Protocol CCN005B

An Open-Label Study of Serum Testosterone and Nestorone in Females After Secondary Exposure to Nestorone ® (NES) + Testosterone (T) Combined Gel Applied to Shoulders and Upper Arms in Males: Effect of Washing or Clothing Barrier to the Application

Statistical Analysis Plan

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STATISTICAL ANALYSIS PLAN APPROVAL

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LIST OF ABBREVIATIONS

AE	Adverse Event
AUC	Area Under the Curve
BMI	Body Mass Index
CBC	Complete Blood Cell (count)
CRF	Case Report Form
CS	Clinically Significant
CV	Coefficient of Variation
HEENT	Head, Eyes, Ears, Nose and Throat
MedDRA	Medical Dictionary for Regularity Activities
NCS	Not Clinically Significant
NES	Nestorone
PI	Principal Investigator
PK	Pharmacokinetic
PT	Preferred Term
PTF	Peak Trough Fluctuation
RBC	Red Blood Cell (count)
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
T	Testosterone
TEAE	Treatment-Emergent Adverse Event
WBC	White Red Blood Cell (count)
WHO	World Health Organization

1.0 INTRODUCTION

This statistical analysis plan (SAP) was developed after review of the CCN005B study protocol (Version 1.0, dated as 16NOV2016) and e-case report forms (eCRFs, dated as 26JAN2017), but before any analysis of the data had begun. Detailed information is given to aid in the production of the statistical output and the statistical section of the Final Study Report. This document gives a summary of the protocol and describes the populations that will be analyzed. All subject characteristics and the efficacy and safety parameters that will be evaluated, along with the specific statistical methods, are described.

2.0 PROTOCOL SUMMARY

2.1 Background

Contraception options for men are limited to condoms and vasectomy, yet international surveys have shown that a large number of men would use a new contraceptive method if one were available. In order to develop a hormonal contraceptive method for men to be effective, safe, reversible, self-delivered, and affordable, a few clinical trials have already been completed, using combined Nestorone (NES) and testosterone (T) gel applied to men's upper arms. Possible transfer of transdermal NES from men to women upon close skin contact has not been studied yet. This clinical trial will be conducted to assess maximum T and NES transfer from the skin of the healthy male volunteers to non-dosed female partners after application of the combined NES and T gel over the shoulders and upper arms of the male participants.

2.2 Objectives

The primary objectives of the study is to investigate the transference effects of the combined NES and T gel in female participants after skin contact with male participants who dosed with a gel containing T and NES applied to the shoulders and upper arms. In order to conduct the study similar to the real-world situations, the skin contact has 3 variations:

(a) With a 100% cotton T-shirt clothing barrier;
(b) After the application site is washed with soap and water in a shower and dried;
(c) Without washing or clothing barrier to the skin to skin contact.

The secondary objectives are:

1. To determine the effects of showering on the pharmacokinetics of testosterone and Nestorone levels in male participants after application of testosterone and Nestorone combined gel on shoulders and upper arms in men.
2. To determine the amount of testosterone and Nestorone that remained on the skin after application in men.
3. To assess the safety and tolerability of the combined gel in men.
4. To assess the safety in women possibly exposed to the gel after skin contact at the site of application of the gel in men.

2.3 Trial Design

This is a two-center, open-label study conducted in healthy male and female volunteers at two academic research centers in the United States. Based on the results of a 4-week study (CCN005A) applying a combined NES + T gel delivering approximately 62.5 mg T and 8.3 mg NES per day in 5 mL volume, this study will consist of three single applications of the NES + T combined gel on the shoulders/upper arms of male participants followed 2 hours later by supervised skin contact with non-dosed female participants on the application site on Study Days 1, 8, and 15, where Day 1 is the date of first application of the gel. The final follow-up visit is on Day 31.

The protocol will enroll a total of 12 healthy male subjects and their partners (i.e.12 female subjects), 6 male and 6 female subjects per site. The couples will be instructed to use another highly effective method of contraception for the duration of the study (i.e. at a minimum use double barrier method such as a condom with spermicide).

A study design table outlining the schedule of assessments is provided in the appendix.

2.4 Study Endpoints

2.4.1 Primary Endpoints

The primary study endpoints are:

- Female subjects changes from baseline up to 48 hours for serum testosterone levels in pharmacokinetic (PK) parameters C_{avg}, C_{max}, and C_{min} after secondary exposure to NES + T gel.
- Female subjects Nestorone levels after secondary exposure to NES + T gel by presenting C_{avg}, C_{max}, and C_{min}.

These endpoints will be summarized for each of the 3 types of skin contact between the man and woman at 3 study visits at Days 1, 8, and 15, respectively.

2.4.2 Secondary Endpoints

The secondary study endpoints are as follows, which will also be summarized for each of the 3 types of skin contact between the man and the woman after the NES/T gel applied to the man.

