contained within a discrete anatomic unit that shall not exceed 6% body surface area (BSA)**. Location by body region and percent ~~body surface area (~~BSA~~)~~ of disease affected skin in each Treatment Area will be documented. Percent BSA will be

	estimated using the assumption that 1% BSA is equivalent to the area of the subject's hand with fingers held together. [Note: Palms and soles are not eligible; the treatment of skin scalp and folds/intertriginous regions should be avoided]. Additionally for treatment on the arms in subjects participating in the PK portion ~~of the study~~, the antecubital fossa (e.g., approximately 10-15 cm2) will be excluded to minimize contamination of PK blood draws. Footnote #1~~7~~6: **Prior to Visit 2/Baseline, after laboratory results have been received and reviewed, a randomization request will be placed by the site in order for the test article to be provided to the site prior to baseline. Note: the ordered test article is specific to each subject and shall not be used for any other subject.**
Schedule of Events, Section 6.2, and Section 9.2	Note: Palms and soles are not eligible; the treatment of **scalp and** skin folds/intertriginous regions should be avoided.
Section 4, Study Design	Subjects will have two comparable Treatment Areas defined per protocol**.** ~~;~~ **Each** Treatment Area~~s~~ must be comparable in size**, with a minimum of** ~~(~~≥150 cm^2~~)~~ **of affected diseased skin** with an identical Investigator's Global Association (IGA) score, with a score of either 3 (moderate) or 4 (severe) at Baseline**; each Treatment Area shall be contained within a discrete anatomic unit as defined in the protocol and shall not exceed 6% body surface area (BSA), excluding palms and soles**.
Section 6.2 Instructions for Use and Application	At Visit 2/Baseline, the investigator will designate two comparable Treatment Areas. **Each Treatment Area shall be contained within a** ~~D~~**d**iscrete anatomic unit~~s~~ (e.g., upper arm, forearm, upper leg, lower leg~~, etc.~~) with bilateral involvement with and a minimum of 150 cm^2 in area of diseased skin **that shall not exceed 6% BSA; these Treatment Areas** will be selected for treatment and designated by right and left sides. … Subjects will **be instructed to** wash their hands before and after each test article application. … Subjects **will be instructed** ~~should~~ not **to** wash the treated area for at least four hours following test article application. *(moved from below) If the subject experiences issues with medication tolerability or other complications arise, ideally*

	the subject will be seen by the investigator at one of the scheduled clinic visits or via an Unscheduled Visit to document the reactions and modifications to the dosing regimen prescribed by the investigator. In the event that a clinic visit is not possible or not warranted in the opinion of the investigator, the change in the subject's management will be clearly documented in the source documents and case report forms (CRFs) with corresponding changes noted in the Subject Diary regarding test article usage and/or concomitant medications/therapies (e.g., moisturizer use). Modifications to the dosing regimen and/or concomitant medication/therapy use may be prescribed by the investigator to manage intense LSRs **and must be documented in the CRFs.** Any dosing modifications or changes to concomitant medications/therapies will be made bilaterally (e.g., if dosing is decreased to once a day given tolerability issues, both sides will be treated once daily, even if only one side is having the tolerability issue). ~~If the subject experiences issues with medication tolerability or other complications arise, ideally the subject will be seen by the investigator at one of the scheduled clinic visits or via an Unscheduled Visit to document the reactions and modifications to the dosing regimen prescribed by the investigator. In the event that a clinic visit is not possible or not warranted in the opinion of the investigator, the change in the subject's management will be clearly documented in the source documents and case report forms (CRFs) with corresponding changes noted in the Subject Diary regarding test article usage and/or concomitant medications/therapies (e.g., moisturizer use).~~ Frequency of dosing may be reduced to once per day (QD) or rest periods of up to several days may be allowed. Treatment per protocol should resume as soon as possible after any notable LSRs have materially subsided as determined by the investigator or designee (if possible via one of the scheduled clinic visits or via an Unscheduled Visit) such that dosing may resume. ~~Dosing modifications prescribed by the investigator must be documented in the CRFs.~~ Additionally, use of provided bland emollient in the Treatment Areas as an aid to managing LSRs may be prescribed with the approval of the investigator and must be documented in the CRFs. In the event that additional moisturizer use is needed (i.e., greater than QD or BID or in lieu of the test articles) in the opinion of the investigator, such therapy may be used~~, with the approval of the Medical Monitor and~~ must be documented

