CLINICAL TRIAL PROTOCOL

Title: **A Prospective, Randomized, Double-blind, Placebo-controlled, Single-center Study of the Intradermal Injection of rHuPH20 or Placebo in Subjects with Nickel Allergic Contact Dermatitis**

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1. BACKGROUND AND RATIONALE

1.1. Hyaluronidases and rHuPH20

Mammalian hyaluronidase preparations differing in source, species, and manufacturing process have been the subject of multiple investigations and regulatory approvals in Europe, the United States, and Asia. The extent of human administration of these products in the U.S. has been estimated to be in the tens of millions of patients. Additionally, patients have been treated with other regulatory-approved preparations of hyaluronidase in Europe and Asia. Collectively, this usage spans nearly 60 years of clinical history in humans.

The U.S. Food and Drug Administration (FDA) contracted a review of the efficacy and safety of several hyaluronidase drug products through a program known as the Drug Efficacy Study Implementation (DESI). The studies were conducted by the National Academy of Sciences and the National Research Council. The DESI review findings published in the (Federal Register Sept 1970) established that hyaluronidase injection was "effective" for the following indications: For use as an adjunct to increase the absorption and dispersion of other injected drugs; for hypodermoclysis [subcutaneous fluid administration]; as an adjunct in subcutaneous urography; for improving the resorption of radiopaque agents.

The hyaluronidase drugs included in the DESI reviews included injectable hyaluronidase preparation derived from bovine testes. Replacing animal-derived slaughterhouse products with recombinant human biotechnology-developed materials potentially alleviates risks associated with animal pathogens, transmissible spongiform encephalopathies, and allergy and immunogenicity to foreign proteins.

rHuPH20 is a 447-amino acid single chain polypeptide with N-linked and O-linked glycan structures. rHuPH20 is synthesized in Chinese hamster ovary (CHO) cells that have been transfected with a plasmid containing the DNA sequence encoding the GPI-anchor deleted human PH20 hyaluronidase. The protein is purified through a series of chromatographic steps that results in a purified protein with high specific activity. rHuPH20 is up to 100 times more pure than the reference standard, slaughterhouse-derived hyaluronidase product based on specific activity. rHuPH20 depolymerizes hyaluronan (HA) by hydrolysis of the β-1,4 linkage between the C1 position of N-acetyl glucosamine and the C4 position of glucuronic acid.

A drug product formulation of rHuPH20 (HYLENEX) obtained FDA approval on 2 December 2005. The approval indication is an adjuvant to increase absorption and dispersion of other injected drugs; for subcutaneous fluid administration; and as an adjunct in subcutaneous urography for improving resorption of radiopaque agents. HYLENEX was made available as saleable product beginning October 2006 and as of 31 December 2008 a total of 7,284 vials of HYLENEX had been sold. HYLENEX was made available through a product sampling program beginning June 2006, and as of 31 December 2008 a total of 4,384 vials had been received at physician offices. Thus, cumulative patient exposure from marketed HYLENEX product outside of clinical studies could be a high as 11,668 based on the total vials of saleable product and sample product distributed and the unit dose of 150 Units per treated patient.

Across 19 studies, a total of 525 study subjects had been enrolled as of December 31, 2008 among whom 510 subjects are known to have been exposed to at least one dose of HYLENEX/rHuPH20. Of the 510 subjects exposed to HYLENEX/rHuPH20 in clinical studies, 100 received an intradermal injection of a test dose of 15 Units of HYLENEX and 410 subjects received a subcutaneous (SC) injection of HYLENEX/rHuPH20 either immediately before or admixed with a co-injected drug or fluid administration. Table 1 shows the cumulative number of subjects known to have been exposed according to the dose of HYLENEX/rHuPH20. There have been six studies to date in which at least some study subjects are known to have received more than a single exposure to HYLENEX: HZ2-07-03 (two doses per subject), 1838-003 (more than one dose permitted), HZ2-07-02 (a two-part study with some subjects participating in both parts), HZ2-07-04 (up to four doses per subject), HZ2-08-04 (up to six doses per subject) HZ2-08-05 (up to five doses). Table 1 presents the completed HYLENEX/rHuPH20 clinical studies.

Table 1: Cumulative Number of Subjects Exposed to rHuPH20 by Dose in Halozyme-Sponsored Clinical Studies

Dose of rHuPH20 (Units)	Number of Subjects Exposed (N = 510[a])
15[b]	100
150	236
240	13
288	4
300	12
750	16
1152	4
1,500	15
1,600	3
3,000	4
3,200	3
6,000	6
6,400	3
12,000	17
12,800	6
24,000	30
36,000	4
48,000	6
96,000	6

[a] Note: Amongst the 38 subjects exposed to rHuPH20 in Study HZ2-07-02 and 8 subjects in HZ2-08-04, only the patient's highest dose from either study stage was included in this table. Eleven subjects exposed to HYLENEX in Study HZ2-08-05 were included among the total of 510 subjects. Their dose has not yet been verified and they are not listed in this table. Amongst the 38 subjects exposed to rHuPH20 in Study HZ2-07-02 and 8 subjects in HZ2-08-04, only the patient's highest dose from either study stage was included in this table. The 11 patients in Study 160602 were also included in the total of 510. However, their information was not included in the table since there was variability among each subject's dose between 1050-7800 U (based on U/g of IgG).

[b] The 15 Unit dose was an intradermal test dose; all other administration was subcutaneous.

The most commonly reported adverse events (AEs) have been self-limited, transient, localized injection/infusion site observations. Comparison of the nature and incidence of AEs for HYLENEX versus the saline placebo in the double-blinded, placebo-controlled study designs shows that, with few exceptions, there were no AEs clearly attributable to HYLENEX, and in general the AE profile for HYLENEX was similar to that for saline placebo. The clinical data have not prompted any consideration of changes to the HYLENEX product label. The Investigator is to refer to the rHuPH20 Investigator's Brochure (IB) Version 1.0 for all current safety information.

1.2. Eczema, Spongiosis, and the Role of Hyaluronan

Spongiosis is a characteristic histopathological feature in acute eczema[1]. It is believed to be caused by the secondary loss of cohesion between epidermal cells due to the influx of tissue fluid into the epidermis. Serous exudate extends from the dermis; as it expands, epidermal cells remain in contact with each other only at the site of desmosomes, acquiring a stellate appearance and giving the epidermis a sponge-like morphology[2]. Investigators have conducted research to better understand the pathogenesis of spongiosis, specifically to understand whether HA may have a functional role in its pathogenesis.

HA is a well-known component of the connective tissues, such as in the cartilage of joints and the dermis of the skin. In the human epidermis, Tammi and Wells[3,4] have used hyaluronic-acid-binding protein (HABP) to localize HA in the matrix between keratinocytes in the middle and upper parts of the spinous layer. In addition, Sakai reported that even the normal stratum corneum contains HA supplied by keratinocytes[5].

In the process of assessing whether HA participates in epidermal hyperplasia, Maytin and colleagues[6] delivered Streptomyces hyaluronidase (Strep H) topically to degrade epidermal HA and blunt the accumulation of epidermal HA after acetone application. Strep H significantly reduced epidermal HA levels and also significantly inhibited the development of epidermal hyperplasia. This reduction in epidermal thickness was not attributable to any decrease in keratinocyte proliferation, but rather to an apparent acceleration in terminal differentiation. Overall, the data showed that HA is a significant participant in the epidermal response to barrier injury.

Ohtani and colleagues[7] conducted a series of experiments to clarify the mechanisms for the influx of tissue fluid into the epidermis and the loss of cohesion between keratinocytes in acute eczema that results in spongiosis. First, they demonstrated increased intercellular accumulation of HA in the spongiotic epidermis by immunohistochemical staining using HABP and augmented hylauronan synthase 3 (HAS3) mRNA expression by spongiotic keratinocytes. Secondly, they showed that the epidermis where the intercellular space was strongly stained with HABP showed weaker expression of membrane E-cadherin. Thirdly, IL-4, IL-13, and IFN-γ increased HA production, enhanced HAS3 mRNA expression, and decreased membrane E-cahedrin expression by normal human epidermal keratinocytes in both low- and high Ca+ media. Lastly, they demonstrated that IL-4, IL-13, their combination, and IFN-γ could induce intercellular space widening in the epidermis with increased HA accumulation and decreased E-cadherin expression. These results suggest that the augmented production of HA and the decreased E-cadherin expression by keratinocytes stimulated with IL-4/IL-13 or IFN γ cause spongiosis in acute eczema.

Based on these recent preclinical studies, HA appears to be directly involved in the pathogenesis of spongiosis. Further investigation is merited to better understand the role of hyaluronidase, more specifically, rHuPH20 in the prevention and treatment of spongiosis.

1.3. Rationale for Intra-dermal Injection of rHuPH20 in Subjects with Nickel Allergic Contact Dermatitis

As discussed in the previous section, HA plays an important role in the pathogenesis of spongiosis, the characteristic histopathological feature in acute eczema. However, there are no clinical data in the current medical literature that demonstrate the safety and efficacy of hyaluronidase for the treatment of eczema. Eczema is one of the most common skin diseases affecting up to 20% of children and up to 3 % of adults[8,9]. While mild cases can be treated with emollients alone, most cases require the use of pharmacologic interventions. Topical corticosteroids have been the mainstay of pharmacologic treatment for eczema. However due to potential side effects including both local effects (skin atrophy and pigmentary changes) and systemic effects (adrenal suppression) new topical modalities have been developed. The most efficacious of theses topical agents have been the topical calcinerin inhibitors (TCIs), tacrolimus ointment and pimecrolimus cream[10]. These were widely used until 2006 when the FDA issued a boxed warning due to rare cases of cutaneous and systemic malignancy. Thus there is a significant need for novel safe and effective topical therapies.

The dose of rHuPH20 selected for this proof of concept study (3,000 U/dose) is intended to model a future topical formulation of rHuPH20 that will provide controlled release of rHuPH20 into the epidermis through the stratum corneum. The intradermal administration of rHuPH20 in this study will not require diffusion through the stratum corneum, and it is therefore considered a more direct route of administration for this proof of concept study. While daily intradermal injection of 3,000 U of rHuPH20 in 0.25mL is not likely to provide sustained release of enzyme at the injection site, it is anticipated that this dose will be sufficient to temporarily depolymerize the hyaluronan present in the dermis and epithelium.