- The PK parameters of testosterone and Nestorone in males after wearing a T-shirt and after washing will be compared to serum testosterone and Nestorone pharmacokinetics after application of the combined gel without washing.
- Serum testosterone pharmacokinetics in males after applying NES + T gel with or without T-shirt and with washing will be compared to baseline pharmacokinetic parameters.
- Average testosterone and Nestorone levels 90 and 150 minutes after application in men as measured by adhesive D-square strips with and without showering.
- Incidence of adverse events and serious adverse events for both partners.
- Changes from baseline in safety lab tests (hematology and clinical chemistry) in both partners.
- Percentage of female subjects with increased (relative to baseline) acne and hirsutism at each visit.

2.5 Sample Size Consideration

The protocol is expected to enroll a total of 12 healthy male subjects and their partners (i.e.12 female subjects) at 2 study sites, with 6 male and 6 female subjects per site. Couples who do not complete the study will be replaced. Couples who discontinue will not be re-enrolled into this study. Though no formal sample size calculation was performed, the sample size was selected to be in accordance with size of typical phase Ib studies, as well as to facilitate collection of sufficient safety and PK data.

3.0 STATISTICAL METHODS

3.1 Statistical Handling Policy

3.1.1 Interim Safety Review

An independent, autonomous Data Safety and Monitoring Board (DSMB) will be chartered by NICHD to review the adverse events and safety considerations at periodic routine intervals and on an ad hoc basis if required by an unexpected serious adverse event that could be attributable to the treatment regimen.

3.1.2 Analysis Conventions

This section details general policies to be used for the statistical analyses. Departures from these general policies may be given in the specific detailed sections of this statistical analysis plan. When this situation occurs, the rules set forth in the specific section take precedence over the general policies. The following policies will be applied to all data presentations and analyses.

- Summary statistics will consist of the number and percentage of responses in each category for discrete (categorical) variables, and the number of non-missing observations (n), mean, median, standard deviation (SD), minimum, and maximum (abbreviated as 6-number summary statistics) for continuous variables, and may be for categorical variables with quite a few number of ordinary categories.
- All mean values will be formatted to one more decimal place than the measured value, and standard deviation values will be formatted to two more decimal places than the measured value. For median values, they will be kept the same decimal place as the measured values if that is doable without losing accuracy; otherwise, they will be formatted to one more decimal place than the measured values.
- All percentages will be rounded to one decimal place. The number and percentage of categorical responses will be presented in the form XX (XX.X), where the percentage is in the parentheses. The denominator for percentage calculations will be the number of non-missing observations (n) when this number is shown, or will be the total sample size in the relevant analysis population for tables of adverse events, medical histories, or other tables where this number of non-missing observations (n) is not presented.
- All listings will be sorted for presentation in order of site number, subject number, and date of visit, or procedure, or event when applicable.

- When necessary for analysis purposes, partial dates will be completed (i.e., turned into complete dates) using the most conservative approach.
- All analysis and summary tables will have the population sample size for the analysis population in the table heading.
- Baseline is defined as the last data point before the first dose, and "Final Evaluation" is defined to be the last evaluation performed before/during the study exit.
- Calculating change from baseline to a visit will be done as follows: Change from Baseline = Observed value at the visit – Baseline value; Percent (%) change from baseline = 100 * Change / Baseline value.
- Subjects who have only baseline (without post-baseline measurements) for a parameter at a visit, or only have post-baseline value for a parameter at a visit, will be excluded from the summary of change from baseline for that parameter at that visit – because the changes cannot be calculated.
- Version 9.4 of SAS® or higher will be the statistical software package used to produce all summaries, listings, statistical analyses, and graphs.

3.2 Subject Disposition

Subject disposition will be summarized with the following data:

- Total number of subjects who consented and total number of screen failures.
- The number and percentage of subjects who completed or discontinued prematurely from the study.
- A listing of subjects who discontinued prematurely from the study. The listing will include information of study site number, subject number, age, gender, number of days on study, and reason for discontinuation. The number of days on study will be calculated using the following formula: study exit date – date of first dose + 1.
- The number of subjects who were enrolled at each study site, the number and percentage of subjects who completed or discontinued at each study site will be summarized too.

The End of Trial CRF will be used to determine who discontinued prematurely from the study.

3.3 Protocol Deviations

Protocol deviation will be summarized by type of deviations listed on the CRF. Both the number of deviation events and distinct number and percentage of subjects will be presented by type of deviation for males, females, and all subjects.

3.4 Analysis Populations

All Screened: those who signed Informed Consent Form and screened at study sites.

All Enrolled: all couples who are enrolled into the study. This excludes screen failures.

All Treated: All enrolled couples where the man applied at least one dose of study drug.

3.5 Demographics and Pre-Treatment Characteristics

Subject demographics and pre-treatment characteristics will be summarized for the All Enrolled analysis population.