	in the CRFs**, and the investigator must notify the Medical Monitor promptly.** Note: Bland emollients should not applied within four hours of application of the test articles. No other topical therapy within the Treatment Area **or in the surrounding skin within one inch of the Treatment Area** is permitted.
Section 7, Randomization Assignment	**Prior to Visit 2/Baseline, after laboratory results have been received and reviewed, a randomization request will be placed by the site in order for the test article to be provided to the site prior to baseline.**
Section 8.1, Prohibited Medications or Therapies	Prohibited medications or therapies during the study include: • No topical therapy within the Treatment Area **or in the surrounding skin within one inch of the Treatment Area** other than the designated test article or provided bland emollient (e.g., DML Lotion)[31], if needed to manage LSRs (see Section 8.2); • Topical retinoid-containing therapies in the Treatment Areas **or in the surrounding skin within one inch of the Treatment Area** ~~(except emollients)~~ within two weeks of Visit 2/Baseline or any topical retinoid use during the study; • Topical corticosteroids in the Treatment Areas **or in the surrounding skin** within one inch of the Treatment Area within five days of Visit 2/Baseline;
Section 8.2, Allowed Medications or Therapies	Allowed medication or therapies during the study must be documented and include: • Bland emollients, keratolytics, or sunscreen to treat diseased areas that are NOT in the Treatment Area **(but not in the surrounding skin within one inch of the Treatment Area)**; • Topical steroids to treat cutaneous diseased areas that are NOT in the Treatment Area **(but not in the surrounding skin within one inch of the Treatment Area)**; • Inhaled, intranasal, and ophthalmic steroid dosage forms. Additionally, use of provided bland emollients (e.g., DML Lotion)[32] in the Treatment Areas as an aid to managing LSRs may be prescribed by the investigator ~~with the approval of the Medical Monitor~~ as detailed in Section 6.2 and must be documented in the CRFs. Application of such bland emollients should not be applied within four hours of application of the

	test articles.
Section 9.1, Visit 1 (Day -45 to ~~-73~~): Screening	• Confirm the subject has qualified analogous right and left Treatment Areas, with adequate disease (≥150 cm^2) and identical IGA scores (≥ 3) consistent with the inclusion and exclusion criteria (see Section 5.1) **that will likely meet protocol requirements and Baseline, in the opinion of the investigator**. … QUALIFIED SUBJECT DETERMINATION AND TEST ARTICLE REQUEST: Prior to Visit 2/Baseline, after laboratory results have been received and reviewed, and the investigator has confirmed the subject's eligibility, the site will contact the subject to confirm their willingness to participate in the treatment phase of the study. Assuming the qualified subject is willing to participate, then the site will: a) Make a randomization request to order test article for the subject to be delivered to the site prior to the subject's Baseline visit; b) Schedule the subject's Baseline visit at a mutually convenient time when the designated subject's test article will be at the site; **c) NOTE: the ordered test article is specific to each subject and shall not be used for any other subject.** In the event a subject elects not to participate after receipt of their designated test article, please contact your monitor to discuss management of the test article received.
Section 9.2, Visit 2 (Day 1): Baseline	• Take Baseline photographs. **Note: Copy(s) may be provided to the subject at the discretion of the investigator to help the subject consistently identify the two Treatment Areas.** • **For those subjects that do not have documented prior confirmatory genetic testing, collect blood samples and manage genetic testing as detailed in Section 12.4.** • Randomize the subject **using the designated test article specific for that subject that was ordered by the site after completion of Visit 1. Note: the ordered test article is specific to each subject and shall not be used for any other subject.**
Section 9.3, Visit 3 (Day 2) and Visit 7	• Confirm the next scheduled visit and remind the subject to hold the morning application of the test