Doses of rHuPH20 in non-human primates up to approximately 3.6 million U/kg were well tolerated, and daily repeat subcutaneous dosing of 600,000 U/kg showed no histologic findings at the injection site. Additionally, in a Halozyme sponsored clinical study, 6 subjects received a single dose of rHuPH20 at a dose of 96,000 U which is greater than the expected cumulative dose in this clinical study.

rHuPH20 may prevent and treat acute contact dermatitis/eczema. Therefore, we propose to conduct this Phase II pilot study in subjects who have a + or ++ reaction (see Appendix B) to nickel sulfate as a model of spongiosis.

2. STUDY OBJECTIVES

2.1. Primary Objective

- Determine the treatment effect of rHuPH20 or placebo control injection on the exposure to topical nickel allergen (Treatment Regimens 1 and 2)
- Determine the time to onset and severity of the cutaneous reaction to nickel allergen after pre-treatment with rHuPH20 or placebo control (Treatment Regimen 2)
- Assess the safety and tolerability of the rHuPH20 injection

2.2. Secondary Objectives

- Proportion (%) of subjects who, with pre-treatment, have a ≥1 grade reduction of the cutaneous reaction to nickel sulfate in at least one patch region at 48 hours
- Proportion (%) of subjects with a ≥1 grade reduction of the cutaneous reaction to nickel sulfate in at least one patch region after treatment
- Proportion (%) of subjects that have a ≥1 grade reduction of the cutaneous reaction to nickel sulfate in at least one patch region at Days 2, 3, 4, or 5
- Safety and tolerability of the injection based on AEs, physical examinations, and vital signs

2.3. Descriptive-Only Parameters

- Digital photographic images of the allergen test sites at Baseline (Day 1), 48, 72, and 96 hours after the placement of the patches
- Chromometer images of the allergen test sites at Baseline (Day 1), 48, 72, and 96 hours after the placement of the patches
- TEWL (Trans-epidermal water loss) assessments at Baseline (Day 1), 48, 72, and 96 hours after the placement of the patches

3. STUDY DESIGN

3.1. Overview of Study Design

This is a pilot Phase II, prospective, double-blind, placebo-controlled study to compare the efficacy, safety and tolerability of rHuPH20 or placebo control administered intradermally (ID) in the prevention and treatment of subjects with contact allergy to nickel. This study will involve two treatment regimens, which will run in parallel (Treatment Regimens 1 and 2). A maximum of 30 subjects will be enrolled to achieve a likely estimate of 20 evaluable adult subjects. This study will be conducted at a dermatology unit.

Subjects with a known history of contact allergy to nickel will be recruited for the Screening period. During the Screening period, subjects will be tested to confirm the presence of cutaneous nickel sensitivity using the 1, 2.5, and 5% nickel sulfate patch. The concentration of nickel sulfate for each subject that causes no greater than a ++ cutaneous reaction (2 out of 4), International Contact Dermatitis Research Group [ICDRG[11]] scoring scale will be the concentration administered at Baseline.

After re-confirmation of the subject meeting all inclusion/exclusion criteria and prior to dosing, each subject will have the upper half of the posterior aspect of the torso divided into two equal spaces using a template and marking the edges with a medical marking pen.

There will be two treatment regimens in this study (1 and 2), which will be conducted in parallel. Within each regimen, the four patch areas will be randomized to rHuPH20 or placebo control for each subject. The randomization for Treatment Regimen 1 will be independent of the randomization for Treatment Regimen 2; thus, two randomization schemes (one for each Treatment Regimen) will be used. Specifically, for each subject, two random patch areas in Treatment Regimen 1 will be assigned rHuPH20; the other two patch areas in Treatment Regimen 1 will receive Placebo control. This same randomization concept will be used in Treatment Regimen 2.

Treatment Regimen 1:

This regimen will assess the treatment of contact allergy to nickel: At baseline, a single row of four patches (1, 2.5, or 5% nickel sulfate patches; determined for each subject during the Screening period) will be placed on the upper space on the upper back. After 48 hours, the patches will be removed and an assessment will be made of the reaction site as per the ICDRG scoring system. Each subject will receive in the center of the cutaneous reaction an ID syringe push bolus injection of either rHuPH20 or placebo control. Each injection will be administered once daily for 5 days. Prior to each daily injection, subjects will be evaluated for efficacy, safety, and tolerability. A final evaluation will be conducted 7 days after the last dose of study treatment.

Treatment Regimen 2:

This regimen will assess the prevention and treatment of contact allergy to nickel sulfate. Each subject will receive in the center of each lower space on the back, either an ID syringe push bolus injection of rHuPH20 or placebo control. Exactly 10 minutes after the injection, a single

row of four patches (1, 2.5, or 5% nickel sulfate patches; determined for each subject during the Screening period) will be placed over the center of the ID injection. After 48 hours, the patches will be removed and an assessment will be made of the reaction site as per the ICDRG scoring system. The subject will receive an ID injection of the same study drug from pre-treatment in the center of the cutaneous reaction once daily for 5 days. Subjects will be evaluated for efficacy, safety, and tolerability, on a daily basis. A final evaluation will be conducted 7 days after the last dose of study treatment.

Each of the injections will consist of 0.25 mL of rHuPH20 (3,000 U) or 0.25 mL of placebo control.

Safety, tolerability, and efficacy will be assessed through physical examinations, signs and symptoms at injection sites, vital signs, and adverse events.

3.2. Duration Of Time On Study

Study subjects will be screened (Visit 1) for eligibility within 21 days prior to receiving study drug. The baseline nickel allergy patch test must be administered no less than 14 days after the screening nickel allergy test.

- Visit 2 (Day 1) will consist of the nickel patch test (Treatment regimen 1) and pre-treatment and then the nickel patch test (Treatment regimen 2)
- Visit 3 (Day 3) is the day of first treatment dose and conducted 2 days (no less than 48 hours) after V2
- Visits 4-7 (Days 4-7) are dose days
- Visit 8 will be conducted seven days after the last dose

Therefore, the anticipated duration of time on study for a given subject, from Screening to completion of the study is up to 35 days.

3.3. Planned Total Sample Size

At enrollment, subjects will be assigned a unique identifier according to the randomization schedule. A maximum of 30 subjects may be enrolled to ensure that at least approximately 20 evaluable subjects complete the study. The sample size of 20 evaluable subjects is intended to provide a sufficient sample size to allow for a meaningful comparison between rHuPH20 and placebo control.

For Treatment Regimens 1 and 2, an evaluable subject is one who has completed dosing (or prematurely discontinued the administration due to a toxicity) and has undergone sufficient assessments to allow an assessment of the tolerability of the administration. Each subject not meeting the criteria for evaluability will be replaced with the enrollment of another subject. All subjects who receive at least one injection will be included in the safety analysis.

3.4. Stopping Rules

Subjects may withdraw from the study at any time and for any reason. Should any subject withdraw, the Investigator should be informed immediately. The Investigator may decide to terminate the participation of any subject for reasons not limited to the following criteria:

- The occurrence of serious or unexpected unwanted effects attributable to the study drug(s) or study procedure(s)
- In the event of abnormal laboratory results judged to be related to study drug(s) or study procedure(s) and of clinical significance
- Any significant protocol violation (including demonstrated lack of compliance)
- Serious difficulty in obtaining blood samples
- Enrolled subject withdraws consent
- Intercurrent illness requiring medication that might interfere with the study
- Other reasons as determined by the Investigator

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects must satisfy **all** of the following inclusion criteria in order to be enrolled in the study.

1. Females 18-60 years of age. Females of child-bearing potential must use a standard and effective means of birth control for the duration of the study.
2. Known contact dermatitis to nickel with a confirmed positive patch-test result to nickel sulfate.
3. Intact normal skin without potentially obscuring tattoos, acne, dermatitis, pigmentation or lesions on the posterior aspect of the torso (back) in the area intended for allergen testing and dose administration.
4. Vital signs (BP, HR, temperature, respiratory rate) within normal range or, if out of range, assessed by the Investigator as not clinically significant and it is mutually agreed by both Investigator and Sponsor Medical Monitor that the subject need not be excluded from the study for this reason.
5. A negative serum or urine pregnancy test (if female of child-bearing potential) within 14 days of initial study drug administration.
6. Subject should be in good general health based on medical history and physical examination, without medical conditions that might prevent the completion of study drug injections and assessments required in this protocol.
7. Decision-making capacity and willingness and ability to comply with the requirements for full completion of the study.
8. Signed, written Institutional Review Board (IRB)/EC-approved informed consent.

4.2. Exclusion Criteria

Subjects satisfying any one or more of the following exclusion criteria **are not** allowed in this study.

1. Nickel allergen patch test greater than a ++ reaction.
2. Subjects who were treated with chemotherapy agents or systemic corticosteroids within the past 3 months.
3. Use of topical steroids, antihistamines, or immunosuppressants used near the site of allergen testing/injection within 14 days.
4. Use of oral antihistamines within 14 days of study conduct.
5. Extensive ongoing outbreaks of contact dermatitis anywhere on the body.
6. Pregnant or women who are breast-feeding.

7. Subjects with a current disease state that can affect immune response (e.g., flu, cancer, HIV).
8. Known allergy to any hyaluronidase or the ingredients in the dose preparation.
9. History of autoimmune disorder.
10. Subjects with any other medical condition that, in the opinion of the investigator, might significantly affect their ability to safely participate in the study or affect the conduct of this study. Examples might include asthma, diabetes, heart disease, epilepsy, cancer, etc.

4.3. Prohibitions and Restrictions During the Study

The following medications / conditions are prohibited during the subject's time on study:

- Oral antihistamines within 14 days of study conduct
- Topical steroids, antihistamines, or immunosuppressants used near the site of allergen testing/injection within 14 days of study conduct
- A current disease state that can affect immune response (e.g., flu, cancer, HIV)

4.4. Assessments

- Complete medical history at screening
- Complete physical exam at screening
- A physical exam including visual inspection of the injection site at baseline, treatment days 3 – 7, and at follow-up visit
- A complete blood count (WBC with differential, Hgb, Hct, and platelets) at screening
- Vital signs Body Temperature (screening), BP, Heart Rate, Respiration Rate at screening, baseline, before each injection on treatment days 3 - 7, and within 10 minutes following each injection
- Pregnancy test at screening and baseline
- Targeted physical exam (positive findings on a review of systems and follow-up of findings from previous physical examinations) at baseline and treatment days 3 - 7
- Concomitant medications from 21 days before screening through the follow-up evaluation at 7-10 days after final injection
- TEWL (Trans-epidermal water loss) assessment at Baseline (Day 1)and treatment days 3 – 5
- Digital photographs of each allergen test site at Baseline (Day 1) and treatment days 3 – 5
- Chromometer images of each allergen test site at Baseline (Day 1) and treatment days 3 – 5
- Subject questionnaire at treatment days 3 - 5
- Adverse events / toxicity assessment at baseline through follow-up visit

5. STUDY METHODS AND PROCEDURES

5.1. Study Procedures by Visit

5.1.1. Screening Visit (Visit 1; Day -21 to Day -14)

Before the screening takes place, potential subjects for the study will be provided with written and oral information about the study and the procedures involved.

