NCT# 00928447

Statistical Analysis Plan

Halozyme Therapeutics, Inc.

Protocol Number: HALO-114-201

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

Protocol Version 1.0 (27May2008)

Sponsor: **Halozyme Therapeutics, Inc. (Halozyme)**
11388 Sorrento Valley Road
San Diego, California 92121

Prepared by: [redacted]
Synteract, Inc.
5759 Fleet Street, Suite 100
Carlsbad, CA 92008

Version: **Final**

Date of Creation: **28 July 2009**

Last Updated: **9 October 2009**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS **3**

DEFINITIONS **4**

1. INTRODUCTION **5**

2. OBJECTIVES **5**

3. STUDY OVERVIEW **5**

TREATMENT REGIMEN 1 (TR1-1 – TR1-4): 6
TREATMENT REGIMEN 2 (TR2-5 – TR2-8): 7

4. GENERAL ANALYSIS CONSIDERATIONS **7**

5. ANALYSIS POPULATIONS **8**

6. SUBJECT DISPOSITION **9**

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS **9**

8. EFFICACY ANALYSES **9**

8.1 PRIMARY VARIABLES 9
8.2 SECONDARY VARIABLES 10
8.3 DESCRIPTIVE PARAMETERS 10
8.4 BASELINE VALUES 10
8.5 HANDLING MISSING DATA 11
8.6 INTERIM ANALYSES 11

9. STUDY ANALYSIS **11**

9.1 STATISTICAL ANALYSES 11
9.2 EXPLORATORY ANALYSES 12

10. SAFETY ANALYSES **12**

10.1 ADVERSE EVENTS 12
10.2 VITAL SIGNS 13
10.3 PHYSICAL EXAMINATION 13
10.4 PRIOR AND CONCOMITANT MEDICATIONS 13

11. SAMPLE SIZE CALCULATION **14**

APPENDIX A: LIST OF TABLES, LISTINGS AND FIGURES **15**

APPENDIX B: TABLE LAYOUTS **18**

APPENDIX C: LISTING LAYOUTS **34**

APPENDIX D: FIGURE LAYOUTS **61**

LIST OF ABBREVIATIONS

AEs	Adverse Events
ATC	Anatomical/Therapeutic/Chemical
BP	Blood Pressure
CBC	Complete Blood Count
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
ET	Early Termination
ICDRG	International Contact Dermatitis Research Group
ID	Intradermally
ITT	Intent-to-Treat
MedDRA	Medical Dictionary for Regulatory Activities
RBC	Red Blood Cell Count
rHuPH20	Recombinant Human Hyaluronidase enzyme PH20
RTF	Rich Text Format
SAE	Serious Adverse Event
SD	Standard Deviation
TEWL	Trans-Epidermal Water Loss
TEAE	Treatment-Emergent Adverse Event
WBC	White Blood Cells
WHO	World Health Organization

DEFINITIONS

Adverse Event	An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment.
Injection Type	rHuPH20 or Placebo
Pre-Treatment-emergent AE	AEs 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.
Serious AE	An AE occurring at any dose that: results in death; is a life-threatening event; requires in-subject hospitalization or prolongation of an existing hospitalization; results in a persistent or significant disability/incapacity; results in a congenital anomaly/birth defect in the offspring of a subject who received study drug, or is any other important medical event.
Treatment-emergent AE	AEs with an onset time during or after the initial administration of study drug.
Treatment Regimens	Treatment Regimen 1 and Treatment Regimen 2

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Halozyme Therapeutics, Inc. Protocol HALO-114-201 [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]. The purpose of this plan is to provide specific guidelines from which the analysis will proceed. Any deviations from these guidelines will be documented in the clinical study report (CSR).

2. OBJECTIVES

The primary objectives of the study are:

- 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 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

Secondary objectives include:

- 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 4, 5, 6, 7 and 14.
- Safety and tolerability of the injection based on AEs, physical examinations, and vital signs

Descriptive-Only parameters include:

- Chromometer readings of the allergen test sites on Day 1, Day 3 (48 hrs), Day 4 (72 hrs) and Day 5 (96 hrs) after the placement of the patches
- TEWL (Trans-epidermal water loss) assessment on Day 1, Day 3 (48 hrs), Day 4 (72 hrs) and Day 5 (96 hrs) after the placement of the patches

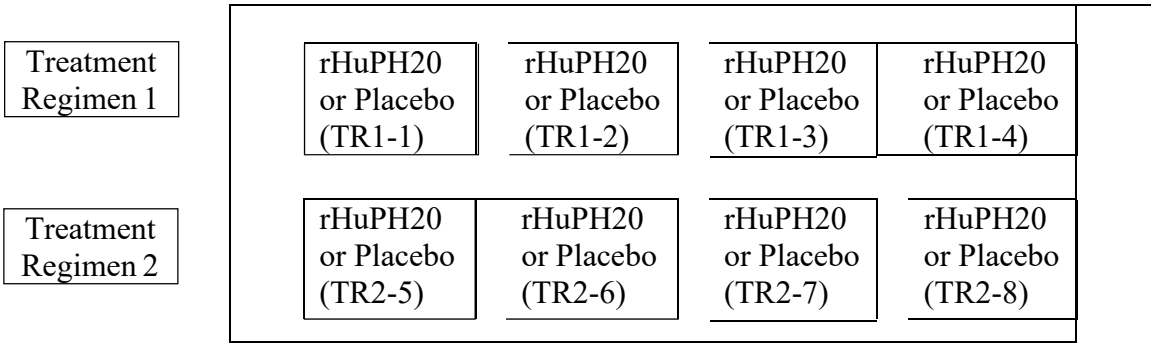
3. STUDY OVERVIEW

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. A maximum of 30 subjects may be enrolled to ensure that at least approximately 20 evaluable subjects complete the study. This study will be conducted at a dermatology unit.

There are two treatment regimens (Treatment Regimens 1 and 2) in this study, which will run in parallel. Within each regimen, four nickel sulfate patches will be used. The four patch areas will be randomized to rHuPH20 or placebo for each subject with 1:1 ratio. The randomization for Treatment Regimen 1 will be independent of the randomization for Treatment Regimen 2.

Figure 1: Study Treatment Arm Randomization



Subjects with a known history of contact allergy to nickel will be recruited. During the screening period, subjects will be tested to confirm the presence of cutaneous nickel sensitivity using 1, 2.5 and 5% nickel sulfate patches. The concentration of nickel sulfate for each subject that causes no greater than a ++ cutaneous reaction using the International Contact Dermatitis Research Group (ICDRG) scoring scale will be the concentration administered on Day 1. Once the concentration is determined for the subject, the patches in Treatment Regimen 1 and Treatment Regimen 2 will use the same concentration patches.

Treatment Regimen 1 (TR1-1 – TR1-4):

This regimen will assess the treatment of contact allergy to nickel: On Day 1, 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 (TR2-5 – TR2-8):

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.

