Statistical Analysis Plan

Protocol CFW-2D
Nielsen BioSciences, Inc.

A PHASE IIA, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF THE SAFETY AND EFFICACY OF VARYING REGIMENS OF CANDIN FOR TREATMENT OF COMMON WARTS

Phase IIa

Original Protocol: April 2, 2014
Amendment 4 Version 5: December 6, 2016

Prepared by [redacted]

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This Statistical Analysis Plan has been reviewed and approved by:

[redacted]

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1 INTRODUCTION

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of Nielsen BioSciences Study CFW-2D. [redacted]

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to assess the efficacy of Candin® (*Candida albicans*) treatment in subjects with common warts (*Verruca vulgaris*) by evaluating the number and proportion of subjects with the primary injected wart(s) completely resolved.

2.2 Secondary Objectives

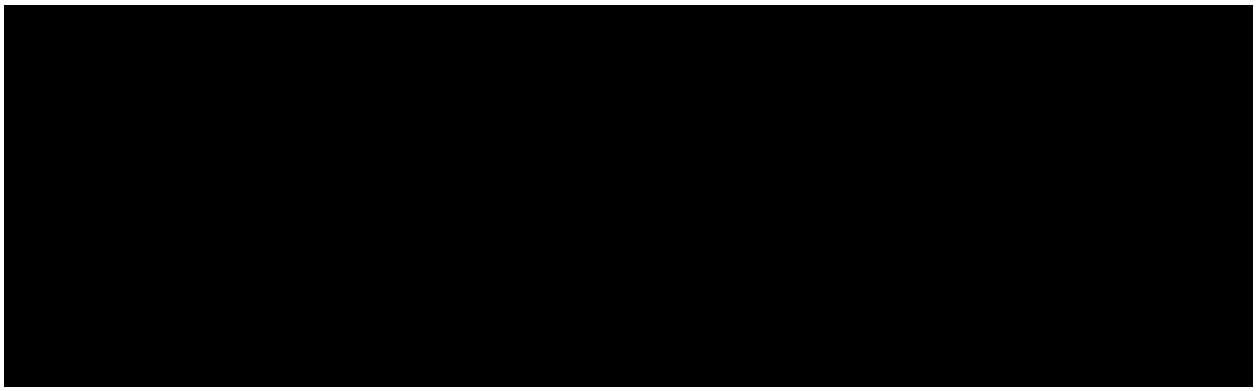
Secondary objectives include the following:

1. To assess the safety and tolerability of Candin.

[redacted]

2.3 Exploratory Objectives

[redacted]



3 STUDY OVERVIEW

3.1 Study Design

This is a placebo-controlled, double-blind (subject, Investigator, and site staff with the exception of unblinded dedicated staff to handle study medication), multi-center, Phase IIa study with 3 dose cohorts, randomized to Candin or placebo in a 3:1 ratio. The main study will be up to 20 weeks (10 doses administered every other week) or until a subject has complete resolution of all injected common warts. Subjects who cannot tolerate dosing every 2 weeks (14 ± 2 days) due to a local tolerance issue may be injected at 3-week (21 ± 2 days) intervals for up to 10 doses, increasing the length of the study to 29 weeks. Subjects will be followed for 4 months after final injection(s) for evidence of new or reoccurring warts and for safety evaluation.

Approximately 156 (male or female) subjects aged 18 to 65 inclusive at the date of consent, with 3 to 20 common warts on hands, feet (excluding soles), limbs, and/or trunk will be included in this study. It is assumed that approximately 80% of the subjects will either complete the study or reach complete resolution. Drop-outs will not be replaced. Refer to Section 9 for sample size and power of the study.

Subjects will be included in three cohorts as follows:

Cohort 1: Approximately fifty-two subjects will receive 0.3 mL of either Candin (n=39) or placebo (n=13) intralesionally in the largest (primary) common wart every second week (14 ± 2 days) for a maximum of 10 injections. If the primary common wart exhibits a complete response, the second largest injectable common wart of all anatomical regions will be injected with the randomized study medication at the same dose. If the second largest common wart exhibits a complete response, the third largest wart of all anatomical regions will be injected. If an injected wart recurs after exhibiting a complete response, it will be re-injected instead of the non-primary injected wart that was injected at the previous visit. This injection strategy will be repeated for a maximum of 10 injections per subject, or until all injectable

common warts exhibits a complete response if that occurs before all 10 injections are used.