3.5.1 Demographics

The summary of demographics will include age, gender, ethnicity, race, weight, and height, body mass index (BMI) at baseline for males, females, and all subjects. The summary will include:

- The number and percentage of subjects within each category of gender, ethnicity, and race
- The 6-number summary statistics (number of non-missing observations, mean, median, SD, minimum, and maximum) for age, weight, and height, BMI, as well as the number and percentage of subjects in each category of BMI: Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25.0 – 29.9), and Obese (≥ 30.0). Weight at baseline will be used for the summary.
- Highest Level of Education Completed and Marital Status will also be summarized by presenting the number and percentage of subjects in the response categories.

3.5.2 Medical History

The number and percentage of distinct subjects reporting medical history for each body system (Dermatological, Respiratory, etc.) will be presented along with total number of events counts by medical history status for males, females, and all subjects:

- Ongoing
- Resolved

3.5.3 Substance Use

Substance use include tobacco, alcohol, and illicit drugs. Categorical responses, e.g., Never, Current, or Former, will be summarized by number and percentage of subjects in each category for males, females, and all subjects.

3.5.4 Urinalysis

Urinalysis includes Color, Clarity, Leukocyte Esterase, Nitrite, Protein, etc., and performed at the screening visit only. They will be summarized for males, females, and all subjects categorically because their results are qualitative with values as “Positive” (including “1+”, “2+”, and “3+”), “Negative”, “Clinically Significant” (CS), “Not Clinically Significant” (NCS), “Reactive”, and “Non-Reactive”.

3.5.5 Contraceptive History

The number and percentage of female subjects with “First Planned Method of Contraception for this Study” will be presented by contraception method:

- Abstinence
- Male Sterization/Vasectomy
- Same-sex relationship
- Female condom

- Male condom
- Diaphragm
- Oral Contraceptive Pill
- Spermicides
- Vaginal Rings
- Contraceptive Patch
- Sponge
- Cervical Cap
- IUD
- Injectable
- Implant
- Partner Surgically Sterile
- Other

Similar summary will also be done for “Second Planned Method of Contraception for this Study”, which has the same list as above “First Planned Method” with one additional choice:

- Not applicable

Then for “Contraceptive History”, the number and percentage of female subjects with each of the above listed contraceptive methods, in addition to “Emergency Contraception”, will be provided.

For “Length of Abstinence”, it will be summarized by 6-number statistics.

Number and percentage of female subjects with responses (Yes, No, Undecided) to the following question on the “Contraceptive History” form will also be presented:

- Does the subject desire to have children after the study?

3.5.6 Physical Examination for Male Subjects

Physical examination will be performed at screening only and for male subjects at body areas of: General Appearance, Skin, HEENT, Thyroid, Lungs, Back, Breast (gynecomastia), Heart, Abdomen, Extremities, Neurological, and Other. The examination results are categorized as “Normal” or “Abnormal”, which will be summarized categorically by body area with the number and percentage of subjects in each category.

3.5.7 Andrological History and Prostate-Specific Antigen for Male Subjects

The number and percentage of male subjects in each of the following andrological history conditions will be presented along with the number and percentage of male subjects with their condition currently ongoing and resolved:

- Vasectomy
- Sexually transmitted disease
- Testicular cancer
- Prostatic disease
- Erectile dysfunction
- Maldescended testes

- Orchitis
- Infection or inflammation of the urogenital tract
- Mumps as an adult
- Genital lesions
- Operations on the genital tract
- Disease of the gonads
- Testicular trauma
- Male infertility
- Varicocele

Prostate-Specific Antigen (PSA) test will be done at the screening visit for male subjects. The data will be summarized both numerically for quantitative measurements (unit: ng/mL), and categorically for the cases of “out of limits”, which classified as NCS, AE, or HALT (Highly Accelerated Life Testing).

3.5.8 Prior Medications

All medications taken by the subject within 30 days of screening and during the study will be recorded on the prior and concomitant medication CRF page. Prior medications are medications that were taken before the first dose, and concomitant medications are medications taken on or after the first dose. A medication may be both “prior” and “concomitant” if the subject took it before the first dose and continued taking it during the study. See section 3.6.1 for more details on concomitant medications.

All medications recorded on the CRF will be coded to the therapeutic drug classes and generic drug names using the World Health Organization (WHO) Drug Dictionary, March 2016 version. The number and percentage of subjects for male and female who had prior medications that were coded to each generic drug name and therapeutic drug class, as well as the number and percentage of subjects who had at least one prior medication will be presented. Subjects reporting more than one drug in each drug class/generic name are only counted once to that drug class/generic name.

3.6 Concomitant Medications and Treatment Compliance

3.6.1 Concomitant Medications

As defined in the Section 3.5.8, concomitant medications are medications taken on or after the first dose. Concomitant medications will be summarized for Safety population by the number and percentage of subjects in each coded drug name and drug class.