Subjects will be fully informed of all the procedures involved in the study, the possible risks and disadvantages of the study drugs and study procedures, and their rights and responsibilities while participating in the study. They will be allowed enough time to consider their participation in the study and will have the opportunity to ask questions. If the patient wishes to participate in the study, the patient will sign and date the IRB approved Informed Consent Form (ICF) prior to any screening procedures. Screening will be performed within 21 days prior to the first dosing visit, Visit 2.

As shown in Appendix A, Study Schedule of Events, the following activities are to be completed during this visit.

- Obtain signed informed consent
- Review subject eligibility based on Inclusion/Exclusion Criteria
- See Section 4.1 and Section 4.2.
- Review demographic information and perform a complete medical history
- Review prior and concomitant medication taken within 21 days of enrollment
- Perform a complete physical exam
- Vital signs collection (BP, heart rate, respiration rate and body temperature)
- Collect blood samples for hematology
- Sample collection for pregnancy testing
- Apply the nickel sulfate and vehicle control patches

Nickel Sulfate and Vehicle Control Patches

Follow the instructions in Appendix C. Follow the manufacturer's instructions for filling the unit chambers. Concentrations of 1%, 2.5% and 5% nickel sulfate solution will be used to determine the subject's allergic reaction to nickel. Apply the test patches to a clean surface on the upper back (at least 2 cm above the area to be used for the post-screening visits). Have the subject return to the study site after 48 hours to have the test results interpreted.

The concentration of nickel sulfate that causes no greater than + + cutaneous reaction (International Contact Dermatitis Research Group [ICDRG[11]] scoring scale, see Appendix B) will be the assigned dose for use per subject for the study. One half (50%) of study subjects will

be treated using the nickel concentration that elicits a + cutaneous reaction and the other half (50%) of study subjects will be treated with the nickel concentration that elicits a ++ cutaneous reaction. Any subjects not meeting the cutaneous reaction scale will be a screen failure.

Record the nickel sulfate concentration to be used for the subject in the subject's source documentation.

5.1.2. Baseline (Visit 2; Day 1)

Subject Arrival at Site:

As shown in Appendix A, Study Schedule of Events, the following activities are to be completed during this visit.

- Confirm subject meets inclusion and exclusion criteria
- Assign Randomization Number (at Baseline visit only)
- Review concomitant medication use
- Vital signs collection (BP, heart rate, respiration rate)
- Pregnancy test (only for females of child bearing potential)
- Targeted physical exam
- Physical examination of the administration site
- Perform baseline TEWL, Chromometer, digital photography assessments
- Mark the upper back into 2 rows of 4 areas each (see Figure 1)
- Treatment Regimen 1 - Apply the nickel sulfate patches (see Appendix C) at the concentration that caused no greater than a ++ cutaneous reaction (ICDRG[11] scoring scale, see Appendix B)
- Treatment Regimen 2 - Administer the intra-dermal injection of rHuPH20 or placebo. Exactly 10 minutes after the injection, apply a single row of four patches (1%, 2.5%, or 5% nickel sulfate patches; determined for each subject during the Screening period) over the center of the intra-dermal injection
- Assess Adverse Events (AE's)
- Assess injection site

After Study Patch Placement:

- Vital signs collection (BP, heart rate, respiration rate) within 10 minutes post-injection
- Physical examination of the administration injection site
- Review for adverse events (**After 30 minutes post-injection if no safety issues are observed, the subject will be allowed to leave**)

5.1.3. Visit 3: Treatment Day 3

As shown in Appendix A, Study Schedule of Events, the following activities are to be completed during this visit.

- Review concomitant medication use
- Targeted physical exam
- Vital signs collection (BP, heart rate, respiration rate)
- Physical examination of the administration injection sites immediately after patch removal (Treatment regimen 2)
- Administer/review the subject questionnaire
- Perform the TEWL, Chromometer, digital photography assessments
- Administer the intra-dermal injection of rHuPH20 or placebo (Treatment regimens 1 and 2).
- Review for adverse events / toxicity

After Study Drug Administration:

- Vital signs collection (BP, heart rate, respiration rate) within 10 minutes post-injection
- Physical examination of the administration site
- Review for adverse events (**After 30 minutes post-injection if no safety issues are observed, the subject will be allowed to leave**)

5.1.4. Visit 4 - 5: Treatment Days 4 - 5

As shown in Appendix A, Study Schedule of Events, the following activities are to be completed during this visit.

- Review concomitant medication use
- Vital signs collection (BP, heart rate, respiration rate)
- Targeted physical exam
- Physical examination of the administration injection site
- Administer/review the subject questionnaire
- Perform the TEWL, Chromometer, digital photography assessments
- Administer the intra-dermal injection of rHuPH20 or placebo (Treatment regimen 1 and 2).
- Review for adverse events / toxicity

After Study Drug Administration:

- Vital signs collection (BP, heart rate, respiration rate) within 10 minutes post-injection
- Physical examination of the administration site
- Review for adverse events (**After 30 minutes post-injection if no safety issues are observed, the subject will be allowed to leave**)

5.1.5. Visit 6 - 7: Treatment Days 6 - 7

As shown in Appendix A, Study Schedule of Events, the following activities are to be completed during this visit.

- Review concomitant medication use
- Vital signs collection (BP, heart rate, respiration rate)
- Targeted physical exam
- Physical examination of the administration injection site
- Administer the intra-dermal injection of rHuPH20 or placebo (Treatment regimen 1 and 2).
- Review for adverse events / toxicity

After Study Drug Administration:

- Vital signs collection (BP, heart rate, respiration rate) within 10 minutes post-injection
- Physical examination of the administration site
- Review for adverse events (**After 30 minutes post-injection if no safety issues are observed, the subject will be allowed to leave**)

5.1.6. Follow-up Visit: Day 14

As shown in Appendix A, Study Schedule of Events, the following activities are to be completed during this visit.

- Review concomitant medication use
- Vital signs collection (BP, heart rate, respiration rate)
- Targeted physical exam
- Physical examination of the administration site
- Review adverse events / toxicity

5.2. Subject Replacement/Completion Criteria

Subjects who are not evaluable will be replaced. An evaluable subject is one who has completed dosing (or prematurely discontinued the administration due to a toxicity) and has undergone sufficient assessments to allow an assessment of the tolerability of the administration.

As this study is being conducted at a single site, the site personnel, in conjunction with the Sponsor, will make the determination when a subject will need to be replaced in the study. This information will be collected on the Enrollment Log. Each subject not meeting the completion criteria will be replaced by the enrollment of an additional subject. In the event that a subject withdraws from the study prematurely or does not meet the completion criteria, every effort will be made to document the reason for termination and obtain follow-up safety data.

5.3. Study Methods and Procedures

5.3.1. Informed Consent

The Investigator or designee must present and explain the study protocol to prospective study subjects prior to any screening procedures. Once the subject has had an opportunity to read the IRB-approved ICF, the Investigator (or designee) must be available to answer any questions the subject may have regarding the study protocol and procedures.

5.3.2. Inclusion/Exclusion Criteria Review

Review the inclusion/exclusion criteria (Section 4.1 and Section 4.2) to ensure the subject qualifies for this study at the screening visit.

5.3.3. Demographics

Collect demographic information, including the subject's initials, date of birth, gender, race and ethnic origin at the screening visit.

5.3.4. Medical History

A complete medical history will be collected at the screening visit.

5.3.5. Complete Physical Exam

Physical examination, including ears/eyes/nose/throat/neck, respiratory, cardiovascular, gastrointestinal including mouth, musculo-skeletal, central and peripheral nervous system and dermatological assessments will be performed by the Investigator at the screening visit.

5.3.6. Targeted Physical Exam

An abbreviated physical exam, reviewing only those body systems for which an abnormality was noted during the complete review of systems or a follow up of previous physical exam(s), will be performed by the Investigator prior to study drug injection at Visits 1-7, and at the Follow-up Visit.

5.3.7. Vital Signs

Assessment of vital signs includes the measurement of blood pressure (systolic and diastolic), heart rate, and respiration rate and body temperature (at screening). Blood pressure and heart rate will be measured with the subject at rest and in supine position for at least 5 minutes prior to recording. Vital signs will be recorded at screening, baseline, prior to injection, immediately after each injection, and before discharge.

5.3.8. Pregnancy Testing

For females of childbearing potential, serum or urine pregnancy testing will be performed at the screening and baseline visits.

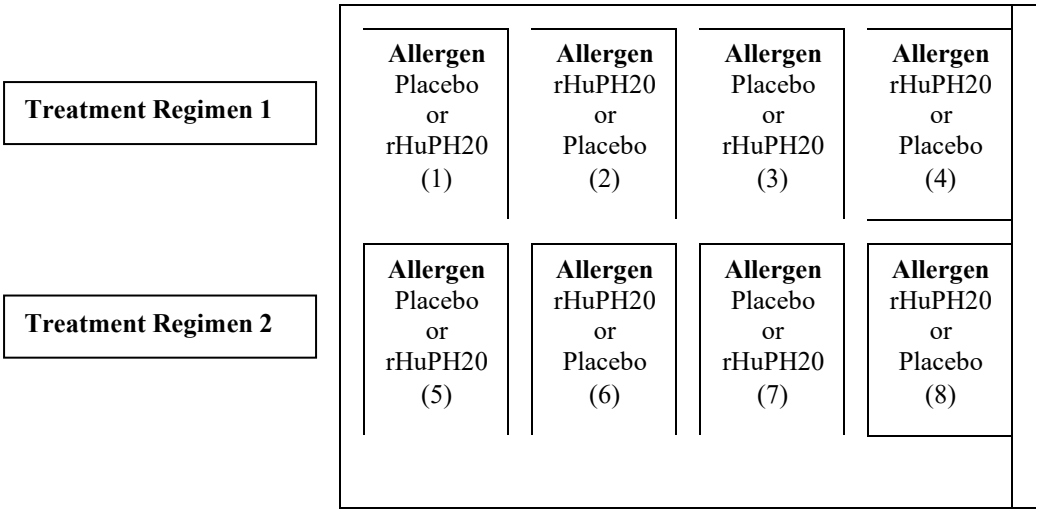
5.3.9. Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count (differential), and platelet count will be determined at the screening visit.