Cohort 2: Approximately fifty-two subjects will receive 0.5 mL of either Candin (n=39) or placebo (n=13) intralesionally in the largest (primary) common wart every second week (14 ± 2 days) for a maximum of 10 injections. The same procedures will be followed in the event of complete response or recurrence as described for Cohort 1.

Cohort 3: If the safety data from Cohort 2 support continuation of the study (defined as medical assessment of the first eight subjects of Cohort 2 completing three injections), approximately 52 subjects planned for Cohort 3 will receive either 0.3 mL/wart Candin (n=39) or placebo (n=13), with a total per visit not to exceed 1.2 mL. Subjects in Cohort 3 must have injectable common warts in at least 2 different anatomic regions. Candin or placebo will be injected under the largest (primary) wart per major anatomical region (left or right; arm, hand, leg, foot excluding sole, or the torso) for a minimum of two and a maximum of four injections per visit, every second week (14 ± 2 days) for a maximum of 10 visits with injections. No more than one wart per anatomical region will be injected on any given visit. If any primary injected wart exhibits a complete response, the next largest injectable common wart will be injected with the randomized study medication at the same dose (maximum of 4 injections per visit), providing the new injectable wart is not within the same anatomical region as other currently injected warts. (If an injected wart recurs after exhibiting a complete response, it will be re-injected instead of the non-primary injected wart that was injected at the previous visit.) This injection strategy will be repeated for a maximum total of 10 injection visits per subject or until all injectable common warts exhibit a complete response, if it occurs before the end of the 10 injection visits.

Two Follow-up visits are included in the study to further assess the efficacy and safety of the study medication. Follow-up information will be obtained for subjects who discontinue their participation in the study. All procedures scheduled for during Follow-up Visit 1 and Follow-up Visit 2 should be completed for early termination subjects, as well as for those subjects who have complete resolution of all common warts prior to their Efficacy Evaluation visit (V13).

3.2 Study Procedures and Visit Structure

The study visit schedule and procedures are described in Table 1. The study includes a maximum of approximately 29 weeks of treatment with 1-month (4 weeks) and 4-months (16 weeks) Follow-up visits after the Efficacy Evaluation Visit (V13).

Table 1. Study Procedures and Visit Structure

	Screening Visits		Baseline Visit (Day 1)	Injections Visits[2]									Efficacy Evaluation Visit[10]	Follow-up Visits	
Visit	**V1[14]**	**V2[1]**	**V3[1]**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13[14]**	**V14**	**V15**
Window (days)	-30d to -2d	±4h[5]		±2d									±3d	±3d	±7d
Procedure															
Informed Consent	X														
Inclusion/Exclusion Criteria	X		X												
Demographics	X														
Medical and Surgical History	X		X												
Blood Draw for Safety Labs[14]	X												X		
Urinalysis	X												X		
Pregnancy Test[3]	X		X		X		X		X		X		X		
Vital Signs (includes weight and height at screening)	X		X	X	X	X	X	X	X	X	X	X	X		
Physical Examination	X												X		
Full Body Dermatologic Examination to identify the presence of any wart type			X				X						X		X
Presence or absence of common warts in designated anatomical areas			X				X						X		X
Evaluation of presence or absence of common warts other than the measured and mapped injectable common warts			X										X	X	X
Common warts measurement and mapping (up to 6 injectable common warts including all primary injectable warts)			X	X	X	X	X	X	X	X	X	X	X	X	X
Evaluation of primary injected wart(s) status				X	X	X	X	X	X	X	X	X	X	X	X
Selection of primary injectable wart(s)[9]		X													
Selection and Mapping of non-primary common wart(s) for injection[8]			X	X	X	X	X	X	X	X	X	X			
DTH Challenge Injection (30-min observation period)	X[13]														
DTH Evaluation		X													
Blood Draw for Biomarkers Evaluation	X[6]				X[6,12]								X[6]		
Randomization			X												
Intralesional Injection (30-min observation period)			X	X	X	X	X	X	X	X	X	X			
Give Subject Diary	X[7]		X	X	X	X	X	X	X	X	X	X			
Review/Retrieve Subject Diary		X[7]		X	X	X	X	X	X	X	X	X	X		
Medical Photographs[4]			X		X		X				X		X	X	X
Hypopigmentation and Scarring Assessments[11]			X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. Screening Visit 2 and Baseline Visit may be performed on the same day if all screening information and data are available.
2. If the medical Investigator deems appropriate because of tolerance issues the injection schema may be changed to every 3 weeks instead of 2 weeks for a maximum of 10 doses.
3. Female of childbearing potential only. Serum pregnancy at screening and urine pregnancy test at other visits.
4. At selected sites, for a maximum of 10 subjects per cohort.
5. Post 48h of DTH injection from V1.
6. Cohort 1 only.
7. DTH Diary
8. Applicable only if there is complete resolution of the primary injected wart(s).
9. One for Cohort 1 and 2; and up to 4 in Cohort 3.
10. If complete resolution of all common warts, not just the primary injected wart(s), is observed at any of the visits following Baseline, the procedures described under Visit 13 will be performed. This visit also will be performed in the event of an early termination.
11. To be initially assessed at Visit 3 and prior to the first injection in case of selection and mapping of non-primary common wart(s) for injection (V4 to V12). To be re-assessed at the site of resolved primary and non-primary injected wart(s) must be recorded as an AE if at Baseline (V3), or prior to the first injection in case of selection and mapping of non-primary common wart(s) for injection (V4 to V12) it was assessed as absent.
12. Prior to injection.
13. On certain occasions, administering the DTH challenge at V1 may result in a difficulty scheduling V2 at the 48 hour time required (for example V1 on a Thursday or Friday resulting in V2 on a weekend). The investigator may perform the DTH challenge on an additional visit after V1 (subvisit) in order to schedule an acceptable V2, provided the DTH challenge is performed within 1 week of V1 and a urine pregnancy test is performed if required for a given subject. Urine pregnancy testing not required for women of non-childbearing potential defined as post-menopausal for at least 2 years or surgically sterile (tubal ligation, oophorectomy, or hysterectomy).
14. V1 and V13 should not be scheduled on a weekend if at all possible due to shipping restrictions of blood samples.

