PROTOCOL SYNOPSIS

Title	A Randomized, Double-Blind, Vehicle-Controlled Study To Evaluate The Safety And Efficacy Of 146-9251 Cream Applied Twice-Daily For Six Weeks In Subjects With Ichthyosis Vulgaris
Study Type	Phase 2
Test Articles	1. 146-9251 Cream (Crown Laboratories) 2. Vehicle Cream
Study Objective	The objective of this study is to determine and compare the safety and efficacy of topical 146-9251 Cream and vehicle cream applied twice daily for up to 6 weeks in subjects with moderate to severe ichthyosis vulgaris (IV).
Study Design	Double-blind, randomized, multicenter, vehicle-controlled study.
Treatment Groups	Eligible subjects will be randomized (1:1) to one of two treatment groups: 1. 146-9251 Cream 2. Vehicle cream The assigned test article will be applied by the subjects twice daily for up to 6 weeks.
Duration of Treatment	Up to 6 weeks
Duration of Study	Up to 6 weeks for an individual subject
Study Population	Male or female subjects at least 12 years of age with moderate to severe IV.
Total Number of Subjects	Approximately 88 subjects will be enrolled (44 per treatment arm).
Number of Sites	Approximately 5 sites will participate in the study.
Inclusion Criteria	To enter the study, a subject must meet the following criteria: 1. Subject is a male or female and is at least 12 years of age at the time of enrollment. 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 and parent/guardian (if applicable) are 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 IV involving a minimum of 5% body surface area (BSA) within the Treatment Area.[1] The Treatment Area is defined as the entire body exclusive of the a) head and neck and b) mucosal areas.

[1] 1% BSA is approximately equal to the surface area of the subject's palm and fingers, with the fingers extended yet grouped together, creating a flat oval-like surface area.

	5. Subject has an Investigator's Global Assessment (IGA) score of at least three (3 = moderate) at the Baseline Visit. 6. Subject is in good general health and free of any disease state or physical condition that might impair evaluation of IV or which, in the investigator's opinion, exposes the subject to an unacceptable risk by study participation. 7. Females must be post-menopausal,[2] surgically sterile,[3] or use an effective method of birth control.[4,5] Women of childbearing potential (WOCBP) must have a negative urine pregnancy test (UPT)[6] at the Baseline Visit.
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 is currently enrolled in an investigational drug or device study. 3. Subject has used an investigational drug or investigational device treatment within 30 days prior to first application of the test article. 4. Subject has used any topical therapy, including urea products, topical corticosteroids, or retinoids, in the Treatment Area within 2 weeks prior to the initiation of treatment. Note: a bland emollient may be used in the Treatment Area up to 3 days prior to the initiation of treatment. 5. Subject has used systemic corticosteroids within 4 weeks or retinoids within 24 weeks prior to the initiation of treatment. 6. Subject has stable use of vitamin or herbal supplements for less than 2 weeks prior to the initiation of treatment. 7. Subject has a history of sensitivity to any of the ingredients in the test articles. 8. 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. 9. Subject has a physical condition or other dermatologic disorders (e.g., atopic, seborrheic or contact dermatitis, psoriasis, tinea infections, etc.) which, in the investigator's opinion, might impair evaluation of IV, or which exposes the subject to unacceptable risk by study participation.
Study Procedures	Subjects can be screened for the study up to 45 days before Visit 1. During screening, the study requirements will be reviewed, written informed consent/assent obtained, and eligibility confirmed. If applicable, the washout from prohibited medications or treatments will be determined and implemented. These procedures may be combined with the Baseline Visit if medication washout is not required. The following procedures will take place according to the visit schedule:

[2] Defined as amenorrhea greater than 12 consecutive months in women 50 years of age and older.
[3] Hysterectomy, bilateral tubal ligation (at least six months prior to initiation of treatment), or bilateral oophorectomy.
[4] Effective forms of birth control include a) hormonal contraceptives [e.g., oral, transdermal, injectable, or vaginal ring] (see footnote 5), b) intrauterine device (IUD) for at least one week prior to test article application, c) barrier methods [condom and spermicidal or diaphragm/cervical cap and spermicidal], d) monogamous relationship with a partner who is sterile [e.g., vasectomy performed at least six months prior to study entry], or e) total abstinence for subjects who are not sexually active. Subjects who become sexually active or begin to have relations with a partner who is not sterile during the study must agree to use an effective form of birth control for the duration of the study.
[5] WOCBP taking hormonal therapy must be on treatment prior to study entry, continued per label, and must not change their dosing regimen during the study; treatment must be for (1) oral: at least one complete cycle (e.g., four to eight weeks); (2) transdermal, injectable (e.g., Depo-Provera), or vaginal ring (e.g., NuvaRing): at least one week.
[6] UPT must have a minimum sensitivity of 25 mIU ß-hCG/mL.