For a given subject, the anticipated duration of time on study is up to 35 days, which include Visit 1 (screening, within 21 days prior to receiving study drug), Visit 2 (Day 1), Visit 3 (Day 3), Visits 4 – 7 (Day 4 – 7) and Visit 8 (Day 14).

4. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, figures, and data listings. Descriptive statistics will be used to summarize all efficacy variables. No formal statistical comparisons between treatments are planned. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. Categorical variables will be summarized by counts and by percentage of subjects in corresponding categories.

Individual subject data obtained from the case report forms (CRFs), local lab and any derived data will be presented by subject in data listings.

The analyses described in this plan are considered a priori, in that they have been defined prior to database lock and prior to breaking the blind. Any analyses performed subsequent to breaking the blind will be considered post-hoc. Post-hoc analyses will be identified in the CSR.

All analyses and tabulations will be performed using SAS® Version 9.1 on a PC platform. Tables and listings will be presented in RTF format. Figures will be presented in PDF format. Upon completion, all SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

5. ANALYSIS POPULATIONS

The ITT population will include all enrolled subjects (all subjects who got a subject identification number assigned at the time of study enrollment in anticipation of receiving a dose of study drug).

The Safety population will include all subjects who receive at least one dose of study drug.

The Evaluable population will include 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 subject is considered to have undergone sufficient assessments to allow an assessment of the tolerability of the administration if the subject has at least one ICDRG score reported on Day 4 or later.

A subject is considered to have prematurely discontinued the administration due to toxicity if the subject has Adverse Event checked as the reason for not completing the study on the Study Completion/Termination CRF page, and has Drug Withdrawn as the action taken with study drug checked on the Adverse Event CRF page.

Efficacy analyses will be run on the Evaluable population and the ITT (Intent-to-Treat) population. Analyses run on the Evaluable population will be considered the primary analyses.

Safety analyses will be run on the Safety population.

6. SUBJECT DISPOSITION

Subject disposition information will be summarized for all subjects. Summaries will include: the number of subjects in each analysis (ITT, Safety, Evaluable) population, the number of subjects replaced, the number of subjects completing the study and the primary reason for discontinuation.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics variables include: age, sex, ethnicity, race and the concentration of nickel sulfate assigned. Other baseline characteristics include: medical history and hematology and CBC with differential, including incidence rates of clinically significant abnormalities at screening. Demographic and baseline characteristics will be summarized for the Safety, ITT and Evaluable analysis populations.

8. EFFICACY ANALYSES

Efficacy analyses will be carried out on both the Evaluable and the ITT analysis populations.

8.1 Primary Variables

The primary efficacy endpoint will be based on the International Contact Dermatitis Research Group (ICDRG) Scoring Scale. Using the ICDRG Scoring Scale, each score will be assigned a Sponsor-defined “grade”. Scores with stronger reactions will be assigned grades with higher values with a maximum grade of 3; scores with weaker reactions will receive lower values with a minimum grade of 0. Grade assignments based on the ICDRG Scoring Scale are shown in the table below.

International Contact Dermatitis Research Group (ICDRG) Scoring Scale

Grade	Score	Interpretation
0	-	Negative reaction
1/2	?	Doubtful reaction; faint macular erythema only
1	+	Weak (nonvesicular) positive reaction; erythema, infiltration, papules, vesicles
2	++	Strong (vesicular) positive reaction; erythema, infiltration, papules, vesicles
3	+++	Extreme positive reaction; bullous reaction
NA	IR	Irritant reaction of different types

Treatment effect of rHuPH20 or placebo control injection on the exposure to topical nickel allergen will be assessed using ICDRG grades for Treatment Regimens 1 and 2 at Day 3 through Day 7 and Day 14.

Regimen 2 only: For each subject, the day of maximal ICDRG score will be determined for each injection type (rHuPH20 and Placebo). The maximal ICDRG score will be the highest score reported for each subject. If the maximal ICDRG score for a particular subject is reported more than one time, the first instance will be used to determine the day when the maximal ICDRG score was reached.

8.2 Secondary Variables

Analyses of the secondary endpoints will be based on the grades shown in ICDRG table in Section 8.1.

For Treatment Regimen 1 and 2, proportion of subjects that have a ≥ 1 grade reduction of the cutaneous reaction to nickel sulfate in at least one patch region after treatment.

For Treatment Regimen 2, proportion of subjects that have a ≥ 1 grade reduction of the cutaneous reaction to nickel sulfate in at least one patch region at 48 hours (Day 3) will be assessed.

8.3 Descriptive Parameters

TEWL (Trans-epidermal water loss) measurements and Chromometer readings will be carried out at Day 1, Day 3, Day 4 and Day 5. On each day, TEWL (Trans-epidermal water loss) measurements and Chromometer readings will be collected for each treatment region.

8.4 Baseline Values

For analyses based on grades, each treatment region will be assigned its own baseline value. The baseline values for regions under Treatment Regimen 1 and 2 will be the values collected at Day 3.

The baseline values for TEWL measurements and Chromometer readings will be the assessments collected on Day 1.

8.5 Handling Missing Data

No missing values will be imputed.

8.6 Interim Analyses

No interim analyses are planned for this study.

9. STUDY ANALYSIS

The hypothesis for this study is that 1) pre-treatment or 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 is that rHuPH20 will not be different than what will be observed from placebo control.

Figures, listings and descriptive statistics will be used to summarize all efficacy variables. No formal statistical comparisons between treatments are planned.

9.1 Statistical Analyses

The primary analysis is the pair-wise intra-subject comparison of endpoint parameters for the injections with and without rHuPH20. The secondary analysis covers safety and other endpoint parameters (see Section 10).

ICDRG scores will be shown for Treatment Regimen 1 and Treatment Regimen 2 by injection types (rHuPH20 or Placebo) at Baseline, Day 4, Day 5, Day 6, Day 7 and Day 14. ICDRG scores will be reported by subject using figures (Figure 1) and listings (Listing 8).

A qualitative medical review of the ICDRG scores will be used to investigate:

- Possible treatment effect of rHuPH20 or placebo control injection on the exposure to topical nickel allergen.
- Proportion of subjects that have a ≥ 1 grade reduction in at least one patch region.

At the conclusion of the study, findings from the medical review will be summarized in the clinical study report.

For Treatment Regimen 2, the day of maximal ICDRG Score will be used to assess the possible effect each injection type has on the onset of reaction to topical nickel allergen. The day of maximal ICDRG Score will be summarized for each injection type using counts and percentages (Table 6.1/6.2). Possible days of maximal ICDRG Score include

the following: Day 4, Day 5, Day 6, Day 7, and Day 14. If the maximal ICDRG Score for an injection type occurred prior to treatment, the subject will be reported as never having had an ICDRG Score more severe than Day 3 for summary purposes.