(Day 43±3): Phone Call	articles on days of clinic visits. Note ~~[for Visit 7]~~: For those subjects participating in the PK portion of the study, the application before a scheduled clinic visit with PK time point (i.e., on Day 56) must be approximately 12 hours ± 30 minutes prior to the blood draw.
Section 9.4, visit 4 (Day 8+1) and Visit 5 (Day 15±1): Follow-Up	• Remind the subject to hold the application of the test articles on days of clinic visits. Note ~~[for Visit 5]~~: For those subjects participating in the PK portion of the study, the application before a scheduled clinic visit with PK time point (i.e., on Day 28) must be approximately 12 hours ± 30 minutes prior to the blood draw.
Section 11, Photography	Photography documentation is required in this study at Visit 2/Baseline/Day 1, Visit 6/Day 29, Visit 8/Day 57, and Visit 9/Day 84. **Copy(s) of the Baseline photos may be provided to the subject, at the discretion of the investigator, to help the subject consistently identify the two Treatment Areas.**
Section 12.1, Blood Chemistries, Hematology and Urinalysis	Blood and urine specimens will collected at Visit 1/Screening, Visit 6/Day 29, Visit 8/Day 57 (End of Part 1), and Visit 9/Day 84 (EOT or early termination) for chemistry, hematology, and urinalysis. Subjects must be fasting (approximately 8 hours) for **screening laboratory tests** ~~Visit 1/Screening~~ and, if possible, **for laboratory tests** at Visit 6/Day 29, Visit 8/Day 57, and Visit 9/Day 84; however, if a subject arrives at the clinic for Visit 6, Visit 8, or Visit 9 without fasting for at least eight hours, laboratory specimens may be collected as non-fasting, at the discretion of the investigator, and with the appropriate fasting status documented on the lab requisition form.
Section 12.4, Genetic Testing	**At Visit 2/Baseline, for those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected for genetic testing. The subject may be enrolled based upon their clinical diagnosis only, with genetic testing to follow, such that the results are available at or before the conclusion of the study. Specifics regarding the testing options for these two ichthyosis subtypes, specimen handling, and related matters are detailed in a separate Study Lab Manual provided by the Sponsor.**

Section 13.2, Subject Discontinuation	**If the subject is discontinued from the study due to pregnancy, the pregnancy and its outcome should be followed.**
Section 14.2, Serious Adverse Event	• **Although not defined as an AE, pregnancy shall be considered as a serious event and must be immediately reported by telephone to the Medical Monitor and, in the event that he/she is unavailable, to the Project Manager listed on the first page of the protocol.** … All SAEs, whether related or unrelated to test article, must be immediately reported by telephone to the Medical Monitor **(619-889-7058)** and, in the event that he/she is unavailable, to the Project Manager **(858-571-1800, ext. 129) [additional contact information** listed on the first page of the protocol**]**. … **v) Confirmed pregnancy at any time during the study or within one month from discontinuing from the study.** … **The investigator must immediately notify the Medical Monitor of the pregnancy and record the pregnancy on the appropriate pregnancy surveillance form.**
Appendix 1, Sample Subject and Parent/Guardian Instruction Sheet (for Both Part 1 and Part 2)	**A body diagram will be given to the subject by the study staff to remind the subject where to apply the test articles. A sample body diagram is included on the back of the Subject Instruction Sheet.** … **Subject Number:_____ Initials~~Name~~: _____ Phone: _____** … **3. Refer to the diagram on the back of this form for the Treatment Areas. In addition, if the study doctor instructs you to, you can refer to the photos that the study staff has taken to help you identify the two Treatment Areas.** … **Your Treatment Areas are:** **(1) _____ and (2) _____** **The study doctor or designee will indicate which areas are to be treated on the diagram below.** … Under 'ADDITIONAL REMINDERS' • **Be extra careful not to use other topical products on the Treatment Area(s), no topical products should be applied within one inch of either Treatment**

	Areas. In Part 2 only: 9. Do not apply the study medication **within 4 hours** prior to Visit 9.
Appendix 3, A3.1, Test Article Packaging and Labeling	The test articles will be packaged and labeled by the Sponsor or designee. PAT 001 Ointment will be packaged in laminate tubes. Each subject will be assigned a subject number sequentially ~~in the order of enrollment~~**at Visit 1/Screening**. **At Visit 2/Baseline, ~~T~~t**he subject will be dispensed the necessary amount of each test article for the designated treatment period during the study based on the size of the Treatment Area; dispensing/return of all test articles will be documented in a Test Article Accountability Log, which is to be kept at the investigational site. Subject Kits**, Cartons,** and Labels **Each Subject Kit will consist of two or more Subject Cartons for Part 1 and one or more Subject Cartons for Part 2. The number of Subject Cartons to be provided will be based on the BSA to be treated by each subject.** Tubes of the test articles will be contained within Subject ~~Kits~~**Cartons**. Each Subject ~~Kit~~**Carton** label will, at a minimum, contain the following information: protocol number, subject identifiers (subject number and subject initials, to be filled in), the contents, the ~~kit~~**carton** number, an investigational test article disclaimer (e.g., Caution: New Drug Limited by United States law to investigational use), and the appropriate storage conditions. In the event of an emergency, the contents of the ~~kit~~**carton** can be unblinded using the proper procedures as outlined in the protocol and by instructions provided to the site.
Appendix 3, A3.3, Dispensing Test Article	Sites will receive shipments of Subject **Cartons**~~Kits as subjects qualify for the study~~**after a randomization request has been placed. At Visit 1/Screening, ~~S~~s**ubjects ~~who are eligible for enrollment into the study~~ will be assigned a three digit subject number by the study staff in ascending order beginning with the lowest available number. **Prior to Visit 2/Baseline, after laboratory results have been received and reviewed, a randomization request will be placed by the site in order for the Subject Carton to be provided to the site prior to Baseline, on a subject-by-subject basis. The test article will only be dispensed to the subjects who qualify for enrollment at Visit 2/Baseline.**