3.3 Randomization Schedule and Blinding Procedures

This is a double-blind study defined as blinding of subjects, investigators, and site personnel not involved in study medication preparation and accountability. A concealed, centralized randomization list generated by an unblinded Sponsor representative will be used to assign the cohort and treatment to the subjects using an internet-based system. Randomization will be unbalanced (3:1) in favor of Candin. To maintain the blind, a qualified, unblinded person at each study site will prepare the syringes containing the medication (CANDIN or saline) independently from the Investigator performing the injection and making the evaluations. Subjects will be randomly assigned to cohorts first, and then to treatment, according to Table 2.

Table 2. Randomization Structure by Stratum, Cohort, and Treatment

Number of Anatomical Regions	Number of Subjects	Randomization Ratio between Cohorts within Stratum	Number of Subjects in Cohorts	Randomized to Candin	Randomized to Placebo
Single	66	1:1	Cohort 1 = 33	25	8
			Cohort 2 = 33	25	8
Multiple	90	4:4:11	Cohort 1 = 19	14	5
			Cohort 2 = 19	14	5
			Cohort 3 = 52	39	13

The first 16 subjects will be randomized (1:1) to Cohort 1 or 2 until medical assessment of the first eight subjects of Cohort 2 (6 on active and 2 on placebo) completing three injections supports continuation of the study to Cohort 3. Once medical assessment supported continuation of the study to Cohort 3, subsequent subjects with warts in at least 2 different anatomical regions will be randomized to Cohort 1, 2, or 3 in a ratio of 4:4:11 to ensure that the treatment assignment for the overall 156 subjects will approximately preserve the above randomization structure.

The treatment randomization assignments will be kept secured from the Investigator and/or blinded site staff in the unblinded pharmacy binder until the database is finalized and hard locked.

The investigational site will assign each subject a subject identifier number during screening that will be used on all subject documentation throughout the study. Numbers will be assigned in ascending order using Sponsor's numbering system.

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the number and proportion of subjects with the primary injected wart(s) completely resolved at any treatment or Follow-up visit.

In Cohort 1 and 2, the largest common wart located on hands, feet (excluding soles), limbs, and/or trunk will be selected as the primary injected wart. In Cohort 3, the largest common wart per anatomical region (left or right; arm, hand, leg, foot (excluding sole) or the torso) will be selected as the primary injected warts for a minimum of 2 and a maximum of 4 warts. In Cohort 3 subjects, injected warts must be in different anatomical regions. Warts in flat, plantar, facial, periungual, or genital or in a region of pre-existing inflammatory condition are excluded from injection.