9.2 Exploratory Analyses

TEWL (Trans-epidermal water loss) assessments at Baseline (Day 1), Day 3, Day 4 and Day 5 will be summarized for Treatment Regimen 1 and Treatment Regimen 2 by injections type (rHuPH20 or Placebo). Summaries of TEWL assessments will be generated by subject using figures (Figure 2) and listings (Listing 9). A review of the TEWL assessments summaries will be used to investigate possible treatment effect of rHuPH20 or placebo control injection on the exposure to topical nickel allergen.

Analysis of Chromometer readings will be carried in the same manner as the analysis for TEWL assessments (Figure 3, Listing 11). All Chromometers readings reported will be presented in listings; however, only reported "a" scale readings will be considered for figures.

10. SAFETY ANALYSES

All subjects who received study drug will be included in the safety analyses, analyzed according to the study treatment actually received.

10.1 Adverse Events

All adverse event summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that occurred after dosing and those existing AEs that worsened during the study. Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using the MedDRA dictionary (version 12.0).

Each adverse event summary will be displayed for the Safety population. Summaries that are displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class. Summaries of the following types will be presented:

- Subject incidence of TEAEs and total number of unique TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and highest severity. At each level of subject summarization a subject is classified according to the highest severity if the subject reported one or more events. A

missing column will be added to the summary table if any TEAEs are reported with missing severity.

- Subject incidence of TEAEs by MedDRA system organ class, preferred term, and closest relationship to study drug (Related/Not Related). At each level of subject summarization a subject is classified according to the closest relationship if the subject reported one or more events. AEs with a missing relationship will be considered related for this summary.
- Subject incidence of serious TEAEs and total number of unique serious TEAEs by MedDRA system organ class and preferred term.
- Subject incidence of TEAEs and total number of unique serious TEAEs leading to discontinuation of study drug or premature withdrawal from study.
- Subject incidence of TEAEs reported after physical examination of injection site and safety review on Day 1 (for Treatment Regimen 2 only), Day 3 through Day 7 and Day 14 will be presented by injection type.

10.2 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). Vital signs will be recorded one time at Screening; pre- and post injection vital sign results will be collected on the following days: Day 1, Day 3, Day 4, Day 5, Day 6, Day 7, Day 14.

Vital signs will be summarized using descriptive statistics at each visit time point. Changes from baseline will also be summarized. Baseline is defined as the pre-dose result for the visit under consideration.

10.3 Physical Examination

Physical examination results will be summarized with shift tables comparing baseline to the most abnormal post baseline assessment. Possible assessments for each body system include: Normal/Return to Normal and Abnormal.

Baseline will be defined as the last non-missing result recorded before injection.

10.4 Prior and Concomitant Medications

Verbatim terms on case report forms will be mapped to Anatomical/Therapeutic/Chemical (ATC) Level 4 categories and Drug Reference Names using the World Health Organization (WHO) dictionary (March 1, 2009).

Prior medications are those medications taken within 21 days prior to the initial dose of study drug. Concomitant medications are those medications taken after the initial dose of study drug. Prior and concomitant medications will be summarized for each treatment by WHO ATC class and medication name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC category and medication. At each level of subject summarization, a subject is counted once if he/she reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and medication within each ATC class.

11. SAMPLE SIZE CALCULATION

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.

APPENDIX A: LIST OF TABLES, LISTINGS AND FIGURES

List of Tables

Table Number	Table Description
1	Subject Disposition
2	Demographic and Baseline Characteristics
3	Abnormal Medical History
4	Hematology and CBC with Differential at Screening
5	Incidence of Clinically Significant Laboratory Abnormalities at Screening
6	Day of Maximal ICDRG Score
7	Adverse Events by System Organ Class (Safety Population)
8	Adverse Events by System Organ Class and Severity [1] (Safety Population)
9	Adverse Events by System Organ Class and Relationship to Study Drug [1] (Safety Population)
10	Serious Adverse Events by System Organ Class (Safety Population)
11	Adverse Events Leading to Discontinuation of Study Drug or Premature Withdrawal of From Study
12	Adverse Events by System Organ Class and Injection Type (Safety Population)
13	Vital Signs (Safety Population)
14	Physical Examination (Safety Population)
15	Concomitant Medications (Safety Population)

List of Data Listings

Listing Number	Listing Description	CRF Plate(s)
1	Subject Disposition	Derived
2	Inclusion/Exclusion Criteria	2,3,4
3	Demographics	1
4	Medical History	5
5	Hematology and CBC with Differential	8
6	Lab Normal - Hematology	350
7	Pregnancy Test	9
8	ICDRG Score	13,15
9	TEWL (Trans-Epidermal Water Loss) Assessment	17
10	Digital Photographs	17
11	Chromometer	18
12	Subject Diary	19
13	Screening Nickel Sulfate and Vehicle Control Patches	11
14	Study Drug Administration – Treatment Regimen 1	12,13,14
15	Study Drug Administration – Treatment Regimen 2	15,16
16	Adverse Events	97
17	Serious Adverse Events	97
18	Vital Signs	7
19	Physical Examination	6,10
20	Comments	96
21	Prior and Concomitant Medications	98
22	Deaths	101
23	Subject Visit	Derived

List of Figures

Figure Number	Figure Description
1	ICDRG Scores by Day
2	Individual TEWL Scores by Day and Injection Site
3	Individual a-Scale Chromometer Baseline Corrected Scores by Day and Injection Site

APPENDIX B: TABLE LAYOUTS

Table 1
Subject Disposition
All Subjects

	Total
ITT Population[1]	N
Safety Population [2]	n (%)
Evaluable Population [3]	n (%)
Number of Subjects Replaced [4]	n (%)
Completed Study	
Yes	n (%)
No	n (%)
Primary Reason for Discontinuation	
Protocol Violation	n (%)
Lost to Follow-up	n (%)
Adverse Event	n (%)
Non-compliance	n (%)
Subject Decision	n (%)
Investigator Decision	n (%)
Other	n (%)

[1] Intent to Treat (ITT): Enrolled subjects who signed informed consent.
[2] Received at least one dose of study drug.
[3] 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.
[4] Enrolled subjects but not meeting the criteria of evaluability.
path\t_program.sas date time

Table 2
Demographic and Baseline Characteristics
All Subjects

	ITT (N=)	Safety (N=)	Evaluable (N=)
Age (years) [1]			
N	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
Sex			
Male	n (%)	n (%)	n (%)
Female	n (%)	n (%)	n (%)
Ethnicity			
Hispanic or Latino	n (%)	n (%)	n (%)
Not Hispanic or Latino	n (%)	n (%)	n (%)
Race			
American Indian or Alaska Native	n (%)	n (%)	n (%)
Asian	n (%)	n (%)	n (%)
Black or African American	n (%)	n (%)	n (%)
Native Hawaiian or Other Pacific Islander	n (%)	n (%)	n (%)
White	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)
More than one race marked	n (%)	n (%)	n (%)
Concentration of nickel sulfate (%)			
1	n (%)	n (%)	n (%)
2.5	n (%)	n (%)	n (%)
5	n (%)	n (%)	n (%)