3.6.2 Treatment Compliance

Treatment compliance is generally defined as percent of dosage a subject received relative to the dosage which should have been received. This is a study with all dosing done on-site and directly supervised by study staff at the clinics. All treated (male) subjects will get the amount of study gel exactly as planned, thus result in a 100% treatment compliance. No table or listing will be dedicated for this simple fact.

3.7 Pharmacokinetic Analyses

The primary objective of this clinical trial is to evaluate the T and NES levels in female subjects after skin contact with dosed male partners. The treatment administration, blood (serum) and non-blood (D-square strips) sampling schedule is as following chart:

Visit ID/ (Study Day)	Visit Name / Time-point	Hormone/ Total T (serum)	T (serum)	NES & T (serum)	NES & T (D-square strips)
1	Female Screening Visit 1	X			
	Male Screening Visit 1	X			
2 (the day before Day 1)	Female Screening Visit 2 (Baseline) / 1, 2, 4, 8, 12, 16, 20 and 24 hrs		X		
	Male Screening Visit 2 (Baseline) / 1, 2, 4, 8, 12, 16, 20 and 24 hrs		X		
3 (Day 1)	Female Study Treatment Visit 3 / 2, 3, 4, 5, 6, 8, 10, 14, 18, 22 and 26 hrs (±15 min)			X	
	Male Study Treatment Visit 3 / Pre-Dose -15, -5 min, 1, 2, 4, 8, 12, 16, 20 and 24 hrs (± 15 min)			X	
4 (Day 3)	Female Study Treatment Visit 4 / 50 hrs after male gel application			X	
5 (Day 8)	Female Study Treatment Visit 5 / 2, 3, 4, 5, 6, 8, 10, 14, 18, 22 and 26 hrs (±15 min)			X	
	Male Study Treatment Visit 5 / **Serum:** -15 min (pre-dose), -5 min (pre-dose), 1, 2, 4, 8, 12, 16, 20 and 24 hrs **D-Square:** 1.5 and 2.5 hrs (±15 min) after gel, shower; Stripped total of 10 times			X	X
6 (Day 10)	Female Study Treatment Visit 6 / 50 hrs after male gel application, i.e., about 48 hrs after skin rub			X	
7 (Day 15)	Female Study Treatment Visit 7 / 2, 3, 4, 5, 6, 8, 10, 14, 18, 22 and 26 hrs (±15 min)			X	
	Male Study Treatment Visit 7 / **Serum:** -15 min (pre-dose), -5 min (pre-dose), 1, 2, 4, 8, 12, 16, 20 and 24 hrs. **D-Square:** T-shirt immediately after gel application, 1.5 and 2.5 hrs (±15 mi) after gel, Stripped total of 10 times			X	X
8 (Day 17)	Female Study Treatment Visit 8 / 50 hrs after male gel application, i.e., about 48 hrs after skin rub			X	
9 (Day 31)	End of Study (Visit 9, Female only)			X	

All analyses described in section 3.7 will be done by subject gender for the All Treated population.

3.7.1 Primary Analyses

Pharmacokinetic parameters, including minimum concentration (C_{min}), maximum concentration (C_{max}), area under the curve (AUC), average concentration (C_{avg}), time to

maximum concentration (T_{max}), and peak trough fluctuation rate (%PTF) will be derived for NES and T, under the following 2 methods, at each of the 3 doses:

- with baseline-correction, i.e., baseline concentration value will be subtracted from the (post-baseline) concentration value
- without baseline-correction, i.e., no subtraction will be done

The baseline value at each of the 3 doses is defined as the following for male and female subjects:

- Male: average of the minus 15- and minus 5-min (pre-dosage) at each of the dosing days (Day 1, 8 and 15).
- Female: 2-hour sample (the sample drawn pre-exposure to the man's site of gel application) at each of the dosing days (Day 1, 8 and 15)

Minimum Concentration (C_{min}): This will be the minimum concentration obtained during the sampling period by the formula given below, with unit = pg/mL. Note that C_0 (for pre-dose concentration) not included, and C_t is the last measurable concentration value.

$$C_{min} = \min (C_1, C_2, \ldots, C_t).$$

Maximum Concentration (C_{max}): This is similar to C_{min}, but takes the maximum value.

$$C_{max} = \max (C_1, C_2, \ldots, C_t).$$

Time to maximum concentration (T_{max}): T_{max} will be the time at which C_{max} is achieved.

Area Under the Concentration time curve (AUC): This will be calculated for time [0 – t], where t is the last time-point with measurable concentration for individual formulation.

$$AUC_{0-t} = \sum \{(C_i + C_{i+1})/2 \times (t_{i+1} - t_i)\}$$, the summation is for i = 0, 1, 2,…, t.