	1. Visit 1 (Day 1) - Screening/Baseline Visit: 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. At this visit, consenting/assenting subjects will have their medical history and demographics, concomitant medications and procedures/therapies, and inclusion/exclusion (I/E) criteria 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. All WOCBP must have a negative UPT. A brief physical exam, vital signs (including height, and weight), clinical laboratory testing, photography, which is optional, at select site(s) per a photo guide provided by the Sponsor, and clinical evaluations will be performed prior to test article application. The Treatment Area will be defined as the entire body exclusive of a) the head and neck and b) mucosal areas*. The location of the IV to be treated and the percent BSA with IV in the Treatment Area will be recorded prior to test article application. Subjects who meet all inclusion criteria and no exclusion criteria will be randomized and assigned to the next available (lowest) subject number in ascending order. The test article will be weighed prior to dispensing to subjects. Test article, Subject Instruction Sheet, and Subject Diary with completion instructions will be dispensed. At this visit, study personnel will review the Subject Instruction Sheet and the subject and parent/guardian (if applicable) will be instructed on how and where to dispense and apply test article to all affected skin in the Treatment Area and to record applications in the Subject Diary. Subjects will apply the first dose of the assigned test article to all affected skin in the Treatment Area under staff supervision. Any adverse events (AEs) post-application will be recorded. Subjects will apply the assigned test article to all affected skin in the Treatment Area twice daily for up to 6 weeks. The subject will then be scheduled for Visit 2. * Note disease on the neck and face if present may be treated with a bland moisturizer, but shall not be evaluated. 2. Visit 2 (Week 2, Day 15 ± 2) and Visit 3 (Week 4, Day 29 ± 2): Subjects enrolled into the study will return to the clinic at Weeks 2 and 4 for the study staff to perform the clinical evaluations, record percent BSA with IV in the Treatment Area, collect, review and dispense a new Subject Diary for test article compliance, update concomitant medications and procedures/therapies, record AEs, collect and weigh used test article and dispense test article if necessary. Photography, which is optional, will be performed at select site(s) per a photo guide provided by the Sponsor. Subjects whose IV is completely clear (IGA score = 0 and all clinical signs of IV = 0 [scaling = 0, fissuring = 0, and erythema = 0]) at Day 15 or Day 29 will complete the end of study (EOS) procedures. These subjects will have completed the study. Subjects whose IV is NOT completely clear will be instructed to continue twice daily treatment until the next visit and to record all applications in the Subject Diary. The subject will be scheduled for the next visit. 3. Visit 4 (Week 6, Day 43 ± 3 [OR Day 15 ± 2 or Day 29 ± 2 for subjects who are clear]) – End of Treatment/End of Study or Early Discontinuation: These activities may occur as scheduled at the end of the 43-day treatment period or earlier if (a) the subject is to be dropped from the study or (b) the subject's IV within the Treatment Area is completely clear at Day 15 or Day 29. At this visit, the study staff will perform the clinical evaluations, record percent BSA

	with IV in the Treatment Area, perform clinical laboratory testing, perform photography, which is optional, at select site(s) per a photo guide provided by the Sponsor, update concomitant medications and procedures/therapies, record AEs, collect and review the Subject Diary for test article compliance and collect and weigh used test article. A UPT will be performed on all WOCBP. All subjects will exit the study.
Study Measurements	At each visit, the skin affected with IV in the Treatment Area defined at the Baseline Visit will be assessed as follows: ***Efficacy:*** <u>Investigator's Global Assessment</u> The IGA score is a static evaluation of the overall or "average" degree of severity of a subject's disease, taking into account all of the subject's scaling, erythema, and fissuring in the Treatment Area by the investigator or designee as the subject appears on the day of the evaluation. This evaluation takes into consideration the three individual characteristics of IV (scaling, fissuring, and erythema) as well as hyperpigmentation with the IGA score at each visit representing the average degree of scaling, fissuring, and erythema (± hyperpigmentation, if present) that is eligible for treatment. IGA will be assessed using the following 5-point scale: clear (0), almost clear (1), mild (2), moderate (3), or severe (4). <u>Clinical Signs of Ichthyosis Vulgaris</u> Scaling, fissuring, and erythema in the Treatment Area will be graded using the following 5-point scale: clear (0), almost clear (1), mild (2), moderate (3), or severe (4). The degree of hyperpigmentation relative to the subject's normal skin color associated with the disease affected skin in the Treatment Area will be graded using the following 5-point scale: none (0), minimal (1), mild (2), moderate (3), or severe (4). [redacted]

