NCT02651688

Study ID: ZA-205

Title: A Randomized, Double Blind, Placebo-Controlled, Multi-Center Study in Men with Acquired Hypogonadotropic Hypogonadism to Compare Changes in Body Composition and Metabolic Parameters with Diet and Exercise in Conjunction with Treatment with 12.5 mg or 25 mg Enclomiphene

Statistical Analysis Plan Amendment 1 Date: 29 July 2016

Repros Therapeutics Inc.
2408 Timberloch Place, B-7
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Statistical Analysis Plan

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Issue Date: May 3, 2016

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List of Abbreviations and Definitions

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CRF	case report form
AUC	Area under plasma concentration curve
AUC_{0-24}	Area under plasma concentration curve over 24 hours after dosing
AUC_{0-t}	Area under plasma concentration curve until last quantifiable value
$AUC_{0-\infty}$	Area under plasma concentration curve extrapolated to infinity
C_{avg}	Average concentration
C_{max}	Maximum measured plasma concentration over the final dosing interval
DHT	dihydrotestosterone
DISF-SR	Derogatis Interview for Sexual Function
dL	deciliter
DVT	deep vein thrombosis
ECG	electrocardiogram
FSH	follicle-stimulating hormone
g	grams
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
hCG	human chorionic gonadotrophin
Hct	hematocrit
Hgb	hemoglobin
HOMA-IR	Homeostasis Model of Assessment – Insulin Resistance
ICH	International Conference on Harmonization
IWQOL-LITE	Impact of Weight on Quality of Life
IND	investigational new drug
IRB	Institutional Review Board
kg	kilogram(s)
LBM	lean body mass
LH	luteinizing hormone
m	meters
mg	milligram(s)
mL	milliliter
ng	nanograms
TE	thromboembolic
PSA	prostate specific antigen
RBC	red blood cell
SAE	serious adverse event
SHBG	sex hormone binding globulin
SF-36	Rand 36-Item Short Form Health Survey
T	testosterone
Total T	total testosterone

$t_{½}$	Apparent elimination half life
T_{max}	Time of the maximum measured plasma concentration
λ_z	Terminal elimination rate constant
VTE	venous thromboembolism
WBC	white blood cell

1. INTRODUCTION/BACKGROUND

This statistical analysis plan (SAP) describes the data analysis specifications for study ZA-205, entitled "A Randomized, Double Blind, Placebo-Controlled, Multi-Center Study in Men with Acquired Hypogonadotropic Hypogonadism to Compare Changes in Body Composition and Metabolic Parameters with Diet and Exercise in Conjunction with Treatment with 12.5 mg or 25 mg Enclomiphene". This SAP adheres to ZA-205 Protocol Amendment I.

2. STUDY OBJECTIVES

The purpose of this study is to compare the effects of 12 months of treatment with enclomiphene 12.5 mg, 25 mg, or placebo capsules on body composition and metabolic parameters in overweight men with acquired hypogonadotropic hypogonadism (confirmed morning T $\leq$ 300 ng/dL) following a 6 month diet and 15 month exercise program. Subjects must not have been treated with testosterone products in the 6 months prior to the study and must not ever have used testosterone products for a year or longer.

3. STUDY DESIGN

3.1 OVERVIEW AND LENGTH OF STUDY

Protocol ZA-205 is a randomized, double-blind, placebo-controlled multi-center study to compare changes in metabolic parameters following treatment with 12.5 mg or 25 mg of enclomiphene or placebo in conjunction with a 6-month diet and 15 month exercise program, in overweight men with acquired hypogonadotropic hypogonadism. Subjects will receive a 15-month gym membership with personal trainer for 12 months, a Fitbit and a 6 month commercial diet program. The study requires 7 clinic visits and is approximately 15 months in duration. Subjects will be treated with enclomiphene or placebo for 12 months.

A schedule of procedures and assessments is displayed in Section 4 of the ZA-205 protocol. The study will enroll 45 male subjects, 15 randomized to treatment with enclomiphene 12.5 mg, 15 randomized to treatment with 25 mg enclomiphene, and 15 randomized to Placebo, in a 1:1:1 ratio.