Average Concentration (C_{avg}): It is the AUC during the dosing interval divided by time interval length.

$$C_{avg} = AUC_{0-t} / t$$

Fluctuation, i.e., Peak Trough Fluctuation (PTF), rate:

$$\%PTF = 100 \times (C_{max} - C_{min}) / C_{avg}$$

The above PK parameters will be calculated for each subject at each of the 3 doses, corresponding to the 3 variations of skin contact, respectively:

- without washing or clothing barrier to the skin to skin contact,
- after the application site is washed with soap and water in a shower and dried,
- with a 100% cotton T-shirt clothing barrier.

For each of these PK parameters the summary statistics, including (arithmetic) mean, SD, percentage coefficient of variation (%CV), median, minimum, maximum, and geometric mean, will be presented.

3.7.2 Secondary Analyses

Secondary analyses will include:

- Six-number statistics for male and female subjects T levels (concentration values) at baseline, post-baseline, changes from baseline and percentage changes from baseline; NES levels at each visit/time-point.
- Pharmacokinetic parameters C_{min}, C_{max}, AUC, C_{avg}, T_{max}, and %PTF for T and NES in male subjects, which will be compared with and without wearing a T shirt and washing.
- Testosterone and Nestorone levels 6-number statistics on male skin 90 and 150 minutes after gel application as measured by adhesive D-square strips for male subjects at Visits 5 (Day 8) and 7 (Day 15).

3.8 Safety Analysis

All safety analyses will be done for the All Treated population. In addition to the statistical summaries, data listings will also be presented for all safety data.

3.8.1 Treatment Administration

Treatment administration data are collected on the treatment days (Study Days 1, 8, and 15) for male subject as follows, in addition to date and time variables:

(a) What was actual dose administered (mL)?
(b) Did the subject wear a T-Shirt during rubbing? (Yes, No)
(c) Did the subject shower before rubbing? (Yes, No)
(d) How many D-square strips were used to sample during the 90 minute D-square stripping?
(e) Was the 90 minute D-square stripping completed? (Yes, No)
(f) How many D-square strips were used to sample during the 150 minute D-square stripping?
(g) Was the 150 minute D-square stripping completed? (Yes, No)

Categorical data, such as items (b), (c), (f), and (g), will be summarized by the number and percentage of subjects in each response category, and numeric data will be summarized by 6-number statistics.

3.8.2 Adverse Events and Serious Adverse Events

An adverse event (AE) is any symptom, sign, illness, or experience that develops or worsens in severity and/or frequency after the start of study drug. A serious adverse event (SAE) is any AE that results in any of the following outcomes: Death; immediate threat to life; inpatient hospitalization or prolongation of an existing hospitalization; persistent or significant disability/incapacity; congenital anomaly/birth defect. A treatment-emergent AE (TEAE) is an AE that was not present prior to first dose or was present but worsened in severity after the first dose. All AEs will be coded with system organ class (SOC) and preferred term (PT) from the (Medical Dictionary for Regulatory Activities) MedDRA Version 19.0.

Incidence of TEAEs and SAEs will be summarized by SOC and PT with the number and percentage of subjects with each SOC and PT for males, females, and all subjects. The following tables will be presented:

- TEAEs by SOC and PT
- SAEs by SOC and PT
- TEAEs that led to study discontinuation or death by SOC and PT
- TEAEs by SOC and PT by severity
- TEAEs by SOC and PT by relatedness to the study product
- TEAEs in descending order of PT frequencies (no SOC displayed)

For all the above tables, subjects reporting more than one TEAE/SAE in each PT will be counted only once to that PT, using the most severe intensity, for unique number of subjects counting. The only exception to this will be for the summary by relatedness to the study product, where subjects will be counted only once using the strongest relatedness to the study product. The same principle also will be applied to the summary at the SOC level.

A high-level summary table for overall TEAEs/SAEs will also be provided with total number and percentage of distinct subjects (but no SOC or PT) for

- AE severity (Mild, Moderate, Severe)
- AE relatedness (Insufficient data to assess, Not Related, Unlikely, Possible, Probable, Highly Probable, and pool of Possible/Probable/Highly Probable)
- SAE
- Discontinued due to any AE
- Death due to any AE/SAE.

Another high-level summary table will present the counts of events (not distinct subjects) as the following chart. Note that each percentage, if provided, is based on the number on the last row at that column, where “(100.0)” is displayed. This AE summary table provides the cross reference between every level of relatedness and severity at the event-level.

Relatedness to Study Product	AE Severity			
	Mild	Moderate	Severe	Total # (%) of Events
Insufficient data to assess	xx	xx	xx	xx (x.x)
Not Related	xx	xx	xx	xx (x.x)
Unlikely Related	xx	xx	xx	xx (x.x)
Possible	xx	xx	xx	xx (x.x)
Probable	xx	xx	xx	xx (x.x)
Highly Probable	xx	xx	xx	xx (x.x)
Total # (%) of Events	xx (x.x)	xx (x.x)	xx (x.x)	xx (100.0)

Two listing-style tables, one for SAEs and the other for TEAEs that led to premature study discontinuation or death, will also be presented, with the details about AE onset date, resolved date, days of onset since the first dosing, severity, outcome, treatment for the

AE, and relatedness to the study product, as well as other supportive data such as the subject's gender and age.