5.3.10. Study Drug Administration

There will be two treatment regimens in this study (1 and 2), which will be conducted in parallel. Within each regimen, the four patch areas will be randomized to rHuPH20 or placebo control for each subject (Figure 1). The randomization for Treatment Regimen 1 will be independent of the randomization for Treatment Regimen 2; thus, two randomization schemes (one for each Treatment Regimen) will be used. Specifically, for each subject, two random patch areas in Treatment Regimen 1 will be assigned rHuPH20; the other two patch areas in Treatment Regimen 1 will receive Placebo control. This same randomization concept will be used in Treatment Regimen 2.

Figure 1: Study Treatment Arm Randomization



Treatment Regimen 1 (Spaces 1-4):

This regimen will assess the treatment of contact allergy to nickel: At baseline, a single row of four patches (1, 2.5, or 5% nickel sulfate patches; determined for each subject during the Screening period) will be placed on the upper space on the upper back. After 48 hours, the patches will be removed and an assessment will be made of the reaction site as per the ICDRG scoring system, Appendix B. Each subject will receive in the center of the cutaneous reaction an ID syringe push bolus injection of either rHuPH20 or placebo control. Each injection will be administered once daily for 5 days. Prior to each daily injection, subjects will be evaluated for efficacy, safety, and tolerability. A final evaluation will be conducted 7 days after the last dose of study treatment.

Treatment Regimen 2 (Spaces 5-8):

This regimen will assess the prevention and treatment of contact allergy to nickel sulfate. Each subject will receive in the center of each lower space on the back, either an ID syringe push bolus injection of rHuPH20 or placebo control. Exactly 10 minutes after the injection, a single row of four patches (1, 2.5, or 5% nickel sulfate patches; determined for each subject during the Screening period) will be placed over the center of the ID injection. After 48 hours, the patches will be removed and an assessment will be made of the reaction site as per the ICDRG scoring system. The subject will receive an ID injection of the same study drug from pre-treatment in the center of the cutaneous reaction once daily for 5 days. Subjects will be evaluated for efficacy, safety, and tolerability, on a daily basis. A final evaluation will be conducted 7 days after the last dose of study treatment.

Each of the injections will consist of 0.25 mL of rHuPH20 (3,000 U) or 0.25 mL of placebo control.

5.3.11. Determination of Nickel Sulfate Sensitivity

During the Screening period, subjects will be tested to confirm the presence of cutaneous nickel sensitivity using the 1, 2.5, and 5% nickel sulfate patch. The test site will not be in the same area where patches will be placed at Baseline. The concentration of nickel sulfate for each subject that causes no greater than a ++ cutaneous reaction (2 out of 4, International Contact Dermatitis Research Group [ICDRG[11]] scoring scale will be the concentration administered at Baseline (Day 1).

5.3.12. Nickel Sulfate Patch

At baseline the nickel sulfate patch will be applied. For Treatment regimen 1, the nickel sulfate patches will be applied and the subject will return within 48 hours for removal and to begin treatment intra-dermal injections. For Treatment regimen 2, the nickel sulfate patches will be applied at baseline after 10 minutes post-injection of either rHuPH20 or placebo.

The concentration of nickel sulfate (1, 2.5, or 5%) will be determined during the Screening period. Once the concentration is confirmed, this will be the concentration applied on the subject at the baseline visit.

At the baseline visit, the patches will be inoculated with the correct nickel sulfate concentration. The procedure for using the allergy patch system is found in Appendix C.

5.3.13. Trans-Epidermal Water Loss (TEWL)

All measurements should be conducted in an enclosed room in which air movement is minimized. Subjects must equilibrate for 30 minutes prior to testing in the controlled environment of 72 plus/minus 2 degrees F and a relative humidity (RH) of less than 50% prior to measurement reading. Make sure the skin area to be read is dry and clean. Press and securely hold the evaporimeter probe to the skin surface for 45 seconds. A validated Evaporimeter Operator should only be used to collect data.

5.3.14. Digital Photographs

In these clinical photographs, for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (jewelry, clothing, furniture, walls, etc.) is to be eliminated from the fields to be photographed, from the baseline through the final photographs. The necessity of good end-of-study photos should be stressed to the subjects to ensure their cooperation. Lighting, framing, exposure and reproduction ratios must be held constant. In the end, the pictures should read like a time-lapse movie. Detailed instructions are found in Appendix D.

5.3.15. Chromometer

Make sure the skin area to be read is dry and clean. To collect data, position the device directly over the skin area without applying pressure to the skin surface. Ensure the position of the device on the skin is level or parallel with the surface of the skin. Press the trigger once on the chromometer. A reading will be recorded on the program. Data collection should be done by a validated Chromometer Operator only.

5.3.16. Adverse Events

Each study participant will be carefully monitored for the development of adverse events (Section 7).

5.3.17. Injection Site Assessment

An assessment of local tolerability at the injection site will be performed prior to and 10 minutes after the injection for site reactions such as erythema, pruritus, and edema. If an injection site reaction is observed, it must be recorded as an adverse event. Local tolerability will be assessed by a qualified person.

5.3.18. Prior/Concomitant Medications

Review any concomitant medications the subject is taking at each study visit, beginning 21 days prior to Visit 1. See Section 4.3 for a list of prohibited medications.

5.4. Premature Termination of Treatment/Withdrawal of Subjects

The Investigator must guard the subject's welfare and should discontinue study drug treatment at any time that this action appears to be in the subject's best interest. Subjects may discontinue study drug treatment and may withdraw or be removed from the study at any time. Possible reasons for such actions may include, but are not limited to, the following:

- The occurrence of serious or unexpected unwanted effects attributable to the study drug(s) or study procedure(s)
- In the event of abnormal laboratory results judged to be related to study drug(s) or study procedure(s) and of clinical significance
- Any significant protocol violation (including demonstrated lack of compliance)
- Serious difficulty in obtaining blood samples
- Enrolled subject withdraws consent
- Intercurrent illness requiring medication that might interfere with the study
- Other reasons as determined by the Investigator

It is the right and duty of the Investigator to interrupt the treatment of any study subject whose health or well-being may be threatened by continuation in this study.

Once a study subject has received study drug under this protocol, the subject must be followed for safety as required in the protocol (see Section 7). In the event that a study subject discontinues treatment prematurely, every effort will be made to document the reason for premature termination and obtain follow-up safety data.

Should the enrollment rate lag or significant numbers of clearly non-eligible and/or non-evaluable subjects be entered in the study, Halozyme may elect to terminate the study at any and all investigational sites. Halozyme also has the right to terminate the study at any time for non-adherence to protocol, unavailability of the Investigator or his or her study staff for Halozyme or its designated monitoring personnel, or for administrative reasons, at any time.

6. STUDY MEDICATIONS AND ADMINISTRATION

6.1. Study Medication

rHuPH20 (recombinant hyaluronidase human injection), also designated as Study Drug, will be provided as 12,000 USP units/mL in 1 mL vial. This Study Drug is a concentrated formulation of the FDA-approved rHuPH20 drug product known as HYLENEX (150 USP units/mL), with the exception that Study Drug does not contain calcium chloride and disodium edentate.

Clinical Study Drug placebo will consist of the same formulation of rHuPH20 Clinical Study Drug without active drug substance.

The manufacturing and packaging of the study products will be in accordance with GMP.

6.2. Packaging and Labeling of Study Products

Labeling of study products will be in accordance with local law and study requirements.

Blinding of the study products will be done at the investigational site. Before dosing, the unblinded person at the investigational site, the pharmacist or designee, will prepare the dosing syringe containing the study products. The pharmacist or designee will give the dosing syringe to the physician for dose administration, making sure that the content of the syringe is not revealed to the subject or the study staff.

6.3. Storage and Drug Accountability of Study Products

All study drug products will be stored refrigerated (2ºC to 8ºC) at the Investigator's site and should not be exposed to excessive heat, direct sunlight and never be frozen.

All used and unused vials must be kept by the Investigator and stored between 2ºC and 8ºC. Used and unused vials must be stored separately.

All study-specific supplies must be kept in a secure area with access limited to only authorized clinical investigation personnel.

No study products may be dispensed to any person not enrolled in the study.

In order to ensure that the vials reach room temperature prior to performing the study drug preparation procedure, they will be removed from the refrigerator / storage approximately 1-2 hours prior to dose administration. The study drug preparation procedure must take place within 2 hours of dosing.

The Investigator must keep an accurate record of all study products received and the products used for each subject.

The Monitor will check the drug accountability periodically and after completion of the study. The Sponsor will maintain a record of supplies dispatched to and returned from the site. **Study drug will only be destroyed on the authorization of the Sponsor.** The destruction of study products will be recorded on a Destruction Form signed by the person responsible for the destruction.

The drug supplies will be stored at the site as noted on the Form FDA 1572. These samples will be stored under conditions consistent with the product labeling, in an area segregated from the area where testing is conducted. Access will be limited to authorized personnel only. Retained clinical supplies will be kept at the site until the completion of the study. Once the study is completed, the Sponsor will inform the site of any final disposition or shipment of retained study materials. None of the retained clinical supplies may be destroyed by the site without the written permission of Halozyme Therapeutics.

6.4. Randomization and Blinding

This is a double-blind randomized study. Subjects and the investigative staff will be blinded to the contents of each study drug injection. The pharmacist or designee at the investigative site preparing syringes for injection will not be blinded. The randomization list will be provided by the designated data management team. When a subject is randomized in the study, they must always be assigned to the lowest randomization number (e.g., subject number) available at the time of randomization.

Replacement subjects will be added if a subject discontinues prior to fulfilling the evaluability criteria (Section 5.2). Replacement subjects must always be assigned to the lowest available subject ID number available from the replacement randomization code.