[1] Age at the date of informed consent signed.
path\t_program.sas date time

Table
Abnormal Medical History
All Subjects

Body System	ITT (N=)	Safety (N=)	Evaluable (N=)
Respiratory	n (%)	n (%)	n (%)
Cardiovascular	n (%)	n (%)	n (%)
Gastrointestinal	n (%)	n (%)	n (%)
Hepatic	n (%)	n (%)	n (%)
Endocrine/Metabolic	n (%)	n (%)	n (%)
Central and Peripheral Nervous System	n (%)	n (%)	n (%)
Hematopoietic/Lymphatic	n (%)	n (%)	n (%)
Dermatological	n (%)	n (%)	n (%)
Musculoskeletal	n (%)	n (%)	n (%)
Genitourinary/Reproductive	n (%)	n (%)	n (%)
Psychiatric	n (%)	n (%)	n (%)
Alcohol/Drug Abuse	n (%)	n (%)	n (%)
Drug Allergy	n (%)	n (%)	n (%)
Non-Drug Allergy	n (%)	n (%)	n (%)
HEENT	n (%)	n (%)	n (%)
Other	n (%)	n (%)	n (%)

path\t_program.sas date time

Table
Hematology and CBC with Differential at Screening
All Subjects

Laboratory Parameter	ITT (N=)	Safety (N=)	Evaluable (N=)
WBC (X 1000/uL)			
N	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
RBC (X Mil/uL)			
N	n	n	n
Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Median	xx.x	xx.x	xx.x
Min, Max	xx, xx	xx, xx	xx, xx
..			

path\t_program.sas date time

Programmer note: Table will include the following hematology parameters: Hemoglobin (g/dL), Hematocrit (%), Platelets (X 1000/uL), Neutrophils (segs) (%), Neutrophils (bands) (%), Lymphocytes (%), Monocytes (%), Eosinophils (%) and Basophils (%).

Table
Incidence of Clinically Significant Laboratory Abnormalities at Screening
All Subjects

Any Clinically Significant Abnormalities?	ITT (N=)	Safety (N=)	Evaluable (N=)
WBC	n (%)	n (%)	n (%)
RBC	n (%)	n (%)	n (%)
Hemoglobin	n (%)	n (%)	n (%)
Hematocrit	n (%)	n (%)	n (%)
Platelets	n (%)	n (%)	n (%)
Neutrophils (segs)	n (%)	n (%)	n (%)
Neutrophils (bands)	n (%)	n (%)	n (%)
Lymphocytes	n (%)	n (%)	n (%)
Monocytes	n (%)	n (%)	n (%)
Eosinophils	n (%)	n (%)	n (%)
Basophils	n (%)	n (%)	n (%)

path\t_program.sas date time

Table 6.1
Day of Maximal ICDRG Score
Evaluable Population

	Treatment Regimen 2 (N=)	
Day of ICDRG Maximal Severity Score	rHuPH20	Placebo
Never had an ICDRG Score More Severe than Day 3	n (%)	n (%)
Day 4	n (%)	n (%)
Day 5	n (%)	n (%)
Day 6	n (%)	n (%)
Day 7	n (%)	n (%)
Day 14	n (%)	n (%)

Note: For both injection types (rHuPH20 and Placebo), each subject will contribute one result based on the single most severe patch assessment reported.
path\t_program.sas date time

Programmer Note: Table 6.2 will contain the same information for the ITT population.

Table
Treatment Emergent Adverse Events by System Organ Class
Safety Population

System Organ Class / Preferred Term	Safety Population (N=) Number of Subjects [1]	Number of Events
Subjects Reporting at Least One Adverse Event	n (%)	n
System Organ Class 1	n (%)	n
Preferred Term 1	n (%)	n
Preferred Term 2	n (%)	n
.		
.		
System Organ Class 2	n (%)	n
Preferred Term 1	n (%)	n
Preferred Term 2	n (%)	n

[1] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event are counted only once.
path\t_program.sas date time

Table
Treatment Emergent Adverse Events by System Organ Class and Severity
Safety Population

System Organ Class / Preferred Term [1]	Safety Population (N=)				
	Mild	Moderate	Severe	Life Threatening	Fatal
Subjects Reporting at Least One Adverse Event	n (%)	n (%)	n (%)	n (%)	n (%)
System Organ Class 1	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)
.					
.					
System Organ Class 2	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 1	n (%)	n (%)	n (%)	n (%)	n (%)
Preferred Term 2	n (%)	n (%)	n (%)	n (%)	n (%)
.					
.					

[1] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event are counted only once using the highest severity.
path\t_program.sas date time

Table
Treatment Emergent Adverse Events by System Organ Class and Relationship to Study Drug
Safety Population

	Safety Population (N=)	
System Organ Class / Preferred Term [1]	Related	Not Related
Subjects Reporting at Least One Adverse Event	n (%)	n (%)
System Organ Class 1	n (%)	n (%)
Preferred Term 1	n (%)	n (%)
Preferred Term 2	n (%)	n (%)
.		
.		
System Organ Class 2	n (%)	n (%)
Preferred Term 1	n (%)	n (%)
Preferred Term 2	n (%)	n (%)

[1] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event are counted only once using the closest relationship to study drug.
path\t_program.sas date time

Table 28
Treatment Emergent Serious Adverse Events by System Organ Class
Safety Population

System Organ Class / Preferred Term	Safety Population (N=) Number of Subjects [1]	Number of Events
Subjects Reporting at Least One Serious Adverse Event	n (%)	n
System Organ Class 1	n (%)	n
Preferred Term 1	n (%)	n
Preferred Term 2	n (%)	n
.		
.		
System Organ Class 2	n (%)	n
Preferred Term 1	n (%)	n
Preferred Term 2	n (%)	n

[1] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one serious adverse event are counted only once.
path\t_program.sas date time

Table 29
Treatment Emergent Adverse Events Leading to Discontinuation of Study Drug or Premature Withdrawal of From Study
Safety Population

	Safety Population (N=)	
System Organ Class / Preferred Term	Number of Subjects [1]	Number of Events
Subjects Reporting at Least One Serious Adverse Event	n (%)	n
System Organ Class 1	n (%)	n
Preferred Term 1	n (%)	n
Preferred Term 2	n (%)	n
.		
.		
System Organ Class 2	n (%)	n
Preferred Term 1	n (%)	n
Preferred Term 2	n (%)	n

[1] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event are counted only once.
path\t_program.sas date time

Table 12
Treatment Emergent Adverse Events by System Organ Class and Injection Type
Safety Population