A 4.2 Protocol Amendment #2: v3.0

Summary:

1. Genetic testing will be performed at Visit 1/Screening instead of Visit 2/Baseline.
2. Inclusion Criteria #4 was updated such that subjects will be enrolled based on clinical diagnosis, but must agree to genetic testing at Visit 1/Screening.
3. Clarification of parent/legal guardian assistance with application and diary completion was included.
4. Changes from Administrative Amendment #1 were incorporated.

SPECIFIC CHANGES: Added text has been **bolded** and deleted text has been ~~redlined~~.

Section # / Name	Revised Text
Title Page	Amendment 2, Date of Amendment 2 and updated name of file
Headers	Date of Protocol Amendment 2 updated and v3.0
Protocol Approval	The following individuals approve version **3**~~2~~.0 of the 205-9051-201 protocol dated ~~September 30, 2016~~**January 6, 2017**.
Study Acknowledgement	Version: **3**~~2~~.0 Date of original version (v1.0): July 19, 2016 Date of Amendment #1 (v2.0): September 30, 2016 **Date of Amendment #2 (v3.0): January 6, 2017**
Synopsis, Inclusion Criteria and Section 5.1.1	4. Subject has a clinical~~ly and genetically[6] confirmed~~ diagnosis of either Lamellar (e.g., transglutaminase 1-deficient) or X-Linked (e.g., deletion of steroid sulfatase gene) subtypes of CI **and agrees to genetic testing[6] to confirm such clinical diagnosis during the study**. ~~[6] Fluorescence in situ hybridization (FISH) positive confirmation of steroid sulfatase gene deletion is also acceptable to diagnose X-Linked subtype of CI. If the investigator is highly confident in the clinical diagnosis of X-Linked or Lamellar CI without confirmatory genetic testing, the subject may be enrolled in the study as detailed in Section 12.4 with the genetic testing being performed at Baseline.~~ **[6] Fluorescence in situ hybridization (FISH) positive confirmation of steroid sulfatase gene deletion is also acceptable to diagnose X-Linked subtype of CI.**
Synopsis, Study Procedures, Visit 1	**For those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected for genetic testing.** … Prior to Visit 2/Baseline, after **clinical** laboratory results have been received and reviewed, and the investigator has

	confirmed the subject's eligibility, the site will contact the subject to confirm their willingness to participate in the study.
Synopsis, Study Procedures, Visit 2	~~For those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected for genetic testing.~~
Synopsis, Study Procedures, Visits 3 and 7	The site staff will remind the subject **(and parent/legal guardian, if applicable)** to continue to apply test article twice daily until the next clinic visit.
Schedule of Events	Genetic Testing at Screening (instead of Baseline)
Section 6.2, Instructions for Use and Application	**If the subject is a minor, the parent/legal guardian will be given the Subject Instructions with their child and instructed to apply or supervise application on the subject; the level of involvement (i.e., application vs. supervision) by the parent/legal guardian will be determined by the investigator.** … Subjects **(and parent/legal guardians, if applicable)** will be instructed to wash their hands before and after each test article application. Subjects **(and parent/legal guardians, if applicable)** will be instructed to wash the Treatment Areas with a mild non-medicated cleanser and water and then to dry the area gently. Subjects **(with parent/legal guardian supervision, as required)** will be instructed to apply a sufficient amount of the test article to provide a thin uniform film over the disease affected skin within the Treatment Area (Note: the volume of test article applied will vary with disease severity). For Part 1, the subject **(and parent/legal guardians, if applicable)** will be instructed to take great care to use the assigned test article to the right Treatment Area (on the subject's right side) and the other test article to the left Treatment Area (on the subject's left side). Subjects **(with parental supervision, as required)** will apply a thin uniform film of the assigned test article twice daily to the designated Treatment Area for eight weeks. Subjects **(and parent/legal guardians, if applicable)** will wash their hands after application with the first test article and prior to applying the second test article. For Part 2, the subject **(and parent/legal guardians, if applicable)** will be instructed to apply the assigned test article to both Treatment Areas by applying a thin uniform film twice daily for an additional four weeks. The test article will be applied at approximately the same time every day and at least eight hours apart. <u>Note: for those subjects who are participating in the optional PK portion of the study, the</u>