Eligible subjects must have 2 consecutive screening assessments of morning testosterone $\leq$ 300 ng/dL; however testosterone measured at the baseline visit may be > 300 ng/dL. LH must be > 1.4 mIU/mL and below 9.4 mIU/mL at screening. Waist circumference must be $\geq$ 40 inches (101.6 cm).

[redacted]

In addition to a central lab used for blood analyses, a second lab using LCMS will analyze testosterone, estradiol, free testosterone, and dihydrotestosterone. The results from each lab will be treated as separate analytes.

3.2 SAMPLE SIZE CALCULATION/JUSTIFICATION

As this is a hypothesis-generating study sample size was not determined based on statistical

[redacted]

4. ANALYSIS SETS

4.1 INTENT-TO-TREAT POPULATION

The ITT population will consist of all patients randomized to treatment with enclomiphene or placebo.

4.2 SAFETY POPULATION

The Safety population will consist of all patients who take at least one dose of study drug and are assessed for safety.

5. ENDPOINTS

Efficacy endpoints include:

- Changes in lean body mass (LBM), assessed using DXA
- Changes in waist circumference, comparing enclomiphene to placebo
- Changes from baseline in testosterone, comparing enclomiphene to placebo
- Values and changes in values from baseline in luteinizing hormone (LH), hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), high sensitivity C-reactive protein, Interleukin-6, tumor necrosis factor (TNF-α) receptor 2, and leptin, comparing enclomiphene to placebo
- Change in strength assessed from maximum chest and leg press weight achieved
- Changes in insulin resistance determined by homeostasis model of insulin resistance (HOMA-IR) and Quantose IR™ (Metabolon Inc.), comparing enclomiphene to placebo
- Change in weight and BMI, comparing enclomiphene to placebo
- Values for dihydrotestosterone (DHT) and estradiol (E2), and the ratios of DHT:testosterone and testosterone:E2

[redacted]

6. STATISTICAL METHODOLOGY AND ANALYSES

6.1 General Considerations

Standard statistical methods will be employed to analyze all data. The following techniques may be used: paired t-test; independent two-sample t-test; ANOVA; chi-square test; and Fisher's exact test. Assumptions of normality will be tested using the Shapiro-Wilk test. If distributional assumptions are violated, non-parametric techniques, such as the Wilcoxon signed-rank test, Wilcoxon rank-sum test, and Kruskal-Wallis test, will be employed. Summaries for quantitative variables will include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables will include the number and percent of patients for each outcome. All summaries will be prepared for each dose level and treatment group, resulting in 4 analysis groups: 12.5 mg enclomiphene, 25 mg enclomiphene, pooled 12.5 and 25 mg enclomiphene, placebo.

Baseline will be defined as the most recent assessment that occurs on or before the start of study medication, unless otherwise specified.

[redacted]

Statistical significance will be declared if the two-sided p-value is ≤ 0.05.

Additional statistical analyses, other than those described in this SAP, may be performed if deemed appropriate.

6.2 Interim Analyses and Final Analyses

Interim analyses will be conducted after all subjects have been assessed for 3, 6, and 12 months. Although the results will be unblinded, per-subject randomization will not be disclosed to subjects, site personnel and the sponsor's clinical research staff to maintain the blind at the subject-level for the duration of the study. The study will not be stopped for claims of efficacy at these analyses. However, the study may be stopped for futility or safety at any time. No adjustments for the interim analyses will be conducted.

6.3 Adjustment for Multiple Comparisons

No adjustments for multiple comparisons will be made in this study.

6.4 Extent of Exposure

The duration of exposure will be calculated for each subject. Summary statistics will be presented for each treatment group using the Intent-to-Treat population.

6.5 Subject Disposition

Subject disposition will be summarized in terms of the number of subjects who completed the study and discontinued early from the study. Disposition will be summarized for each treatment group using the Intent-to-Treat population.