6.5. Unblinding Procedures

The randomization code will be kept in a secure, limited-access area, so that no one other than the pharmacist or designee preparing the syringes has access. The rest of the investigational staff, the study subjects, and the Sponsor and representatives of the Sponsor will not have access to the randomization code until the study as a whole has been unblinded, after the last data have been collected for the last subject in the study.

7. ADVERSE EVENTS AND SAFETY MONITORING

The safety parameters collected and monitored during this study include AEs, concomitant medications, laboratory determinations, physical examination, vital signs, and local tolerability at injection sites.

All AEs that occur during the study should be treated appropriately to protect and ensure the patient's well-being. If such treatment constitutes a deviation from this protocol, Halozyme must be notified and the Investigator should comply with applicable IRB reporting requirements. If the patient is withdrawn from the study as a result of this AE, the reason will be appropriately documented.

7.1. Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonization and the U.S. Code of Federal Regulations (21 CFR 1998) and are included herein. The terms "serious adverse event" and "adverse event," inserted in parentheses, are commonly used terminology.

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.

Serious adverse drug experience (serious adverse event, SAE) is any adverse drug experience (AE) occurring at any dose that results in any of the following outcomes:

- Is fatal or immediately life-threatening (life-threatening is defined as a medical event during which the patient is at immediate risk of death from the reaction as it occurred; it does not include an event that, had it occurred in a more serious form, might have caused death);
- Requires hospitalization, or prolongs existing hospitalization. Any in-patient hospital admission, regardless of duration of hospital stay, will be considered as in-patient hospitalization. Hospitalizations for procedures scheduled prior to enrollment into the study and emergency room visits do not constitute a serious AE.
- Results in persistent or significant disability/incapacity;
- Results in a congenital anomaly or birth defect; or
- Is any other Important Medical Event. Important Medical Events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 hospitalization of the patient, or the development of drug dependency or drug abuse.

Life-threatening is any adverse drug experience (adverse event) that places the patient or subject, in the view of the Investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

Associated with the use of the drug means that there is a ***reasonable possibility*** that the experience (adverse event) may have been caused by the drug.

Unexpected adverse drug experience means any adverse drug experience (adverse event), the specificity or severity of which is not consistent with the current IB.

7.2. Pre-Treatment-Emergent Adverse Events

Halozyme considers AEs that occur between the time the subject signs the informed consent document for the study to the time leading up to when that subject is first exposed to study drug as "pre-treatment-emergent" events. All known pre-treatment-emergent AEs that are serious (see Section 7.1) should be immediately reported to Halozyme. The reason for collection of serious pre-treatment-emergent AEs is to allow for an assessment of whether or not the SAE was causally associated with any protocol-related activities. Halozyme does not intend to collect information on pre-treatment-emergent AEs that do not meet at least one accepted criterion for a serious classification under the most rigid and comprehensive of the applicable regulatory agency criteria for this study, unless the event was related to a study procedure. Events occurring during or immediately after first administration of study drug will be considered treatment-emergent AEs and will be captured on the AE CRF.

7.3. Laboratory Abnormalities as Adverse Events

It is anticipated that many laboratory abnormalities observed during the course of a study will be encompassed under a reported AE describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or elevated SGOT/SGPT in the setting of an AE of hepatitis). In these cases (e.g., an AE of renal failure), the laboratory abnormality itself (e.g., elevated creatinine) does not need to be recorded as an AE.

In the absence of a reported AE identifying a clinical syndrome that encompasses the observed laboratory abnormality that isolated laboratory abnormality itself should be reported as an AE if it is judged by the Investigator to be clinically significant for that patient.

For the purposes of this study, criteria defining a "clinically significant" laboratory abnormality are:

a. Laboratory abnormality leads to a dose-limiting toxicity (e.g., judged to be associated with study drug administration and resulting in study drug dose reduction, suspension or discontinuation), or
b. Laboratory abnormality results in any therapeutic intervention (i.e., concomitant medication or therapy), or
c. Other laboratory abnormality judged by the Investigator to be of other particular clinical relevance.

7.4. Classification of Adverse Events by Severity

The Investigator must categorize the severity of each AE according to the following guidelines. The level of severity is guided by the National Cancer Institute (NCI) Common Terminology Criteria (CTC) for adverse events, which will be provided to each study center and is available on line at http://ctep.cancer.gov/reporting/ctc.html (CTCAE, National Cancer Institute).

Mild:

Grade 1 NCI Common Terminology Criteria AE; if not found in the Common Terminology tables, an AE that is asymptomatic or barely noticeable to the patient; not interfering with patient's daily activity performance or functioning; generally not requiring alteration or cessation of study drug administration; and/or ordinarily not needing therapeutic intervention.

Moderate:

Grade 2 NCI Common Terminology Criteria AE; if not found in the Common Terminology tables, an AE of sufficient severity as to possibly make the patient moderately uncomfortable; possibly influencing the patient's daily activity performance or functioning; generally not impairing the patient's ability to continue in the study; and/or possibly needing therapeutic intervention.

Severe:

Grade 3 or 4 NCI Common Terminology Criteria AE; if not found in the Common Terminology tables, an AE generally causing severe discomfort; significantly influencing the patient's daily activity performance or functioning; generally requiring alteration or cessation of study drug administration; life-threatening; resulting in significant disability or incapacity; and/or generally requiring therapeutic intervention.

7.5. Classification of Adverse Events by Relationship to Study Drug Administration

The relationship of each AE to the study drug administration will be assessed by the Investigator after careful consideration and according to the following guidelines. Investigators will consider AEs to be either causally related to the therapy or to be not causally related; the following definitions apply:

Causally Related:

The event follows a reasonable temporal sequence from administration of the study drug or in which the drug level has been established in body fluid or tissue; it follows a known or expected pattern of response to the study drug; or it can not be readily explained by well-documented concurrent or co-existent pathological processes, environmental or toxic factors, or other therapy administered to the subject. A causal relationship may be confirmed by improvement following cessation of the study drug or dose reduction, especially if the

reaction reappears following subsequent study drug exposure. The Investigator should refer to the SAE sections in the protocol and to the IB for additional guidance.

If the clinical data are not clear, the Investigator must use his or her best judgment. The AE should be recorded as causally related if the Investigator considers the balance of the available data to be consistent with a study drug effect.

Not Causally Related:

The event does not meet the "causally related" criteria. The Investigator should record an AE as not causally related if the Investigator concludes that the balance of all available data is in keeping with an effect unrelated to the study drug.

7.6. Known Toxicity Profiles of Study Drugs

As noted in Section 7.5 the Investigator is expected to make his/her best assessment of the causal relationship of each AE in this clinical study. The Investigator should base the assessment on all available information including, but not limited to, the Investigator's Brochure.

7.7. Reporting of Adverse Events

For the purpose of this study, all AEs, regardless of seriousness, severity, expectedness, or relationship to the study drug, will be collected if the date and time of onset of the AE was after the subject's first exposure to any study drug and through Visit 8 (Day 14 follow up visit). There is no time limitation on the reporting of AEs that are treatment-emergent and assessed as reasonably associated with study drug (i.e., a drug-associated AE should be reported even if after Visit 8).

Events that occur prior to first study drug administration will be considered pre-treatment-emergent because the time of onset preceded the first exposure to study drug (see Section 7.2), and these observations will be captured on the patient's Medical History CRF. Events occurring during or after first administration of study drug will be considered treatment-emergent AEs and will be captured on the AE CRF.

Subjects will be questioned and/or examined by the Investigator and his/her designee for evidence of AEs. The questioning of study subjects with regard to the possible occurrence of AEs will be generalized such as, "How have you been feeling since your last visit?" Information gathering for AEs should generally not begin with direct solicitation from subjects regarding the presence or absence of specific AEs.

All serious AEs (SAEs) occurring with any patient participating in this clinical study must be immediately reported to Halozyme as described in Section 7.7.1.

7.7.1. Reporting of Serious Adverse Events

All SAEs must be reported to Halozyme or designee **WITHIN 1 BUSINESS DAY** of discovery or notification of the event. Initial SAE information and all amendments or additions must be recorded on a Serious Adverse Event Form and faxed along with all available pertinent information to:

Halozyme Safety Department

Fax: [redacted]

The minimum required information for an initial report of an SAE is:

1. Reporter's name and contact information,
2. Protocol number,
3. Site and patient identification information, and
4. The SAE term(s) with a brief summary of the event(s) including the causality assessment, if possible.

7.7.2. Duration of Follow-Up of Adverse Events

Ongoing AEs and laboratory abnormalities that are considered by the Investigator to be CAUSALLY RELATED to the study drug will be followed until resolved, returned to pre-study drug exposure level, stabilized at a level acceptable to the Investigator, or later determined by the Investigator to be Not causally related to the study drug. Ongoing events and laboratory abnormalities that are considered Not Causally Related to the study drug need only be followed until the patient's final study visit (i.e., Visit 8, or earlier if the patient is withdrawn from study).

7.7.3. Other Information on the Reporting of Adverse Events

Follow-up information regarding serious AEs must be provided to Halozyme promptly as it becomes known to the Investigator.

The Institutional Review Board (IRB) that approved the clinical investigation must be notified of any fatal, life-threatening and/or serious AEs regardless of cause on a timely basis, according to the IRB's established procedures (see Section 7.7.4).

A written report of all serious AEs and deaths will be submitted by the Investigator to the IRB and to Halozyme. In this report, the Investigator will advise whether or not the AE is judged to be related to the study drug administration. All such subjects with AEs should be followed clinically and by the appropriate diagnostic evaluations.

All AEs, regardless of severity, and whether or not ascribed to the study drug administration, will be recorded in the appropriate section of the CRF.

7.7.4. Reporting of Safety Information to the Institutional Review Board

It is the responsibility of the Investigator to inform the study center's Institutional Review Board (IRB) of all SAEs and other safety information in accordance with applicable IRB's requirements. At the completion or early termination of the study, a final report should be made to the IRB by the Investigator within the applicable IRB time frames.

7.7.5. Pregnancy

A negative pregnancy test during screening for women of childbearing potential and the use of effective contraceptive methods for the duration of the study are required.

Any pregnancy in a study patient must be immediately reported to the Investigator and in turn to Halozyme (see Section 7.7.1 for contact information). Pregnancy during the study period will be reported and followed until final resolution (i.e., delivery or early termination). Any birth defect or congenital anomaly will be reported to Halozyme immediately as an SAE.