	Pruritus At the Baseline Visit, prior to the first application of the test article, the subject's overall experience of pruritus within the previous two weeks will be assessed using a questionnaire (5-D Pruritus Scale). At all follow-up visits, the overall experience of pruritus, in the previous two weeks, will be scored using the same questionnaire. Pruritus assessed by this evaluation should be reported as an AE only if therapy is required. Percent Body Surface Area with Active Ichthyosis Vulgaris in the Treatment Area The percent BSA with active IV within the designated Treatment Area will be calculated at Baseline and at all follow-up visits. ***Safety:*** Test Article Compliance Subjects will apply the first dose of test article to skin affected with IV within the Treatment Area under staff supervision. Subjects will be instructed to record the date and time that each dose was applied. At each visit, subject diaries will be reviewed and subjects will be counseled regarding compliance, if necessary. All dispensed test article will be weighed at each visit and will be recorded. Adverse Events All AEs will be recorded. At each visit after the Baseline Visit/Day 1, subjects will also be questioned specifically about the status of any ongoing AEs. Clinical Laboratory Testing and Pregnancy Testing Chemistries, hematology, and urinalysis and UPTs will be performed at Baseline and EOS.
Study Endpoints	***Efficacy Endpoint(s):*** IGA scores and the clinical signs and symptoms of IV will be dichotomized to "treatment success" or "treatment failure" where "treatment success" is defined as at least a two grade decrease in severity score relative to Baseline. Dichotomization of scores for clinical signs and symptoms of IV will exclude subjects with Baseline scores of 0 or 1 unless the corresponding sign score at follow-up visits is >1. The primary efficacy endpoint will be the proportion of subjects with IGA "treatment success" at EOS, where EOS is the subjects last completed post-Baseline visit. Secondary efficacy endpoints (observed data only) include: • The proportion of subjects with IGA "treatment success" at Days 15 and 29. • The proportion of subjects with a IGA score of 0 or 1 representing "cleared" or "almost cleared" at EOS. • The proportion of subjects rated "treatment success" for each of the clinical signs and symptoms of IV at Days 15, 29, and EOS. • Changes in percent BSA with IV in the Treatment Area at Days 15, 29, and EOS relative to Baseline. • Change from Baseline in 5-D pruritus score at Days 15, 29, and EOS. • Changes in [redacted] at Days 15, 29, and EOS relative to Baseline.

	Safety Endpoint(s): Safety endpoints will include assessment of UPT (as applicable), clinical laboratory testing, and AEs, including serious adverse events (SAEs).
Sample Size Calculations	No formal power calculations were conducted to establish sample size. The sample size was selected empirically to enable sample size calculations for future pivotal studies.
Statistical Methods	All statistical analyses and summaries will be prepared using SAS® unless otherwise stated. All subjects enrolled in the study who were dispensed and applied test article at least once will be included in the analysis of safety and will be considered the Safety population. All randomized subjects who were dispensed the test article will be considered the intent-to-treat (ITT) population. The per-protocol (PP) population will be a subset of the ITT population consisting of subjects who have completed the study without significant protocol deviations. The statistical analysis plan will provide details regarding inclusion in the PP population. Missing values for the IGA score at EOS in the ITT population will correspond to IGA "treatment failure". All other analyses for both ITT and PP populations will use observed data only. Efficacy analyses will be performed on both the ITT and PP populations with the ITT population considered primary. Demographic and baseline characteristics will be summarized by treatment group for the Safety, ITT, and PP populations. Frequency counts and percentages will be reported for categorical data and sample size, mean, median, standard deviation (SD), minimum and maximum will be reported for the continuous variables. ***Efficacy Analyses:*** For each of the efficacy endpoints (IGA and signs of IV), the following summaries will be prepared at Days 15, 29, and EOS: • Frequency distribution of observed scores • Frequency distribution of change from Baseline • Shift tables for changes from Baseline to Visits 2, 3, and 4 • Frequency distribution of treatment success rates[7] At EOS, 95% confidence intervals will be calculated for the difference in proportions between treatment groups for rates of treatment success. The treatment groups will be compared with respect to "treatment success" rates for IGA and each sign of IV using Fisher's Exact Test. The proportion of subjects with an IGA score of 0 or 1 will be analyzed likewise using Fisher's Exact Test. Descriptive statistics (including mean, median, SD, minimum, and maximum) for observed and change from Baseline values in the percent BSA affected in the Treatment Area at each visit will be presented. For 5-D pruritus score and [redacted], descriptive statistics for observed and change from baseline values will be provided by treatment group at Baseline and at Days 15, 29, and EOS. The treatment groups will be compared with respect to the change from Baseline using mixed model of repeated measures (MMRM) including terms for treatment, visit, treatment by visit interaction, and the Baseline value serving as the covariate.