	Treatment Regimen 1 (N=)				Treatment Regimen 2 (N=)			
	rHuPH20		Placebo		rHuPH20		Placebo	
System Organ Class / Preferred Term	Number of Subjects [1]	Number of Events	Number of Subjects [1]	Number of Events	Number of Subjects [1]	Number of Events	Number of Subjects [1]	Number of Events
Subjects Reporting at Least One Serious Adverse Event	n (%)	n	n (%)	n	n (%)	n	n (%)	n
System Organ Class 1	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Preferred Term 1	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Preferred Term 2	n (%)	n	n (%)	n	n (%)	n	n (%)	n
.								
.								
System Organ Class 2	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Preferred Term 1	n (%)	n	n (%)	n	n (%)	n	n (%)	n
Preferred Term 2	n (%)	n	n (%)	n	n (%)	n	n (%)	n

Note: For this summary, only Adverse Events reported during the physical examinations/safety reviews at Day 1 (TR 2 only), Day 3 through Day 7, and Day 14 are considered.
[1] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one adverse event are counted only once.
path\t_program.sas date time

Table 31
Vital Signs
Safety Population

Vital Sign	Time Point	Safety Population (N=)
Systolic BP (mmHg)	Screening	
	N	n
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
	Day 1 Pre-Injection	
	N	n
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
	Day 1 Post-Injection	
	N	n
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
	Day 1 Change from Baseline [1]	
	N	n
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
	…	
Diastolic BP (mmHg)		

[1] Baseline is defined as pre-injection assessment for the visit under consideration.
path\t_program.sas date time

Programmer note: Table will include the following vital signs: systolic BP (mmHg), diastolic BP (mmHg),Heart Rate (bpm) and Respiration (breaths/min). for each vital sign, time points will include: Screening, Day 1 Pre-Injection, Day 1 Post-Injection, Day 1 Change from Baseline, Day 3 Pre-Injection, Day 3 Post-Injection, Day 3 Change from Baseline, Day 4 Pre-Injection, Day 4 Post-Injection, Day 4 Change from Baseline, Day 5 Pre-Injection, Day 5 Post-Injection, Day 5 Change from Baseline, Day 6 Pre-Injection, Day 6 Post-Injection, Day 6 Change from Baseline, Day 7 Pre-Injection, Day 7 Post-Injection, Day 7 Change from Baseline, Day 14.

Table 32
Physical Examination
Safety Population

	Safety Population (N=) Baseline Assessment	
Most Abnormal Post-Baseline Assessment	Normal	Abnormal
HEENT	(N=)	
Normal	n (%)	n (%)
Abnormal	n (%)	n (%)
Respiratory	(N=)	
Normal	n (%)	n (%)
Abnormal	n (%)	n (%)
Cardiovascular		
.		
.		

path\t_program.sas date time

Programmer note: Table will include all physical examination body systems.

Table 15
Concomitant Medications [1]
Safety Population

ATC Drug Class / Medication Term	Safety Population (N=)
Subjects Receiving any Concomitant Medications	n (%)
Drug Class 1	n (%)
Medication Term 1	n (%)
Medication Term 2	n (%)
.	
.	
Drug Class 2	n (%)
Medication Term 1	n (%)
Medication Term 2	n (%)
.	
.	

[1] At each level of summation (overall, ATC drug class, medication term), subjects reporting more than one medication are counted only once.
path\t_program.sas date time

APPENDIX C: LISTING LAYOUTS

Listing
Subject Disposition

Subject	ITT[1]	Safety[2]	Evaluable[3]	Replaced[4]	Concentration of Nickel Sulfate Used	First Injection Date	Last Injection Date	Total # of Injection(s)	Complete?	Primary Reason for Not Completing

[1] Intent to Treat (ITT): Enrolled subjects who signed informed consent.
[2] Received at least one dose of study drug.
[3] 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.
[4] Enrolled subjects but not meeting the criteria of evaluability.
path\t_program.sas date time

Listing
Inclusion/Exclusion Criteria
Part 1 of 4

Inclusion Criteria:

1:
2:
3:
4:
5:
6:
7:
8:

Exclusion Criteria:

1:
2:
3:
4:
5:
6:
7:
8:
9:
10:

path\t_program.sas date time

Listing 2(cont.)
Inclusion/Exclusion Criteria
Part 2 of 4: Inclusion Criteria

Subject	Date Informed Consent Signed	Inclusion Criteria 1	2	3	4	5	6	7	8

path\t_program.sas date time

Listing 2(cont.)
Inclusion/Exclusion Criteria
Part 3 of 4: Exclusion Criteria

Subject	Date Informed Consent Signed	Exclusion Criteria 1	2	3	4	5	6	7	8	9	10

path\t_program.sas date time

Listing 2(cont.)
Inclusion/Exclusion Criteria
Part 4 of 4: Waiver

Subject	Comply with ALL Entry Criteria	Entry Criteria Not Met	Exemption Explanation	Exemption Granted By	Date
		Inclusion:1			

path\t_program.sas date time

Listing 3
Demographics

Subject	Date of Birth	Age	Sex	Ethnicity	Race

[1] Age is calculated by comparing the date of birth and the informed consent date.
path\t_program.sas date time

Listing 4
Medical History

Subject	Mark if None	MH #	Body System	Description	Diagnosis/Onset	Mark if Ongoing

path\t_program.sas date time

Listing 5
Hematology and CBC with Differential
Part 1 of 2

Subject	Visit	Mark if Not Done	Not Done Reason	Collection Date/Time	WBC (X1000/uL)	RBC (XMil/uL)	Hemoglobin (g/dL)	Hematocrit (%)	Platelets (X1000/uL)	Neutrophils (segs) (%)	Neutrophils (bands) (%)

Note: A result marked with "*" indicates a result that is abnormal and clinically significant.
path\t_program.sas date time

Halozyme Therapeutics, Inc.
Protocol HALO-114-201
Page 1 of x

Listing 5 (cont.)
Hematology and CBC with Differential
Part 2 of 2

Subject	Visit	Mark if Not Done	Not Done Reason	Collection Date/Time	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)	Other

Note: A result marked with "*" indicates a result that is abnormal and clinically significant.
path\t_program.sas date time

Programmer note: for "other", put test name instead of "other" in the column name.

Listing 6
Lab Normal - Hematology

Lab Test	Sex	Lab Low	Lab High	Lab Units	If Other, Specify
WBC				X1000/uL	

path\t_program.sas date time

Listing 7
Pregnancy Test

Subject	Visit	Mark if Not Done	Not Done Reason	Collection Date	Sample Type	Result

path\t_program.sas date time

Listing
ICDRG Score [1]

Subject	Visit	Treatment Date	Treatment Regimen 1				Treatment Regimen 2			
			TR 1-1	TR 1-2	TR 1-3	TR 1-4	TR 2-5	TR 2-6	TR 2-7	TR 2-8
	Day 3		? (A)	+ (P) *						
	Day 4									

Note: A= rHuPH20; P= Placebo
Note: Results marked with "*" indicate Maximal Severity Score.
[1] ICDRG Score:

Score	(Grade)	Score Interpretation
?	(1/2)	Doubtful reaction; faint macular erythema only
+	(1)	Weak (nonvesicular) positive reaction; erythema infiltration, possibly papules
++	(2)	Strong (vesicular) positive reaction; erythema, infiltration, papules, vesicles
+++	(3)	Extreme Positive reaction; bullous reaction
-	(0)	Negative reaction
IR	(NA)	Irritant reaction of different types

path\t_program.sas date time

Programmer Note: Each subject will have one Maximal Severity Score marked for each injection type (for a total of 2 scores marked per subject).