7.8. Precautions/Over-Dosage

Normal precautions taken for a human study, including the provision of emergency equipment, will be taken during this study. Qualified and well trained physicians and medical staff will instruct the subjects.

7.9. Prior/Concomitant Medications and Procedures

Any medication taken during the study other than study drug is regarded as concomitant medication. A history of current medications will be obtained from each subject during screening and recorded in the CRF under Prior/Concomitant medications. Subjects must be queried regarding both prescription and over-the-counter medications that they take. Prior/Concomitant medications taken during the time period beginning 21 days prior to initial dosing, Visit 1, through the last visit on study, anticipated to the be the follow-up visit, Visit 8, will be collected for all subjects.

Concomitant medications will be updated at each subsequent visit according to the Study Schedule of Activities (see Appendix A), including any medication taken to treat an AE. At each study visit, subjects will be asked if there has been any change in the medications they have taken since their last study visit. Changes will be recorded on the Prior/Concomitant Medications CRF.

Recording of concomitant medications will include the name of the drug, dosage, route, frequency, date of treatment, and the clinical indication for which the medication was taken.

Subjects may receive medical care during the study including but not limited to antibiotics, analgesics, antipyretics, etc., when clinically indicated. Whenever possible, the subject should avoid starting any new medications during the treatment period of this study (including over-the-counter medications) unless the Investigator deems such medication medically necessary. A list of medications prohibited during the study is provided in Section 4.3 of this protocol.

8. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

Primary and Secondary Analysis

The primary analysis is the pair-wise intra-subject comparison of endpoint parameters for the injections with and without rHuPH20. The primary analysis is the observer's assessment of the nickel sulfate allergen reaction site. The ICDRG scoring system will be used to conduct this assessment, which is either + (Weak [non-vesicular] positive reaction: Erythema, infiltration, possibly papules) or ++ (Strong [vesicular] positive reaction: Erythema, infiltration, papules, vesicles). Secondary analysis of the study is the comparison of safety and other endpoint parameters for the SC administration between rHuPH20 and placebo control.

Dataset for Analysis

The primary analysis data set for this study will consist of all evaluable subjects. An evaluable subject is one who has completed dosing (or prematurely discontinued the administration due to a toxicity) and has undergone sufficient assessments to allow an assessment of the tolerability of the administration. A secondary analysis data set will consist of all intent-to treat subjects (ITT) (i.e., all subjects enrolled, defined as subjects assigned a subject identification number at the time of study enrollment in anticipation of receiving a dose of study drug). The safety analysis data set is all subjects exposed to rHuPH20 or placebo control.

The hypothesis is that 1) pre-treatment of rHuPH20 prior to nickel allergy testing will decrease the severity of the allergic skin reaction as compared to placebo control and 2) rHuPH20 will decrease the severity of nickel contact dermatitis as compared to control. The null hypothesis for this study is that rHuPH20 will not be different than what will be observed from placebo control. The alternative hypothesis is that rHuPH20 will be better than placebo control.

The sample size of 20 evaluable subjects is intended to provide a sufficient sample size to allow for a meaningful comparison between rHuPH20 and placebo control.

All data collected, including demographics, baseline information, contact dermatitis scoring, safety data, will be summarized by treatment group. Descriptive statistics including the number of observations (N), mean, standard deviation, median, and range will be presented for the continuous variables. Frequency and percentage will be presented for categorical variables. Figures of the individual measurements over time by subject and means by treatment group may also be provided.

Descriptive statistics will be used to summarize all efficacy variables. No formal statistical comparisons between treatments are planned.

All safety data will be examined, including AEs, physical examination findings, and vital signs. The incidence of subjects with AEs will be tabulated by MedDRA System Organ Class (SOC) and Preferred Term, seriousness, severity grade, relatedness to study drug, and localization to infusion site. Descriptive statistics will be used to summarize all safety variables.

9. REGULATORY/ADMINISTRATIVE PROCEDURES AND DOCUMENTATION

9.1. Ethics

This study will be conducted under a U.S. Investigational New Drug (IND) Application. All applicable U.S. regulations governing human subject protection must be followed. All ethical and regulatory requirements are necessary to comply with the principals of Good Clinical Practice (GCP).

To ensure ethical conduct of this clinical study, Investigators will be expected to adhere to basic principles provided from generally recognized guidelines such the Belmont Report and the International Ethical Guidelines for Biomedical Research Involving Human Subjects. The study has been designed to involve the participation of representative subjects affected by the disease under investigation. Participants must have provided written informed consent to document their voluntary participation in this study. Updated safety information will be provided to the Investigators, Institutional Review Boards (IRBs) and subjects as necessary in order that they may consider relevant and emerging information that could affect their willingness to continue participation in this study.

9.2. Institutional Review Board and Approval

In accordance with 21 CFR Parts 50 and 56, the Investigator agrees to provide the appropriate Institutional Review Board (IRB) with all appropriate material, including a copy of the protocol, ICF, IB, and any proposed advertisement for the study prior to the start of the study.

The proposed ICF and any proposed advertisement must also be agreed to by the Sponsor (Halozyme). A copy of the IRB approval letter of the protocol and the ICF must be supplied to Halozyme prior to consent of any subjects for the study. A copy of the IRB approval letter of any protocol amendments and any advertisements must be supplied to Halozyme prior to implementing these documents. The study may not begin screening or enrolling subjects until the Investigator has obtained IRB approval of the protocol and ICF and Halozyme has received a hardcopy documentation of each.

The Investigator will supply to Halozyme a list of the names, professions, and affiliations of IRB members to demonstrate compliance with membership requirements. If the Investigator or a sub-investigator is a routine voting member of the IRB, Halozyme will be provided with a statement from the IRB that the Investigator/sub-investigator did not and will not vote on the subject of this investigation.

During the course of the study, the Investigator shall make timely and accurate reports to the IRB on the progress of the study, at intervals not exceeding one year, as well as satisfying any other local IRB regulations regarding reporting. Copies of all reports to and correspondence with and from the IRB must be provided to Halozyme. Furthermore, at the completion or early termination of the study, a final report should be made to the IRB by the Investigator within the applicable IRB time frames. A copy of this report will be provided to Halozyme.

Any significant changes or revisions in the study protocol or any changes that may alter subject risk must be approved by Halozyme (and may require FDA/other regulatory agency review and/or approval) and must be approved in writing by the IRB prior to implementation (see Section 9.7 for protocol amendments). The Investigator must also receive a written notice of approval from Halozyme prior to initiating the revised changes to the study protocol. A protocol change intended to eliminate an apparent immediate hazard may be implemented immediately, provided that Halozyme is immediately notified and an amendment is subsequently provided by Halozyme and approved by the IRB.

It is the Investigator's obligation to maintain an IRB correspondence file, and to make this available for review by Halozyme or its designated representatives as part of the study monitoring process.

9.3. Informed Consent

A copy of the proposed ICF document must be submitted to Halozyme for review and comment prior to submission to the reviewing IRB. The ICF must be approved by the IRB and contain all elements required by all applicable federal, state, local, and institutional regulations or requirements prior to consenting a subject. Authorization to use or disclose Personal Health Information (PHI) in accordance with requirements of the Health Insurance Portability Act of 1996 (HIPAA) should be covered in the ICF or in a separate document to be signed by the subject.

The proposed ICF must contain a full explanation of the purpose and nature of the study, a description of the procedures, the possible advantages, risks, alternate treatment options, and a statement of confidentiality of subject study records, a statement regarding voluntary compensation and availability of treatment in the case of injury, an explanation of whom to contact about the research, the subject's rights, and notification that participation is voluntary and refusal will involve no penalty or loss of medical benefits. These requirements are in accordance with the U.S. Federal Regulations as detailed in the 21CFR50.25 and the Declaration of Helsinki. The ICF should also indicate by signature that the subject, or where appropriate, legal guardian/representative, permits access to relevant medical records by the Sponsor (Halozyme) and/or the Sponsor's duly appointed agent and by representatives of the U.S. Food and Drug Administration (FDA) or other applicable regulatory agency and permits their data to be used in publications.

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study specific screening and entry into the study. The research study will be completely explained to each prospective study subject. The Investigator or designee must explain that the subject is free to refuse to enter the study, and free to withdraw from it at any time for any reason. If new safety information becomes available and results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated if necessary. Under this circumstance, all subjects (including those already being treated) should be informed of the new information, given a copy of the revised ICF, and be allowed to re-evaluate their consent to continue in the study.

Each subject (and/or legally authorized representative if the subject is a minor, mentally incompetent or physically incapacitated) found to be eligible for the study must have voluntarily provided written informed consent using the IRB-approved ICF prior to screening procedures or enrollment in the study (i.e., before performing any protocol-dictated procedures that are not part of normal subject care). A copy of the signed and dated ICF document will be provided to the subject, and a copy will be maintained with the subject's CRFs, or in the study documentation. The original will be retained by the Investigator along with the CRFs. The ICF must be in a language that the subject can read and understand.

9.4. Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation. Reference values and/or normal ranges for the test results must be provided to Halozyme. Halozyme must be notified immediately in writing of any changes occurring in reference values during the course of the study.

All local and central laboratories used in the study must have, as necessary, the following.

- College of American Pathologists (CAP) accreditation, and/or
- Clinical Laboratory Improvement Amendments (CLIA) accreditation
- Listing of laboratory normal reference values (for all protocol required tests)
- Laboratory license
- Curriculum vitae of laboratory director may also be requested

9.5. Drug Accountability

Upon receipt of study drug(s), the Investigator, pharmacist or qualified designee is responsible for taking an inventory of the study drug(s). A record of this inventory must be kept and all usage of study drugs must be documented. All vials of study drug, both used and unused, must be retained as discussed in Section 6. The investigational drug is to be administered/ prescribed only by the Principal Investigator or appropriately qualified physician sub-investigators named on the Form FDA 1572. Under no circumstances will the Investigator(s) allow the investigational drug to be used other than as directed by this protocol. Although appropriate personnel may be designated to administer/dispense drug and maintain drug accountability records, the Principal Investigator is ultimately responsible for all drug accountability.