[7] Subjects with Baseline scores of 0 or 1 will be excluded from summaries and analyses of success rates unless the corresponding sign score at follow-up visits is >1.

	Safety Analyses: Dosing Compliance Descriptive statistics will be used to summarize test article compliance for the ITT population. Measures of test article compliance will include the duration of treatment (number of days dosed), the total number of applications (determined from the actual number of applications reported by the subject), and the percent of expected doses applied. A subject will be considered compliant with the dosing regimen if the subject applies at least 80% but no more than 120% of the expected number of applications. Extent of Exposure The total amount of test article used (grams of test article applied) will be calculated from the weights of the returned test articles. Descriptive statistics (mean, median, SD, minimum and maximum) will be determined for the total amount of test article used by each subject by treatment group. Clinical Laboratory Testing, and Urine Pregnancy Testing A listing of the clinical laboratory results and UPT results will also be prepared. Adverse Events All AEs reported during the study will be listed, documenting onset, whether therapy was required, any change in test article dosing, severity, possible relationship to test article, and outcome. Verbatim terms on the case report forms (CRFs) will be linked to preferred terms (PTs) and system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) mapping system. All reported AEs will be summarized by the number of subjects reporting AEs, SOC, PT, severity, and relationship to test article by treatment group.

SCHEDULE OF EVENTS

Study Day	Visit 1 Screening/ Baseline[1] Day 1	Visit 2 Week 2 Day 15 (±2)	Visit 3 Week 4 Day 29 (±2)	Visit 4 Week 6 EOT/EOS Day 43 (±3)[2]
Informed Consent/Assent	X			
Inclusion/Exclusion Criteria	X[3]			
Urine Pregnancy Testing[4] for WOCBP[5]	X[3]			X[2]
Medical History/Demographics	X			
Brief Physical Exam	X			
Vital Signs, Height, & Weight	X			
Clinical Evaluations (IGA, Clinical Signs of IV, [redacted], Pruritus)	X[3] (prior to test article application)	X	X	X
Record percent BSA with IV in the Treatment Area	X	X	X	X
Randomization to Treatment Regimen (Subject # Assignment)	X			
Provide (or review) Instruction Sheet to Subject & Parent/Guardian (if applicable) and Demonstrate How to Apply the Test Article[6]	X	X	X	
Provide Subject Diary to Subject & Parent/Guardian (if applicable) and Completion Instructions	X			
Clinical Laboratory Assessments	X[7]			X[2]
Photography (Select Sites)	X	X	X	X
Review/Dispense/ Collect Subject Diary		X	X	X
Weigh/Dispense Test Articles	X	X	X	
Weigh/Collect Test Articles		X	X	X
Instruct Subject to Continue Twice Daily Treatment	X	X	X	
Record Concomitant Medications and Procedures/Therapies	X	X	X	X
Record Adverse Events	X	X	X	X[8]

1. Screening assessment may be performed up to 45 days prior to the Baseline Visit for those qualified subjects that are eligible to enroll in the study but require wash-out of medications prior to enrolling into the treatment phase of the study. Screening and Baseline activities may be combined into a single visit if the subject does not require washout.
2. This activity may occur at an earlier visit if the subject is discontinued from the study.
3. For those subjects that required a washout period related to exclusionary medications, need to reaffirm these subjects meet all protocol requirements at the Baseline Visit.
4. UPTs must have a minimum sensitivity of 25 mIU ß-hCG/mL of urine.
5. 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 (within six months of initiation of treatment), or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea >12 consecutive months in women 50 years of age and older).
6. See application guidelines per protocol and in the subject instruction sheet.
7. Perform laboratory tests (blood chemistries, hematology, and urinalysis).
8. Any treatment related AEs that are ongoing at EOS must be followed until resolution or stabilization.