Listing
TEWL (Trans-Epidermal Water Loss) Assessment (g/m^{2}h)

Subject	Visit	Was TEWL Completed?	Collection Date/Time	Result							
				TR 1-1	TR 1-2	TR 1-3	TR 1-4	TR 2-5	TR 2-6	TR 2-7	TR 2-8
	Day 1										
	Day 3										
	..										

path\t_program.sas date time

Listing 45
Digital Photographs

Subject	Visit	Were Digital Photos Taken? No:reason	Collection Date	Collection Time	Uploaded to Website? No:reason

path\t_program.sas date time

Listing 46
Chromometer
Part 1 of 3: a-Scale

Subject	Visit	Was a Chromometer Reading Completed?	Collection Date	Collection Time	Category	TR 1-1	TR 1-2	TR 1-3	TR 1-4	TR 2-5	TR 2-6	TR 2-7	TR 2-8
	Day 1	No:reason											
	Day 3				Result								
					Change from Day 1								

Listing 11
Chromometer
Part 2 of 3: b-Scale

Subject	Visit	Was a Chromometer Reading Completed?	Collection Date	Collection Time	Category	TR 1-1	TR 1-2	TR 1-3	TR 1-4	TR 2-5	TR 2-6	TR 2-7	TR 2-8
	Day 1	No:reason											
	Day 3				Result								
					Change from Day 1								

Listing 11
Chromometer
Part 3 of 3: l-Scale

Subject	Visit	Was a Chromometer Reading Completed?	Collection Date	Collection Time	Category	TR 1-1	TR 1-2	TR 1-3	TR 1-4	TR 2-5	TR 2-6	TR 2-7	TR 2-8
	Day 1	No:reason											
	Day 3				Result								
					Change from Day 1								

Listing 47
Subject Diary

Subject	Visit	Mark if Not Done	Not Done Reason	Date	Start Time	End Time	Symptom	Severity[1]	Comments	Dispense next Diary to subject?
						ongoing				

[1] 1 – Least Discomfort, 5 – Most Discomfort.
path\t_program.sas date time

Listing 48
Screening Nickel Sulfate and Vehicle Control Patches

	Application of Patches			Test Results (48 Hours After Application)							
							ICDRG				
Subject	Patches Applied?	Date	Time	Date	Time	48 hours After App.?	1%	2.5%	5%	Dose Assigned?	Assigned Dose
	No:reason					No:reason				No:reason	

path\t_program.sas date time

Listing 49
Study Drug Administration – Treatment Regimen 1
Part 1 of 4: Application of Nickel Sulfate Patches

Subject	Visit	Treatment Date	8 Areas Normal? No:reason	Application Time	4 Patches applied?	Concentrations of Nickel Sulfate

Listing 14 (cont.)
Study Drug Administration – Treatment Regimen 1
Part 2 of 4: Physical Examination Prior to Injection

					ICDRG Score				AE #			
Subject	Visit	Subject Randomized?	Treatment Date	Asse. Time	TR 1-1	TR 1-2	TR 1-3	TR 1-4	TR 1-1	TR 1-2	TR 1-3	TR 1-4
									None	None	None	None

Listing 14 (cont.)
Study Drug Administration – Treatment Regimen 1
Part 3 of 4: Study Drug Administration

Subject	Visit	Treatment Date	TR 1-1		TR 1-2		TR 1-3		TR 1-4	
			Drug Injected?	Time	Drug Injected?	Time	Drug Injected?	Time	Drug Injected?	Time
			No:reason							

Halozyme Therapeutics, Inc. **Page 1 of x**
Protocol HALO-114-201

Listing 14 (cont.)
Study Drug Administration – Treatment Regimen 1
Part 4 of 4: Physical Examination and Safety Review after Injection

Subject	Visit	Treatment Date	Test Category	Asse. Time	AE #			
					TR 1-1	TR 1-2	TR 1-3	TR 1-4
			Physical Exam. (10 mins. Post)		None	None	None	None
			Safety Review (30 mins Post)					

Listing 15
Study Drug Administration – Treatment Regimen 2
Part 1 of 4: Physical Examination Prior to Injection

Subject	Visit	Subject Randomized?	Treatment Date	Asse. Time	ICDRG Score				AE #			
					TR 2-5	TR 2-6	TR 2-7	TR 2-8	TR 2-5	TR 2-6	TR 2-7	TR 2-8
									None	None	None	None

path\t_program.sas date time

Halozyme Therapeutics, Inc. **Page 1 of x**
Protocol HALO-114-201

Listing 15 (cont.)
Study Drug Administration – Treatment Regimen 2
Part 2 of 4: Study Drug Administration

Subject	Visit	Treatment Date	TR 2-5		TR 2-6		TR 2-7		TR 2-8	
			Drug Injected?	Time	Drug Injected?	Time	Drug Injected?	Time	Drug Injected?	Time
			No:reason							

path\t_program.sas date time

Listing 15 (cont.)
Study Drug Administration – Treatment Regimen 2
Part 3 of 4: Physical Examination and Safety Review after Injection

Subject	Visit	Treatment Date	Test Category	Asse. Time	AE # TR 2-5	TR 2-6	TR 2-7	TR 2-8
			Physical Exam. (10 mins. Post)		None	None	None	None
			Safety Review (30 mins Post)					

path\t_program.sas date time

Halozyme Therapeutics, Inc.
Protocol HALO-114-201
Page 1 of x

Listing 15 (cont.)
Study Drug Administration – Treatment Regimen 2
Part 4 of 4: Application of Nickel Sulfate Patches