3.8.3 Clinical Laboratory Tests

Hematology and chemistry data, collected at screen/baseline and last treatment day (Day 15) for both male and female subjects, include:

- Complete Blood Counts (CBC): RBC, WBC, Hemoglobin, Hematocrit, Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Platelet Count
- Clinical chemistries: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, calcium, as well as liver function tests: total bilirubin, alkaline phosphatase (ALPH), alanine aminotransferase (ALT), aspartate transaminase (AST), BUN, and albumin.

These data will be first summarized (for males, females, and all subjects) for observed values and mean changes from baseline to final evaluation (study exit). Then a summary of shifts from baseline to final evaluation will be given for each lab test parameter. The normal range for each lab parameter will be used to create categories of "Low", "Normal", or "High". Any result that is higher (lower) than the upper (lower) limit of normal will be categorized as "High" ("Low"); any result within the lower and upper limits of normal will be categorized as "Normal". The number and percentage of subjects in each shift category from baseline to final evaluation will be presented by lab test parameter.

3.8.4 Vital Signs and Weight

Vital signs assessments include pulse rate, respiration rate, weight, systolic and diastolic blood pressures (which are collected 3 times, at approximately 5 minute intervals), as well as mean systolic and mean diastolic blood pressure (i.e., average of the 3 times measurements). The results will be summarized (for males, females, and all subjects) by visit with 6-number statistics, except for the question "Blood Pressure or Pulse Abnormal?" with responses of Normal, Abnormal- NCS, AE, or SAE, which will be summarized categorically.

Body mass index (BMI) will be calculated numerically as Weight in kilogram / square of Height in meter, and rounded to 1-decimal place, and then categorized as: Underweight (< 18.5), Normal (18.5 – 24.9), Overweight (25.0 – 29.9), and Obese (≥30.0). BMI will be summarized categorically.

3.8.5 Skin Examination for Female Subjects

Skin examination for females includes facial acne and hirsutism assessment, which will be performed at Screening, Visits 4, 6, 8, and 9 (Study Exit). Acne will be assessed at areas of face, back, and chest, with rating as follows:

- 0 = Normal
- 1 = Skin is almost clear
- 2 = Some non-inflammatory lesions are present
- 3 = Non-inflammatory lesions predominate
- 4 = Inflammatory lesions are more apparent
- 5 = Highly inflammatory lesions predominate

The acne assessment results will be summarized categorically for each visit by location where exams are done.

Changes in hirsutism are assessed using the Ferriman-Gallwey scale in female subjects exposed to the combination NES + T gel. A score of 0, 1, 2, 3 and 4 is assessed for 9 different body areas: between the nose and mouth, on the chin and neck, chest, stomach, pubic area, upper arms, upper leg, upper back, and lower back/buttocks. Then a total score from these 9 areas will be tallied and categorized as follows. The number and percentage of subjects in each category will be presented by visit.

- Absence of terminal hair, if total score = 0
- Normal, if the total score is below 8
- Mild hirsutism, if the total score is between 8 and 15
- Moderate or severe hirsutism, if the total score is over 15.

Other skin exam data collected on the CRF as follows will also be summarized categorically by visit:

- Areas of hair removal (Between Nose and Mouth, Chin and Neck, Chest, Stomach, Pubic area, Upper arms, Upper leg, Upper back, Lower back/buttocks)
- Method of hair removal (Shaving, Waxing, Laser, Other)
- Frequency of hair removal (Daily, Twice per week, Weekly, Monthly, Other).

3.8.6 Pregnancy Tests

All pregnancy related data, test results, pregnancy notification, and outcomes, if any, will be presented in data listings.

3.8.7 Contraception and Menstrual Bleeding

The number and percentage of female subjects for the question of “methods of contraception have you used since the last time” will be summarized by study visit for All Treated population with all the categories listed on the CRF as follows:

- Abstinence
- Female condom
- Male condom
- Diaphragm
- Oral Contraceptive Pill
- Spermicides
- Vaginal Rings
- Contraceptive Patch
- Sponge
- Cervical Cap
- IUD
- Injectable
- Implant
- Partner Surgically Sterile
- Same-sex relationship
- Other

“Date of last menstrual period”, together with above detailed data, will be presented in a data listing.

4.0 APPENDICIES

4.1 Schedule of Assessments

The follows are copied from the study protocol.