4.2 Secondary Endpoints

Secondary endpoints include the following:

1. Assessment of safety and tolerability of Candin:

   Incidences of DTH Challenge immediate reactions and immediate injection hypersensitivity/reactions after study treatment, and all other treatment-emergent adverse events.

2. [redacted]

[redacted]

4.4 Safety Endpoints

Safety and tolerability will be assessed by evaluating the treatment-emergent adverse events and, the clinical laboratory results, and vital signs.

5 ANALYSIS POPULATIONS

The following populations will be used for the summaries and analyses of the study data.

5.1 DTH Safety Population

The DTH Safety population consists of all subjects who signed the informed consent and received the DTH Test treatment at the Screening visit.

The DTH Safety population will be used to summarize the adverse events including reactions due to DTH challenge injection that occurred prior to the randomized study treatment if the subject received any randomized treatment. Note that this population may include subjects that never got randomized and received no study treatment.

5.2 Randomized Population

The Randomized population is defined as all subjects who are randomized to a treatment group.

5.3 Safety Population

The Safety population consists of all randomized subjects who received at least one intralesional dose of study medication.

The Safety population will be used in all safety/tolerability analyses unless otherwise stated. Subjects will be analyzed according to the dose they received.

5.4 Modified Intent-to-Treat (mITT)

The mITT population consists of all subjects in the Safety population who had at least one post-baseline measurement of the primary wart(s).

The mITT population will be used for analyses all efficacy endpoints including exploratory efficacy endpoints.

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

6 STUDY SUBJECTS

6.1 Subject Disposition

Subject disposition information, including the number and percent of subjects who completed treatment, discontinued treatment further broken down by primary reason for treatment discontinuation, subjects who completed the study and terminated early from the study further broken down by reason for early termination will be summarized by cohort and treatment for the Randomized population.

Subjects who completed treatment will be defined as those who completed all 10 injections, or with all injectable warts resolved by Efficacy Evaluation Visit (Visit 13). An injectable wart is defined as any measured wart.

Subjects who completed the study will be defined as those who completed treatment and both follow-up visits (Visit 14 and Visit 15).

6.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively by cohort and treatment for the Safety, mITT, and Evaluable populations. The demographic characteristics include, but are not limited to: gender, age, age group (<45 years or ≥45 years), race, and ethnicity. Baseline characteristics include:

- body weight, height, and body mass index (BMI).
- number of common warts mapped.
- mean area of common warts initially mapped and measured.
- location of common warts by anatomical region (left arm, right arm, left hand, right hand, left leg, right leg, left foot excluding sole, right foot excluding sole, torso) and number of anatomical regions (single vs multiple).
- mean area of primary injected wart(s)
- age (weeks) of primary injected wart(s). For Cohort 3 subjects use the maximum age of the primary injected warts.

The medical histories of subjects will be provided in a data listing.

6.3 Treatment Compliance

Subjects are to receive injections every 2 weeks (or 3 weeks for those subjects who cannot tolerate dosing every 2 weeks due to a local tolerance issue). The Investigator will inject the entire volume of drug into a single wart (0.3 mL for Cohort 1; 0.5 mL for Cohort 2; and 0.3 mL per wart up to 1.2 mL total injected volume for Cohort 3). If the entire volume cannot be injected in a single injection, the Investigator will document that in the CRF and will divide

the randomized study medication between two or more injection sites around the same wart until the entire dose of randomized study medication has been injected, if possible. Treatment compliance data will be reviewed manually based on comments provided by the Investigator.

For each subject, the treatment compliance will be calculated by dividing the total number of injections administered by the sum of the total number of warts eligible for injection (as defined by study Protocol) at each injection visit multiplied by 100. The treatment compliance will be summarized descriptively by cohort and treatment for the Safety Population.

6.4 Protocol Deviations

Protocol deviations based on the inclusion/exclusion criteria at the time of enrollment will be summarized by cohort and treatment for the Randomized population. All protocol deviations occurring during the study period will also be summarized by cohort and treatment for the Safety Population. Subjects with any important protocol deviations that would affect efficacy will be identified and excluded from the Evaluable population. Important protocol deviations will be determined prior to treatment unblinding and database lock.