Subject	Visit	Treatment Date	Application Time	Mark if Not Done	4 Patches Not applied Reason	Concentrations of Nickel Sulfate

path\t_program.sas date time

Listing 16
Adverse Events

Subject	Mark if None	AE Term	Start Date/Time	Resolved Date/Time	Serious	Severity (CTCAE3)	Action Taken with Study Drug	Relationship to Study Drug	Other Action Taken	Outcome

path\t_program.sas date time

Listing 17
Serious Adverse Events

Subject	Mark if None	AE Term	Start Date/Time	Resolved Date/Time	Severity (CTCAE3)	Action Taken with Study Drug	Relationship to Study Drug	Other Action Taken	Outcome

path\t_program.sas date time

Listing 18
Vital Signs

Subject	Visit	Mark if Not Done	Not Done Reason	Visit Date	Category	Visit Time	Heart Rate (bpm)	Blood Pressure (mmHg)	Respiration (breaths/min)	Body Temperature (ºF)
	Screening							Sys/Dia		
	Day 1				Pre-injection					
					Post-injection					
	…									
	Day 14									

path\t_program.sas date time

Listing 19
Physical Examination

Subject	Visit	Mark if Not Done	Not Done Reason	Date of Exam	Any Change from Previous Exam	Body System	Result	Description of Abnormality
							Normal Abnormal Abnormal, Clinically Significant	

path\t_program.sas date time

Listing 20
Comments

Subject	Mark if None	Comment #	Pertains to Visit Date	CRF Page	Comment

path\t_program.sas date time

Listing 21
Prior and Concomitant Medications

Subject	Mark if None	CM #	Medication	Indication	Start Date	Stop Date	Dose	Unit	Route	Frequency	Taken for AE?	AE #
						onging						

path\t_program.sas date time

Listing 22
Deaths

Subject	Date of Death	Date Death Reported to Site	Primary Cause of Death	Was Autopsy Performed?	Comment	Signature of Investigator	Signature Date