Assessment	Screening Phase			Treatment Phase[a]							End of Study[a]	UNS
Visit Number	1	2[j]		3	4	5	6	7	8		9	
Study Day	-28 to 0			1	3	8	10	15	17		30	
Both Partners												
Informed Consent	X											
Assign Subject Number	X											
Determine/Confirm Eligibility	X											
Demographics	X											
Medical, Reproductive, and Contraceptive History	X											
Questions on Contraceptive and Pregnancy Planning	X											
Vital Signs[d]	X			X	X[l]	X	X[l]	X	X[l]		X[l]	X
Fasting CBC and Clinical Chemistry[b]	X							X				X
Lipid panel[c]	X											X
24-hour T PK sampling[k]		X										
Overnight Stay		X		X		X		X				X
Supervised Skin Contact				X		X		X				X
Adverse Events		X		X	X	X	X	X	X		X	X
Concomitant Medications	X	X		X	X	X	X	X	X		X	X
Male Partner												
Andrological History	X											
Complete Physical Exam[e]	X											X
PSA	X											X
Urinalysis	X											X
Gel Application				X		X		X				X
Wear T-shirt				X								X
Shower						X						X
NES and T sampling[f]				X		X		X				X
Residual Nestorone Measurements[g]						X		X				X
Phone Contact											X	X
Female Partner												
Gynecological and Menstrual History	X											
Pregnancy Test	X											X
Facial Acne and Hirsutism Assessment [i]	X											
Skin and Hair Growth Questions				X	X	X	X	X	X		X	X
Contraception and Menstrual Bleeding Questions				X		X		X				X
Post Skin Contact Washing				X		X		X				X
NES and T sampling[h]				X	X	X	X	X	X		X	X

Footnotes:

[a] Only the female partner is required to come in for visits on days 3, 10, 17 and 30.

[b] CBC (complete blood counts) and Clinical Chemistry panel (glucose, liver and renal function tests including urea, creatinine, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, bilirubin) will be done for both men and women at screening and then again on day 16 prior to leaving the in-patient clinic.

[c] Full lipid panel (Total cholesterol, HDL, LDL, triglycerides and HDL/LDL ratio) will be done for both men and women at screening and then on day 16 prior to leaving the in-patient clinic.

[d] Vitals includes weight, pulse, blood pressure and respiratory rate. Height will also be collected at screening in order to calculate BMI. Three blood pressure measurements will be taken with 5-minute rest period in between readings and the mean of the three measurements will be documented.

[e] Complete physical exam should include a detailed andrological exam

[f] For the male partner, serial blood draws for Nestorone and testosterone measurements will be collected at -15 and -5 minutes before gel application and at 1, 2, 4, 8, 12, 16, 20 and 24 hours after gel application.

[g] Using adhesive D-square strips a single location on the application site will be stripped on the male partner a total of ten times and the strips will then be analyzed for testosterone and Nestorone.

[h] For the female partner, serial blood draws for Nestorone and testosterone measurements will be collected at 0 minutes and then 1, 2, 3, 4, 6, 8, 12, 14, 16, 20 and 24 hours after female exposure to male participant gel application site. She will also return at around 10 am on days 3, 10 and 17 for a single 48 hour post contact blood draw. A single blood draw at Visit 9(Day 30) will occur to assess residual levels of testosterone and Nestorone.

[i] For the female partner, an examination should be done at screening to assess any kind of facial acne or hirsutism.

[j] Screening Visit 2 should occur one day prior to Visit 3/Day 1.

[k] 24-hour Testosterone PK assessment before the first dose.

[l] Vitals signs will only be collected for female subjects.

4.2 Table of Contents for Data Display

Following is the list of planned tables, listings, and figures. Tables will be numbered according to the nomenclature used to support the final clinical study report.

The format of each unique table is provided in a separate document of "Table Shells for CCN005B", but no data listing shells or figure shells are provided. Some outputs from statistical programming may be slightly different in layout from that illustrated in "Table Shells for CCN005B". The table shells will not be amended to match the actual tables in such cases.

Table Number	Table Title	Analysis Population
14.1.1	Summary of Subject Disposition and Reasons for Discontinuation	All Screened
14.1.2	List of Subjects Who Prematurely Discontinued the Study	All Enrolled
14.1.3	Summary of Protocol Deviations	All Enrolled
14.1.4	Demographics and Pre-Treatment Characteristics	All Enrolled
14.1.5	Summary of Medical History	All Enrolled
14.1.6	Summary of Substance Use	All Enrolled
14.1.7	Summary of Urinalysis	All Enrolled
14.1.8	Summary of Contraceptive History	All Enrolled
14.1.9	Summary of Physical Examination for Male Subjects	All Enrolled
14.1.10	Summary of Prostate-Specific Antigen Test for Male Subjects	All Enrolled
14.1.11	Summary of Andrological History for Male Subjects	All Enrolled
14.1.12.1	Number and Percentage of Subjects with Prior Medication Use	All Enrolled
14.1.12.2	Number and Percentage of Subjects with Concomitant Medication Use	All Treated
14.1.12.3	Number and Percentage of Subjects with Both Prior and Concomitant Medication Use	All Treated
14.2.1F	Analysis of Pharmacokinetic Parameters for Female Subjects	All Treated
14.2.1M	Analysis of Pharmacokinetic Parameters for Male Subjects	All Treated
14.2.2F	Summary of Testosterone and Nestorone Levels and Changes from Baseline for Female Subjects	All Treated
14.2.2M	Summary of Testosterone and Nestorone Levels and Changes from Baseline for Male Subjects	All Treated