	application before a scheduled clinic visit with PK time point (i.e., on Days 7, 14, 28, 56, and 83) must be approximately 12 hours ± 30 minutes prior to the blood draw. Subjects **(with parent/legal guardian supervision, as required)** will be instructed to record the date and time of each application in a Subject Diary (see Appendix 2). Subjects **(and parent/legal guardians, if applicable)** will be instructed to bring all containers of the test articles (used and unused) and the completed Subject Diary to each visit. **If the subject is a minor, the parent/legal guardian will be given the Subject Diary and instructed to complete or supervise the completion of the Subject Diary; the level of involvement (i.e., completion vs. supervision) by the parent/legal guardian will be determined by the investigator.** At each visit, the study staff will review the application instructions with the subject and/or parent/**legal** guardian**, if applicable** (see Appendix 1) paying particular attention to proper use of the labeled test article for the Left and Right Treatment Areas (Part 1 only). If possible, at each clinic visit, the subject will apply one of the daily doses in the clinic under staff supervision to reinforce proper use. Subjects **(and parent/legal guardian, if applicable)** will be instructed not to wash the treated area for at least four hours following test article application.
Section 9.1, Visit 1	• **For those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, collect blood or buccal samples for genetic testing (see Section 12.4).** … Visit 2/Baseline, after **clinical** laboratory results have been received and reviewed, and the investigator has confirmed the subject's eligibility, the site will contact the subject to confirm their willingness to participate in the treatment phase of the study.
Section 9.2, Visit 2	• ~~For those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, collect blood or buccal samples for genetic testing (see Section 12.4).~~ … • Dispense the Subject Instruction Sheet **to the subject (and parent/legal guardian, if applicable)**. Instruct

	the subject **(and parent/legal guardian, if applicable)** where and how to apply the test articles to the designated Treatment Areas. … • Dispense the Subject Diary **to the subject (and parent/legal guardian, if applicable)** and provide completion instructions. … • Instruct the subject **(and parent/legal guardian, if applicable)** to apply the test articles to the designated Treatment Areas twice per day, once in the morning and once in the evening with at least eight hours between applications, and to hold the application of the test articles on days of clinic visits.
Section 9.3, Visit 3 and Visit 7	• Confirm the next scheduled visit and remind the subject **(and parent/legal guardian, if applicable)** to hold the morning application of the test articles on days of clinic visits.
Section 9.4, Visit 4 and Visit 5	• Review proper test article use and application guidelines with the subject **(and parent/legal guardian, if applicable)**, stressing the importance that care should be taken so that the correct test article is applied to the two Treatment Area(s) on the subjects RIGHT and LEFT side. … • Remind the subject **(and parent/legal guardian, if applicable)** to hold the application of the test articles on days of clinic visits.
Section 9.5, Visit 6	• Review proper test article use and application guidelines with the subject **(and parent/legal guardian, if applicable)**, stressing the importance that care should be taken so that the correct test article is applied to the two Treatment Area(s) on the subjects RIGHT and LEFT side.
Section 9.6, Visit 8	• Re-educate the subject **(and parent/legal guardian, if applicable)** with respect to dosing and related activities for Part 2.
Section 12.4, Genetic Testing	At Visit ~~2~~**1**/~~Baseline~~**Screening**, for those subjects who do not have confirmation of their clinical diagnosis of X-linked or lamellar ichthyosis, blood or buccal samples will be collected for genetic testing. **As/if required, this test may be repeated during the study as determined by the investigator (e.g., specimen quality, loss or handling concerns, indeterminate**

	outcome). The subject may be enrolled based upon their clinical diagnosis only, with genetic testing to follow, such that the results are available at or before the conclusion of the study. Specifics regarding the testing options for these two ichthyosis subtypes, specimen handling, and related matters ~~are detailed in a separate Study Lab Manual provided by the Sponsor.~~**will be determined by the company used for genetic testing. In the event the genetic testing results do not concur with the clinical diagnosis the subject may complete the study as the inclusion criteria are based upon the clinical assessment of their skin disease by the Investigator at Baseline.**
Appendix 1, Subject and Parent/Guardian Instruction Sheet: For Part 1 and Part 2	Please follow these instructions carefully. **Parents/guardians should apply or supervise each application on their child, as determined by the study doctor.** … You will be instructed how to apply the study medication. **If you need help, ask your parent/guardian.**
Appendix 2, Sample Subject Diary	**Parents/legal guardians should complete or supervise the diary entry for their child, as determined by the study doctor.**