6.5 Extent of Exposure

The extent of exposure to randomized study medication will be presented as a frequency table of the total number of injections administered over study assessment period.

6.6 Concomitant Medications

All medications are to be coded using the current versions of WHO Drug Dictionary and Anatomical Therapeutic Chemical (ATC) classification system.

Medications will be classified as:

- Pre-treatment medications: medications taken and stopped prior to the first dose date.
- Concomitant medications: medications taken after receiving the first injection of the randomized study medication. These belong to the following categories:
    - Prior concomitant medications: medications started prior to the first dose of randomized study medication and continuing past the first dose date.
    - New concomitant medications: medications started during or after the first dose date of the randomized study medication and prior to the first Follow-up visit (Visit 14).
    - New concomitant medications in Follow-up period: medications started during or after the first Follow-up visit (Visit 14) and prior to the second Follow-up visit (Visit 15).

Number and percent of the Safety subjects with each of the above-mentioned medications will be summarized by ATC classification (ATC level 2 and level 4).

7 STATISTICAL METHODS OF ANALYSIS

7.1 General Considerations

In general, all data summaries will be presented by treatment group; 'pooled placebo', 'Cohort 1: 0.3 mL Candin', 'Cohort 2: 0.5 mL Candin' and 'Cohort 3: 0.3 mL Candin'. When statistically comparing the effectiveness of the two Candin doses, 0.3 mL and 0.5 mL, with placebo, Cohort 3 subjects will be pooled with Cohort 1 subjects with common warts at baseline in multiple anatomical regions.

Continuous variables will be summarized by n, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized by frequency and percent in corresponding categories.

A subject's age (years) will be calculated as of the date of informed consent as follows:

$$\text{Age} = \text{Year of informed consent} - \text{Year of birth} - 1 \text{ (if birth day and month are after day and month of informed consent)}$$

7.1.1 Hypothesis Testing

All inferential hypothesis tests will be two-sided at $\alpha = 0.05$ significance level. There will be no adjustment of Type I error for multiple comparisons due to exploratory nature of this early phase study.

7.1.2 Defining the Study Baseline

The baseline value for each variable is defined as the last value recorded on or before the first administration of randomized study medication.

7.1.3 Handling of Multiple Observations

For laboratory data, a subject may have multiple scheduled or unscheduled laboratory values for the same analyte that are associated with a protocol defined visit. To define the baseline, all scheduled or unscheduled lab values prior to the first dose of randomized study medication will be sorted by collection time and last sample collected in chronological order will be taken as the baseline.

For multiple post-baseline values associated with the same scheduled visit, mean values will be computed first and will be used as the value associated with that visit. However, when summarizing the laboratory parameter shift tables, the worst value of the multiple observations will be used when applicable.

All results, scheduled or unscheduled, will be listed.

7.1.4 Handling Missing Data or Outliers

In general, no imputation of missing data will be done except for those described below:

Values below the lower limit of quantification of an assay (<LLOQ) will be assigned LLOQ/2 for the purposes of analysis.

Missing or partial start/stop dates for AEs will be imputed with the following algorithms:

For AE start date, the imputation rule is to conservatively capture as many treatment-emergent AE (TEAE) as possible:

- If "day" is the only missing field, impute the "day" as the later one between the first day of the month and the first dose date if their "month" are the same.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the later one between January 1 of the year and the first dose date if their "year" are the same.
- If "day", "month", and "year" are all missing, to be conservative, the AE will be assumed to occur on the same day as the first dose was administered.

For AE stop dates, imputation is needed to calculate the duration of the event observed during the study period. Note that on AE listings, the duration will be printed with the ">" symbol to indicate the actual duration is longer than the number presented. The algorithms are:

- If "day" is the only missing field, impute the "day" as the former one between the last of the month and the last study visit date if their "month" are the same.
- If "day" and "month" are both missing, impute it as the former one between December 31 of the year and the last study visit date if their "year" are the same.
- If "day", "month", and "year" are all missing, the AE will be assumed to stop on the same day as the last study visit date.

Outliers will not be excluded from analysis.