The Investigator or their designee must maintain accurate records accounting for the receipt of the investigational drug supplies and for the disposition of the drug. Documentation of the disposition of the drug should consist of a dosing record including the identification of the person to whom the drug is dosed, the quantity and the date of dosing, and any unused drug. This record is in addition to any drug accountability information recorded on the CRFs. At study end, unused drug will be reconciled with dosing records. All unused investigational drug shall be returned to Halozyme upon request unless otherwise instructed. A copy of the reconciled

drug inventory record will be provided to Halozyme or its designee, and the original will be retained at the site.

9.6. Protocol Compliance and Protocol Deviations

Except for a change that is intended to eliminate an apparent immediate hazard to a study subject, the protocol shall be conducted as specified. Any such change must be reported immediately to Halozyme and to the IRB.

From time to time, it is possible that Halozyme may prospectively authorize protocol deviations if the deviation is minor, and does not place subject at increased risk or the anticipated risk of potential benefit outweighs the anticipated risk of potential harm. All such protocol "waivers" must be provided *in advance* and *in writing* by Halozyme, and will be forwarded to the Investigator for filing with the subject's study records. The Investigator must notify the IRB of any and all protocol deviations according to the applicable IRB policy.

Written documentation of all major protocol deviations must be kept in the study center file and provided to Halozyme. Examples of possible major protocol deviations include, but are not limited to:

- failure to obtain/maintain approval for research
- failure to obtain required informed consent
- failure to collect, report or file AE reports
- performance of an unapproved study procedure
- performance of research at an unapproved location
- failure to file protocol modifications, and failure to adhere to an approved protocol

9.7. Protocol Amendments

If the protocol is revised, protocol amendments will be prepared and must be approved by Halozyme. All protocol amendments must be submitted to the IRB for review and approval prior to implementation. However, as discussed in Section 9.2, immediate implementation of a protocol amendment may be necessary if the nature of the amendment concerns the safety of subjects and is required to be implemented on an urgent basis to protect the safety of subjects. Any such immediate implementation of protocol amendments must be agreed to in advance and in writing by Halozyme. Hard copy documentation of IRB approval must be forwarded to Halozyme.

If an amendment significantly alters the study design, increases potential risk to the subject or otherwise affects statements in the ICF, the ICF must be revised accordingly and submitted to the IRB for review and approval (see Section 9.3). The approved ICF must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain informed consent from subjects already enrolled if they are potentially affected by the amendment and wish to continue participation.

9.8. Data Collection and Case Report Forms

In accordance with 21 CFR 312.62, a case report form (CRF) must be completed for each subject enrolled in the study. CRFs are an integral part of the study and subsequent reports. All data collected for each study subject will be recorded on CRFs provided or approved by Halozyme.

CRFs need not be completed by the Investigator, but all entries in CRFs are the responsibility of the Investigator and entry of CRF data must be made under the supervision of the Investigator. CRF completion may be formally delegated to other study personnel. However, the Sponsor (Halozyme) must be informed in writing of the name of such persons and the scope of their authority. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of all data reported in the CRFs and all required reports for each study subject. It is the obligation of the Investigator to review each page of the CRFs and to sign the designated and appropriate CRFs as the study's authority. The Investigator is also responsible for maintaining any source documentation related to the study, including, but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs, files or tapes.

CRFs must be completed legibly, preferably with **black ballpoint pen**. A correction should be made by striking through the incorrect entry with a single line and entering the correct information adjacent to the incorrect entry. The correction must be initialed and dated by the person making the correction. Erasure or the use of correction fluid or film is unacceptable. Entries to the CRFs should be made only in the spaces provided, and not in the margins. Information that cannot be accommodated by the spaces provided should be entered on the comments CRF page.

For each study subject, the completed CRFs must be promptly reviewed, and required pages signed and dated by the Investigator. The original copy of all CRFs will be reviewed and retrieved by the Study Monitor representing Halozyme. The Investigator must retain a copy of all CRFs.

9.9. Study Initiation, Monitoring and Closeout Visits and Reports

Representatives of Halozyme, in conjunction with Study Monitor(s) representing Halozyme, will perform a number of on-site visits to the study center. Prior to commencement of the study, representatives of Halozyme will visit the study center to ensure adequacy of facilities to conduct the protocol, and to discuss with the Investigator the general obligations regarding studies with investigational new drugs. This visit will be documented in a report. If the study center has participated in a clinical study in conjunction with Halozyme within one year, this Pre-Study Qualification visit may be waived.

Upon satisfactory receipt of all necessary documentation (including, but not limited to, an allowed IND, the Form FDA 1572, an executed Clinical Trials Agreement, and IRB approval of the protocol and informed consent form), Halozyme or its designee monitor(s) will arrange for all study material to be delivered to the study center and for the scheduling of a mutually convenient appointment for a Study Initiation visit. Subject entry must not begin until this initiation visit by Halozyme or its designee personnel has been made. At this meeting, all personnel expected to be involved in the conduct of the study should undergo an orientation to include review of the study protocol, instruction for CRF completion, and overall responsibilities

including those for drug accountability and study file maintenance. This visit will be documented in a report.

Throughout the course of the study, the Halozyme or its designee monitor(s) will make frequent contacts with the Investigator. Study Monitors representing Halozyme will visit study centers periodically throughout the study for Routine Monitoring visits. The Study Monitor will review CRFs to verify that they are accurate, complete and verifiable from source documents. They will also verify the rights and well-being of the study subjects are protected and that the study conduct is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirements. As part of the data review it is expected that source documents (e.g., hospital records, office records) will be made available for review by Halozyme or its designee monitor(s). The study and its monitors may also be similarly evaluated by auditors representing Halozyme. For these purposes, the Investigator will make CRFs, source documents and study files available when requested. A report will be generated for each monitoring visit.

At fulfillment of subject enrollment, each Investigator will be notified in writing by Halozyme. The study will be terminated and the study center closed when all completed original CRFs have been collected, all data discrepancies resolved, and drug accountability has been reconciled. A Closeout visit will be scheduled for study centers that enrolled at least one subject, during which Halozyme or its representative will review all informed consents, CRFs, drug accountability records, and other study-related documents. Halozyme or its representative will hold a final meeting with the Investigator and study staff to explain procedures for record retention, publication policy, site audit notification, and financial disclosure. A final letter to the site will record the events of this closeout visit. Study-closure activities will be documented in a report. It will be the responsibility of the Investigator to notify the IRB that the study has been completed (see Section 9.11).

The Sponsor (Halozyme) has the right to terminate the study for non-adherence to protocol, unavailability of the Investigator or his or her study staff for Halozyme or its designee monitoring personnel, or for administrative reasons, at any time. In that event, Halozyme will notify each Investigator in writing that the study is to be discontinued. The Investigator will comply with Halozyme's written instructions for study discontinuation, which will include the following:

- Date discontinuation will occur
- Rationale for discontinuation
- Instructions on how discontinuation is to be performed
- Instructions for subjects participating in the study
- Instructions for retention of study documents

In addition to monitoring by Halozyme or its designees, the study may be audited by representatives of the Food and Drug Administration (FDA), who will also be allowed access to study documents. The Investigator should immediately notify the Clinical Research Department at Halozyme of any proposed or scheduled audits with any regulatory authorities.

9.10. Study Documentation and Retention of Records

All records of this clinical study must be retained by the Investigator, including but not limited to, the following.

- Protocol and all protocol amendments
- All signed versions of the Statement of Investigator, Form FDA 1572
- All drug accountability records
- All IRB approvals, correspondence and reports
- Signed and dated informed consent forms for each subject
- Completed CRFs for each subject
- Copies of any other material distributed to subjects
- Any advertisements for this study
- The Investigator's final report to the IRB
- Source documents pertaining to the study, including, but not limited to, any operative reports, laboratory results, radiographic films, tracings, and computer discs, files or tapes

The period of time these documents must be maintained is governed by U.S. law and, when applicable, non-U.S., regulations. Some countries require these documents to be maintained for 15 years or longer. All records are to be retained by the Investigator for a minimum of fifteen (15) years after the FDA has approved the new drug application, or after the Sponsor (Halozyme) has notified the Investigator in writing that all investigations of the drug have been discontinued. However, because of international regulatory requirements, Halozyme may request retention for a longer period of time. Therefore, Halozyme or its designee will inform the Investigator when these documents may be destroyed. The Investigator must obtain written approval from the Halozyme prior to destruction of any records.

The Investigator must advise Halozyme in writing if the records are to be moved to a location other than the Investigator's archives. If the Investigator leaves the institution or study center, the records shall be transferred to an appropriate designee, at the study center, who assumes the responsibility for record retention. Notice of such transfer shall be documented in writing and provided to Halozyme.

In the event of accidental loss or destruction of any study records, the Investigator will immediately notify Halozyme in writing. Halozyme or its designee must be notified in writing at least 30 days prior to the intended date of disposal of any study records related to this protocol.

9.11. Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit a written report to Halozyme. This report may be a copy of the Investigator's end-of-study report to their IRB, which will include, but not be limited to; notification that the study has

concluded, the number of subjects enrolled/ treated, and the number of adverse and serious AEs that occurred during the study. The report to the IRB will be consistent with the applicable IRB regulations and time frames.

9.12. Financial Disclosure

Each investigator is required to provide financial disclosure statements or certifications to Halozyme prior to study initiation. In accordance with 21 CFR 54, Investigators and all subinvestigators are required to disclose all financial interests in the Sponsor (Halozyme) in order to permit complete and accurate certification statements in an application for marketing authorization. This includes compensation affected by the outcome of a clinical study, significant equity interest in the Sponsor (Halozyme), and proprietary interest in the tested product. The investigators must promptly update this information if any relevant changes occur during the course of the investigation and over the period of one year following completion of the investigation (21 CFR 312.64(d)).

9.13. Disclosure of Data and Publication

All information obtained as a result of this study or during the conduct of this study will be regarded as confidential. All unpublished information relating to this drug or to the operations of the Sponsor (Halozyme), including clinical indications, formula, methods of manufacture, and any other related scientific data provided to or developed by the Investigator, is confidential and shall remain the sole property of the Sponsor (Halozyme). The Investigator agrees to use the information for the purpose of carrying out this study and for no other purpose, unless prior written permission from the Sponsor (Halozyme) is obtained. The Sponsor has full ownership of the CRFs and database resulting from this study.