path\t_program.sas date time

Listing 23
Subject Visit

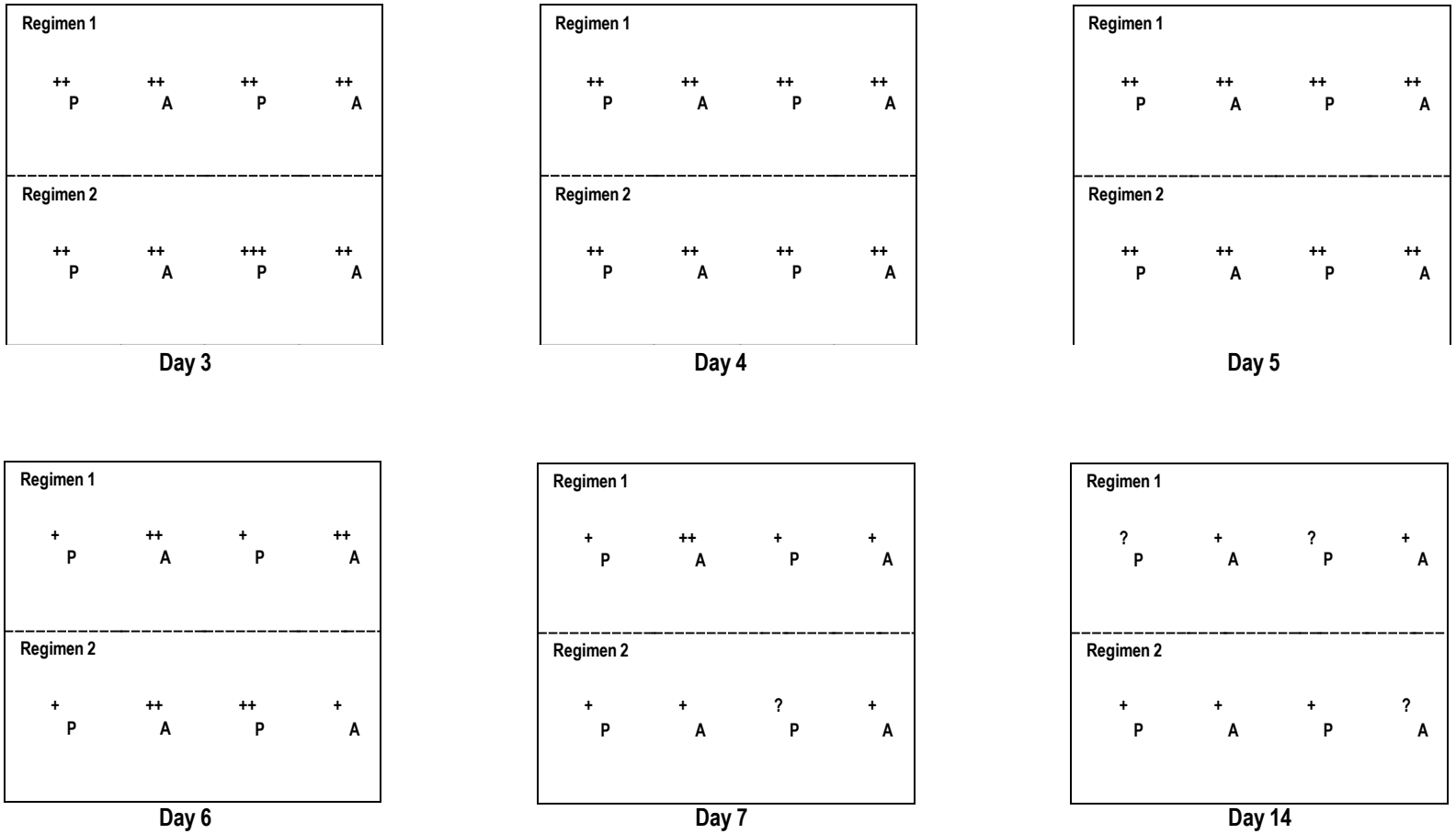
Subject	Initials	Visit	Visit Date

path\t_program.sas date time

APPENDIX D: FIGURE LAYOUTS

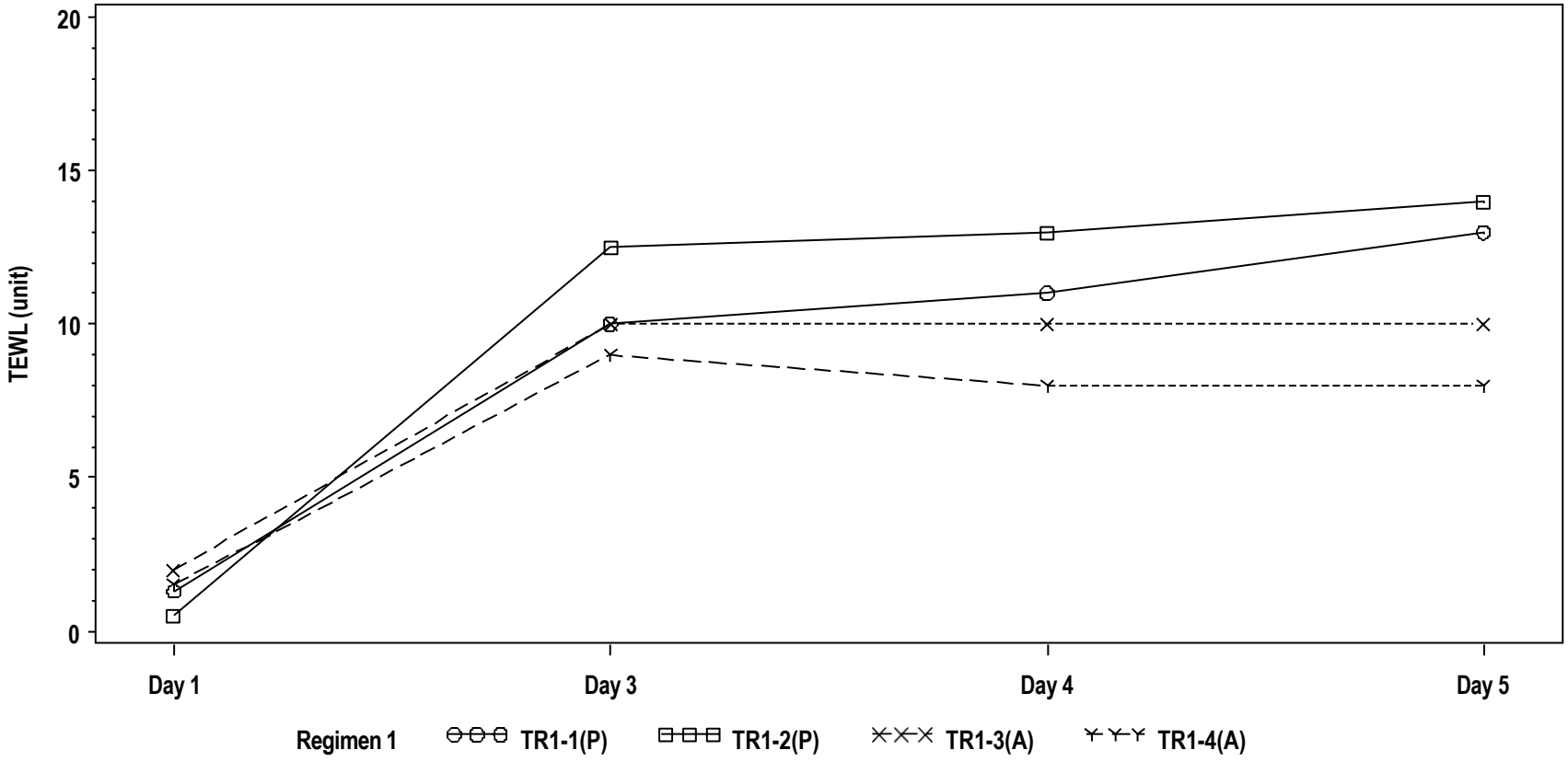
Figure 1

ICDRG Scores- Subject 001XXX



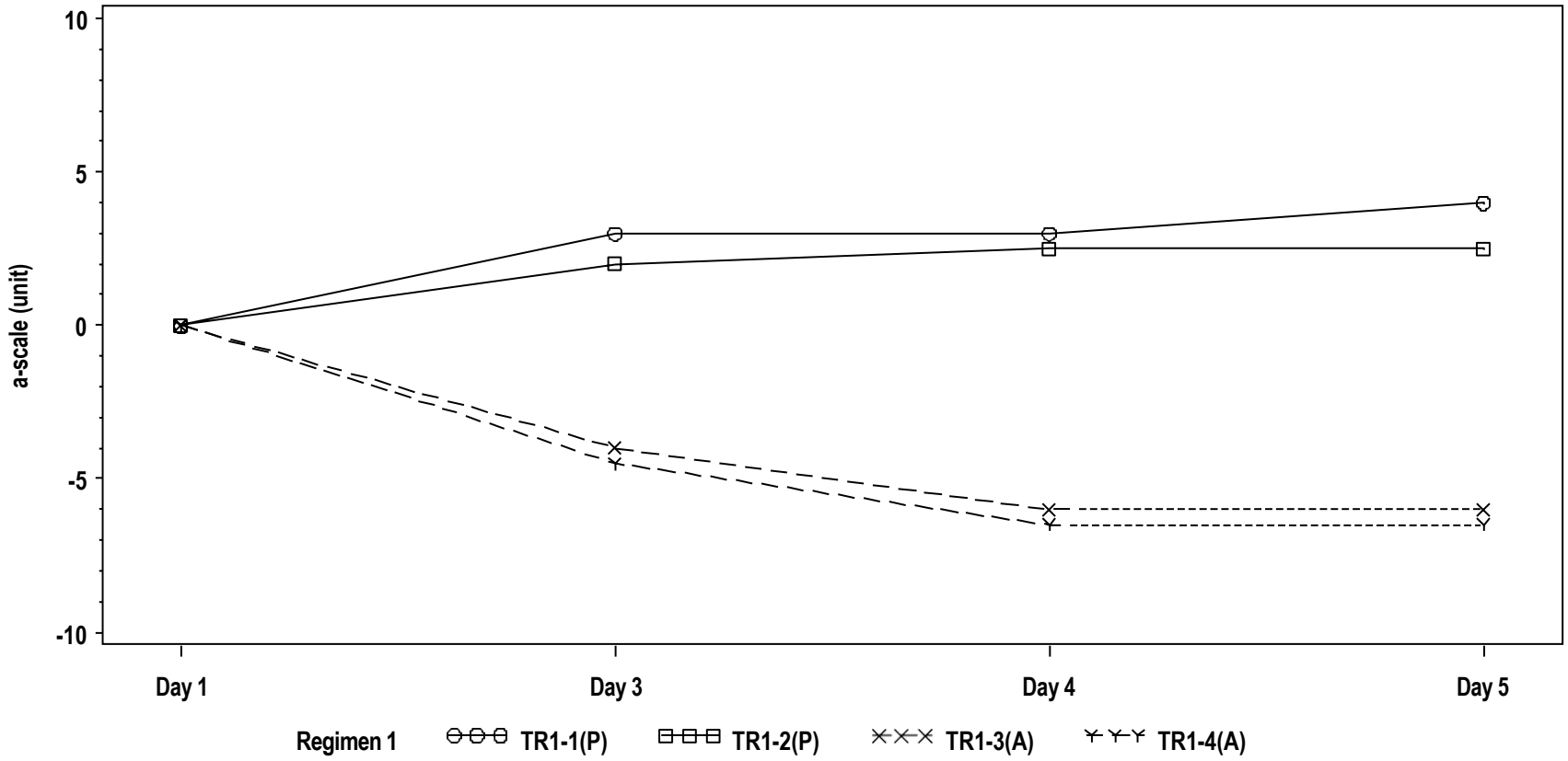
Note: A= rHuPH20, P= Placebo, NR= Not Reported.
Only subjects reported in both the Demographic and ICDRG datasets are considered.
Regimen 1 from left to right- TR1-1, TR1-2, TR1-3, TR1-4 and Regimen 2 from left to right- TR2-5, TR2-6, TR2-7, TR2-8
path\program.sas date time

Figure 2
Individual TEWL Scores by Day and Injection Site
Subject 001XXX- Regimen 1



Note: A= rHuPH20, P= Placebo.
path/program.sas date time

Figure 3
Individual a-Scale Chromometer Baseline Corrected Scores by Day and Injection Site
Subject 001XXX- Regimen 1



Note: A= rHuPH20, P= Placebo.
path/program.sas date time