7.2 Efficacy Analyses

7.2.1 Analyses of Primary Endpoint

If the area of a measured wart at baseline becomes 0 at a post-baseline evaluation visit, the wart will be considered as completely resolved. For each of the four treatment groups, the number and percent of subjects achieving complete resolution of the primary injected wart(s) will be calculated and summarized. [redacted]

[redacted]

[redacted]

[redacted]

Each Candin dose group will be compared to the pooled placebo group using CMH general association test. Further, Mantel-Haenszel common relative risk (RR) and asymptotic 95% confidence interval (CI) will also be presented.

[redacted]

7.2.2 Analyses of Secondary Efficacy Endpoints

[redacted]

[redacted]

[redacted]

[redacted]

7.2.3 Analyses of Exploratory Endpoints

[redacted]

7.2.4 Interim Analyses

There are no formal interim analyses planned for this study; however, there will be a medical assessment of the safety data including review of data from subject diaries from the first eight subjects in Cohort 2 after the last of these subjects receives his/her third injection, before allowing inclusion in Cohort 3. Refer to the definition of cohorts in Section 3.1 for further details. There will also be a medical assessment of the safety data, including subject diaries (See Section 7.3.4) from the first five subjects of Cohorts 2 and 3 after the first injection, before allowing inclusion of more than one subject per day; or else a limited inclusion rate will continue.

7.2.5 Pooling of Sites

Study centers/sites will be pooled according to the following rules:

- Two highest enrolling sites will not be pooled.
- All other sites will be pooled together to create a single pooled site.

Site effect on the primary efficacy endpoint will be descriptively explored by summarizing the primary efficacy endpoint separately for the two highest enrolling sites and pooled site.

7.3 Safety Analyses

The analysis of safety data will be performed for the Safety population unless otherwise stated. The primary safety endpoint is the incidence of TEAEs as defined as any new AEs or existing AEs that have worsened during or following the first wart(s) injection with Candin (Visit 3) through the final Follow-up Visit (V15), or Early Termination/Withdrawal. Other safety endpoints include clinical laboratory evaluations, vital signs, and changes in skin examinations as well as general physical examinations.

7.3.1 Adverse Events

TEAEs are defined as those occurring during or after the first wart injection of randomized study medication, or existing prior to the time of and worsening after the time of the first study dose, through final Follow-up Visit (V15) or Early Termination/Withdrawal. AEs with onset date prior to the first administration of randomized study medication will be classified as pre-treatment AEs.

All AEs are to be coded with Medical Dictionary for Regulatory Activities (MedDRA™) version 17.0.

The frequency (event counts) and incidence (number and percent of subjects) of TEAEs, serious TEAEs, TEAEs leading to withdrawal, TEAEs by severity (most severe grading from

the same preferred terms within the same subjects), and TEAEs by causality (Related versus Not Related), frequent TEAEs (incidence ≥ 5% in any treatment groups) will be summarized.

Injection site TEAEs, defined by any preferred terms containing the phrase of "injection site", will be summarized further.

DTH-related AEs that occurred during the DTH Screening time period (e.g., prior to the receiving the randomized study medication) will be summarized separately for DTH Safety population.

All further details collected for AEs will be presented in a listing.

7.3.2 Clinical Laboratory Evaluations

All laboratory results will be listed by treatment, subject, and visit, including scheduled and unscheduled measurements. Laboratory assessments that are outside of normal ranges will be flagged.

Baseline values, the values at each visit, and changes from baseline values will be summarized for each of the quantitative laboratory assessments by treatment.

Shift tables of laboratory results will be used to summarize changes from Baseline to the end of the Follow-up Visit (V15) or Early Termination/Withdrawal.

Laboratory data collected during Screening will be summarized descriptively.

7.3.3 Vital Signs and Physical Examinations

Vital signs at Baseline (Visit 3), each scheduled visit, and changes from baseline at each visit will be summarized and listed. Physical examination findings will be listed only.

7.3.4 Daily Diary Card

Subject diaries are a source for the Investigator to identify potential adverse events experienced by the subject during the study with the severity of any findings. All signs and symptoms of associated with the warts after randomized study medication injections, as recorded in the daily diary cards, will be summarized by the most severe grading from each subject, and will be provided in listings. Since Diary Card events are recorded by subjects, analysis will not be summarized in the Final Report, but all adverse events will be.

8 CHANGES TO THE PLANNED ANALYSES

[redacted]

[redacted]

9 SAMPLE SIZE AND POWER

[redacted]

10 STATISTICAL SOFTWARE

All analyses will be performed with SAS® version 9.4.