14.2.3	Residual Nestorone and Testosterone on Male Subjects Skin as Measured by Adhesive D-Square Strips	All Treated
14.3.0	Study Drug Administration for Male Subjects	All Treated
14.3.1.1	Overall Number and Percentage of Subjects with Treatment-Emergent Adverse Events	All Treated
14.3.1.2	Overall Treatment-Emergent Adverse Events by Severity and Relatedness to the Study Product	All Treated
14.3.1.3	Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term	All Treated
14.3.1.4	Number and Percentage of Subjects with Treatment-Emergent Adverse Events that Led to Premature Study Discontinuation or Death	All Treated
14.3.1.5	Number and Percentage of Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and by Severity	All Treated
14.3.1.6	Number and Percentage of Subjects with Treatment-Emergent Adverse Events by System Organ Class and Preferred Term and by Relatedness to the Study Product	All Treated
14.3.1.7	Number and Percentage of Subjects with Treatment-Emergent Adverse Events by Preferred Term in Descending Order of Frequencies	All Treated
14.3.2.1	List of Treatment-Emergent Serious Adverse Events	All Treated
14.3.2.2	List of Treatment-Emergent Adverse Events that Led to Premature Study Discontinuation	All Treated
14.3.4	Vital Signs and Weight Changes from Baseline	All Treated
14.3.5.1	Hematology Test Results and Changes from Baseline	All Treated
14.3.5.2	Hematology Test Results Shifts from Baseline	All Treated
14.3.5.3	Clinical Chemistry Test Results and Changes from Baseline	All Treated
14.3.5.4	Clinical Chemistry Test Results Shifts from Baseline	All Treated
14.3.6.1	Acne Assessment Results for Female Subjects	All Treated
14.3.6.2	Hirsutism Assessment Results for Female Subjects	All Treated
14.3.6.3	Summary of Other Skin Examination Results for Female Subjects	All Treated
14.3.7	Summary of Contraception for Female Subjects	All Treated

Listing Number	**Listing Title**	**Analysis Population**
16.2.1.1	Subject Disposition	All Screened

16.2.1.2	Eligibility	All Enrolled
16.2.2	Protocol Deviations	All Enrolled
16.2.4.1	Demographics	All Enrolled
16.2.4.2	Medical History	All Enrolled
16.2.4.3	Substance Use	All Enrolled
16.2.4.4	Contraceptive History for Female Subjects	All Enrolled
16.2.4.5	Physical Exam for Male Subjects	All Enrolled
16.2.4.6	Prostate-Specific Antigen for Male Subjects	All Enrolled
16.2.4.7	Andrological History for Male Subjects	All Enrolled
16.2.4.8	Total Testosterone and Other Hormones	All Enrolled
16.2.4.9	Prior and Concomitant Medications	All Enrolled
16.2.5.1	Study Drug Administration for Male Subjects	All Treated
16.2.5.2F	Pharmacokinetics Parameters for Female Subjects	All Treated
16.2.5.2M	Pharmacokinetics Parameters for Male Subjects	All Treated
16.2.6.1	Testosterone Concentration Values	All Treated
16.2.6.2	Nestorone Concentration Values	All Treated
16.2.7.1	Adverse Events	All Treated
16.2.8.1	Hematology	All Treated
16.2.8.2	Clinical Chemistry	All Treated
16.2.8.3	Urinalysis	All Treated
16.2.8.4	Pregnancy Tests	All Treated
16.2.8.5	Pregnancy Notification	All Treated
16.2.8.6	Pregnancy Outcome	All Treated
16.2.8.7	Contraception and Menstrual Bleeding	All Treated
16.2.9.1	Vital Signs and Weight	All Treated
16.2.9.2	Skin Examination for Female Subjects	All Treated

Figure Number	Figure Title	Analysis Population
14.2.1T_F	Area Under the Curve for Female Subjects Testosterone at the First Dose (with a 100% Cotton T-shirt Clothing Barrier)	All Treated
14.2.1T_M	Area Under the Curve for Male Subjects Testosterone Subjects at the First Dose (with a 100% Cotton T-shirt Clothing Barrier)	All Treated
14.2.1N_F	Area Under the Curve for Female Subjects Nestorone at the First Dose (with a 100% Cotton T-shirt Clothing Barrier)	All Treated
14.2.1N_M	Area Under the Curve for Male Subjects Nestorone at the First Dose (with a 100% Cotton T-shirt Clothing Barrier)	All Treated

Repeat for

- Second Dose (after the Application Site is Washed with Soap and Water in a Shower then Dried)
- Third Dose (without Washing or Clothing Barrier to the Skin to Skin Contact