Disclosures (i.e., any release of information to any third party not noted herein) of any not previously known to be public information and/or results of the investigation for publication or by oral or poster presentation shall not be made earlier than 45 days after submission of the proposed material to the Sponsor (Halozyme) for inspection, unless the Sponsor consents to earlier disclosure. Any proposed publication must be submitted to the Sponsor at least 40 days prior to intended submission for publication. Publication or presentation of any study information, whether presented orally or in writing, may not be undertaken either during or after the study without Sponsor's (Halozyme's) express written approval. The Sponsor (Halozyme) may, for appropriate reason, withhold approval for publication or presentation. If the Investigator is to be listed as an author of a publication prepared by the Sponsor (Halozyme), the Investigator will be given 40 days for review of the manuscript prior to publication. The Investigator expressly agrees that no publication of interim, non-final, data will occur without the written authorization of the Sponsor (Halozyme). The Investigator will take appropriate cognizance of the Sponsor's (Halozyme's) suggestions before disclosure for publication or presentation consistent with protection of the Sponsor's right to its confidential data.

The Investigator agrees that if the Study is part of a multi-center study, any publication of Results by Investigator shall not be made prior to a first multi-center publication, unless the Sponsor has provided prior written consent to do so. The Investigator also agrees that publication by Investigator of interim, non-final Results from any study shall not be made prior

to publication of the Final Results, unless the Sponsor has provided prior written consent to do so.

The Investigator agrees that results from this study may be used by the Sponsor (Halozyme) for purposes of domestic and international new drug registration, for publication, and to inform medical and pharmaceutical professionals. Regulatory authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement.

10. REFERENCES

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11. APPENDICES

APPENDIX A. STUDY SCHEDULE OF EVENTS

Event	Screening	Baseline	Treatment					Follow-up
	Day -21 to Day -14	Day 1	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8
Signed and Dated Informed Consent	X							
Inclusion/Exclusion Criteria	X	X						
Medical History	X							
Concomitant Medications[a]	X	X	X	X	X	X	X	X
Complete Physical Exam	X							
Vital Signs (Body temperature, BP, HR, Resp. rate)	X[b]	X	X	X	X	X	X	X
CBC[c]	X							
Pregnancy Test, Serum or Urine	X	X						
Targeted Physical Exam[d]		X	X	X	X	X	X	X
Physical Examination of the Administration Site[e]		X	X	X	X	X	X	X
Nickel Sulfate and Vehicle Control Patch Placement and Interpretation	X	X						
Dose Administration		X	X	X	X	X	X	
Test Area Assessment			X	X	X	X	X	X
Trans-epidermal Water Loss Assessment[f]		X	X	X	X			

Event	Screening	Baseline	Treatment					Follow-up
	Day -21 to Day -14	Day 1	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14
	VISIT 1	VISIT 2	VISIT 3	VISIT 4	VISIT 5	VISIT 6	VISIT 7	VISIT 8
Digital Photographs of the Allergen Test Sites[f]		X	X	X	X			
Chromometer Images of the Allergen Test Sites[f]		X	X	X	X			
AE/Toxicity Assessment		X	X	X	X	X	X	X

[a] Con meds within 21 days prior to dosing and through the follow-up assessment on Visit 8/Day 14 to be recorded.
[b] Include body temperature at screening visit.
[c] WBC (with differential), Hgb, Hct, and platelets.
[d] Includes positives on a review of systems and follow-up of findings from previous physical examinations.
[e] Conducted immediately before patch administration, after dose administration (Treatment Regimen 2), immediately after patch removal, and prior to and 10 minutes post-dose on Study Days 3-7, and Day 14.
[f] To be conducted at Baseline and on Days 3-5 and includes subject questionnaire (Days 3-5).

APPENDIX B. INTERNATIONAL CONTACT DERMATITIS RESEARCH GROUP [ICDRG] SCORING SCALE[11]

International Contact Dermatitis Research Group Scoring Scale

Score	Interpretation
?	Doubtful reaction; faint macular erythema only
+	Weak (nonvesicular) positive reaction; erythema infiltration, possibly papules
++	Strong (vesicular) positive reaction; erythema, infiltration, papules, vesicles
+++	Extreme positive reaction; bullous reaction
-	Negative reaction
IR	Irritant reaction of different types

APPENDIX C. NICKEL SULFATE ALLERGY SYSTEM

Application for Nickel Sulfate Concentration Determination:

Preparing Patch:

Place a filter paper disc in the chamber and moisten thoroughly with the 1%, 2.5% or 5% nickel sulfate solution.

Applying Patch:

1. Skin should be clean, healthy, and free of ointments, lotions, powders, acne, dermatitis, scars, hair or any other condition that might interfere with the application of the chamber or interpretation of the results.
2. The subject should stand or sit in a relaxed position. Apply prepared patches to the back.
3. Affix tape to the skin at the lower end and slowly roll patches up the back, pushing out air. Gently press patch to skin to ensure an even distribution of allergens. Rub the tape gently but firmly to ensure good adherence.
4. Mark the four corners of each unit with Chemotechnique Skin Markers to indicate each unit's location on the subject's skin.
5. Subjects should refrain from exposing patch tests to excess moisture or sweat and should return for patch test removal in 48 hours.
6. Record in the source documentation the location of the patch and the nickel sulfate concentration for each location.

Removing Patch:

After 48 hours, remove the patch. The initial visual patch imprint on the patient's back indicates excellent occlusion.

Reading the Results:

1. Allow about 20 to 30 minutes for the transient skin irritation and visual patch imprints to subside before interpreting the test results.
2. Reading will be done at approximately48 hours post application.
3. Use the Reading Plate to facilitate the reading.
4. Use the International Contact Dermatitis Research Group Scoring Scale to interpret the test results (Appendix B).

APPENDIX D. PHOTOGRAPHIC PROCEDURE

Serial Photography for Contact Dermatitis

Locations: ID card/color card view: 2 each Close-up view of target area(s): 2 each Anatomical location view of target area(s): 2 each

Digital Format Photography Equipment: Media: SD Memory card, 1GB

Camera: Nikon D80 (10.2MP) Lens: Nikkor 60mm f2.8 Flash: Canfield TwinFlash system Other: Canfield MM scale arm attachment Blue deluxe felt backdrop (3'x8') Color card/Patient ID card holder

Digital Format Photographic Considerations: Each memory card will contain one patient photo session.

Procedure:

In these clinical photographs, for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (jewelry, clothing, furniture, walls, etc.) is to be eliminated from the fields to be photographed, from the baseline through the final photographs. The necessity of good end-of-study photos should be stressed to the patients to ensure their cooperation. Lighting, framing, exposure and reproduction ratios must be held constant. In the end, the pictures should read like a time-lapse movie.

1. The supplied equipment is to be used exclusively for this study. Modifications, adjustments or repairs of the camera equipment are not to be undertaken without the expressed instruction of Canfield Scientific, Inc.
2. After obtaining informed consent, the patients are prepped for photography. All jewelry, makeup and clothing are to be removed from the photographic field prior to photography. Target area(s) are identified for photos. The supplied standardized blue deluxe felt background is to be used for the photographs. Do not use folded or crimped material.
3. Magnifications for digital camera: A standardized reproduction ratio (35MM film equivalent) of 1:3 (red index on lens focusing barrel) is used for the target area close-up views. Focusing at 1:3 is accomplished with the use of the mm scale arm attachment dictating distance. A standardized reproduction ratio of 1:9 (green index on lens focusing barrel) is used for the target area anatomical views. Focusing at 1:9 is accomplished by moving the camera/lens close to/away from the target area until it is in focus.
4. Apertures for digital camera: Each and every target area close-up view is taken at f/22. Each and every target area anatomical location view is taken at f/16.
5. SD is the media format used to capture images. If there is any doubt as to the correctness of technique or data, re-shoots are strongly urged.

6. Each SD memory card at every photographic session includes an exposure series of:
    a. Two exposures of patient's ID card which includes the following legible information in black indelible ink: Protocol No. Date Investigator Number Visit Week Number Patient's Initials Patient's ID Number Photographer's Initials Color card
    b. Two exposures of close-up view of target area(s)
    c. Two exposures of anatomical location view of target area(s)
7. Upon completion of the photographic session, the contents of the SD memory card are uploaded to the Canfield Clinical Website once a patient's photographic session has been recorded on it. A secure, validated, compliant web server set up at Canfield is used for this secure transfer of study images by study sites. Images are transferred the day recorded. Remote access to all images by the sponsor is also provided. Only approved individuals by sponsor have access to the website.
8. Upon a successful upload of all images contained on the SD memory card, the memory card's images are deleted and the memory card re-used for the next photographic session. These memory cards are reserved for use on this project only. Any doubt as to the correctness of technique or data warrants a re-shoot then and there.
9. All images are monitored for technical adherence according to Canfield's internal SOPs. The study site is contacted if errors or deviation from photographic guidelines are observed. All communication to the study site relating to the photography is the responsibility of Canfield.
10. All supplied photographic equipment and photographic originals remain the property of the sponsor. One set of photography result report forms for all photographic time-points is supplied for the Investigators' study records.
11. Questions or problems regarding the photographic portion of this study protocol should be directed to the respective Canfield Project Manager assigned to the study.

Canfield Scientific, Inc. 253 Passaic Ave. Fairfield, NJ 07004 Telephone: [redacted] Toll-Free: [redacted] Facsimile: [redacted] E-mail: [redacted]

APPENDIX E. ABBREVIATIONS

ABBREVIATION	TERM
AE	Adverse event
BP	Blood pressure
BUN	Blood urea nitrogen
ºC	Degrees Celsius
CAP	College of American Pathologists
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DESI	Drug Efficacy Study Implementation
EC	Ethics Committee
FDA	U.S. Food and Drug Administration
GCP	Good Clinical Practice
Hct	Hematocrit
Hgb	Hemoglobin
HIPAA	Health Insurance Portability Act of 1996
HIV	Human immunodeficiency virus
HR	Heart rate
IB	Investigator's Brochure
ICDRG	International Contact Dermatitis Research Group
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Intradermally
IND	Investigational New Drug
IRB	Institutional Review Board
NCI	National Cancer Institute
PHI	Personal Health Information
RH	Relative humidity
rHuPH20	Recombinant human hyaluronidase enzyme PH20
SAE	Serious adverse event

ABBREVIATION	TERM
SC	Subcutaneous
SD	Secure digital
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamate pyruvate transaminase
SOPs	Standard operating procedures
TEWL	Trans-epidermal water loss
USP	United States Pharmacopoeia
VAS	Visual analog scale
WBC	White blood cells