6.6 Deviations

The total number of each deviation type will be summarized for the Intent-to-Treat population.

6.7 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, consisting of previous testosterone therapy use, hypogonadal symptom history, disease history (diabetes, hypertension, hypercholesterolemia, depression, erectile dysfunction, hypothyroidism, and sleep apnea), age, and race will be summarized.

Demographics will be summarized for the Intent-to-Treat population. Demographic and baseline data will be listed for all subjects to supplement summary results. Results will be presented for each treatment group.

6.8 EFFICACY ANALYSES

Efficacy analyses will be conducted using the Intent-to-Treat population, as defined in Section 4.1.

6.8.1 Lean Body Mass

Lean body mass, bone mass, body fat mass, and percentage of total for each will be determined by DXA at baseline and over time. Pairwise comparisons between treatment groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Within each treatment group the statistical significance of the change/percentage change from baseline will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate.

For measures obtained by DXA, baseline will be defined as the earliest assessment, regardless of relation to the start of study medication.

6.8.2 Body Strength

Gains in strength over time will be assessed by changes/percentage changes in maximum single repetition chest/leg press. Pairwise comparisons between treatment groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Within each treatment group the statistical significance of the change/percentage change from baseline will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate.

For body strength measures, baseline will be defined as the earliest assessment, regardless of relation to the start of study medication.

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6.8.4 Testosterone, LH, DHT, E2, DHT:Testosterone, Testosterone:E2

Testosterone, LH, DHT, E2, DHT:testosterone, and testosterone:E2 levels will be measured at baseline and over time. Pairwise comparisons between treatment groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Within each treatment group the statistical significance of the change/percentage change from baseline will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate.

Two separate baselines will be defined for testosterone, a true baseline record as defined in Section 6.1, and a screening baseline, defined as the average of all screening testosterone measurements. A separate 'change from baseline' will be calculated using each.

6.8.5 Metabolic Parameters

HbA1c, FPG, Insulin, HOMA-IR, C-reactive protein, Interleukin-6, TNF-α, leptin, and Quantos IR levels will be measured at baseline and over time. Pairwise comparisons between treatment groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Within each treatment group the statistical significance of the change/percentage change from baseline will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate.

6.8.6 BMI, Weight, and Waist Circumference

BMI, weight, and waist circumference will be measured at baseline and over time. Weight and waist circumference will be measured at both the clinic and gym; however only clinic measurements will be used for analyses. Pairwise comparisons between treatment groups will be performed using t-tests and Wilcoxon rank-sum tests, as appropriate. Within each treatment group the statistical significance of the change/percentage change from baseline will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate.

6.9 SAFETY ANALYSES

The safety analyses will be conducted using the Safety population, as defined in Section 4.2.

6.9.1 Adverse Events (AEs)

Treatment-emergent AEs (TEAEs) are defined as those AEs with an onset date and time equal to or after the start of study medication, or those events in which the onset date and time are before the start of study medication but worsened after the start of study medication. To be conservative, in the case of a missing onset time for an AE, an AE with a start date equal to or after the dosing date will be considered treatment-emergent. AE's with missing onset dates will also be considered treatment-emergent.

All TEAEs will be summarized by treatment group. The number of TEAEs as well as the number and percentage of subjects who experienced at least one TEAE will be summarized for each system organ class and each preferred term. The percentage will be based on the number of subjects in a particular dose group included in the Safety population. Each subject will contribute at most one count per summarization category. TEAEs potentially related to study medication, serious TEAEs, and TEAEs leading to withdrawal will be summarized in a similar manner.

If a subject has more than one AE that codes to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one AE within a system organ class category, the subject will be counted only once for that system organ class category.

TEAEs will also be summarized by maximum severity and by strongest relationship to treatment within each treatment group. Serious adverse events (SAEs) will be tabulated and listed in a manner similar to TEAEs. A listing of all AE data will be provided to supplement the tabulated results.

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Statistical Analysis Plan

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Issue Date: July 29, 2016
Amendment I

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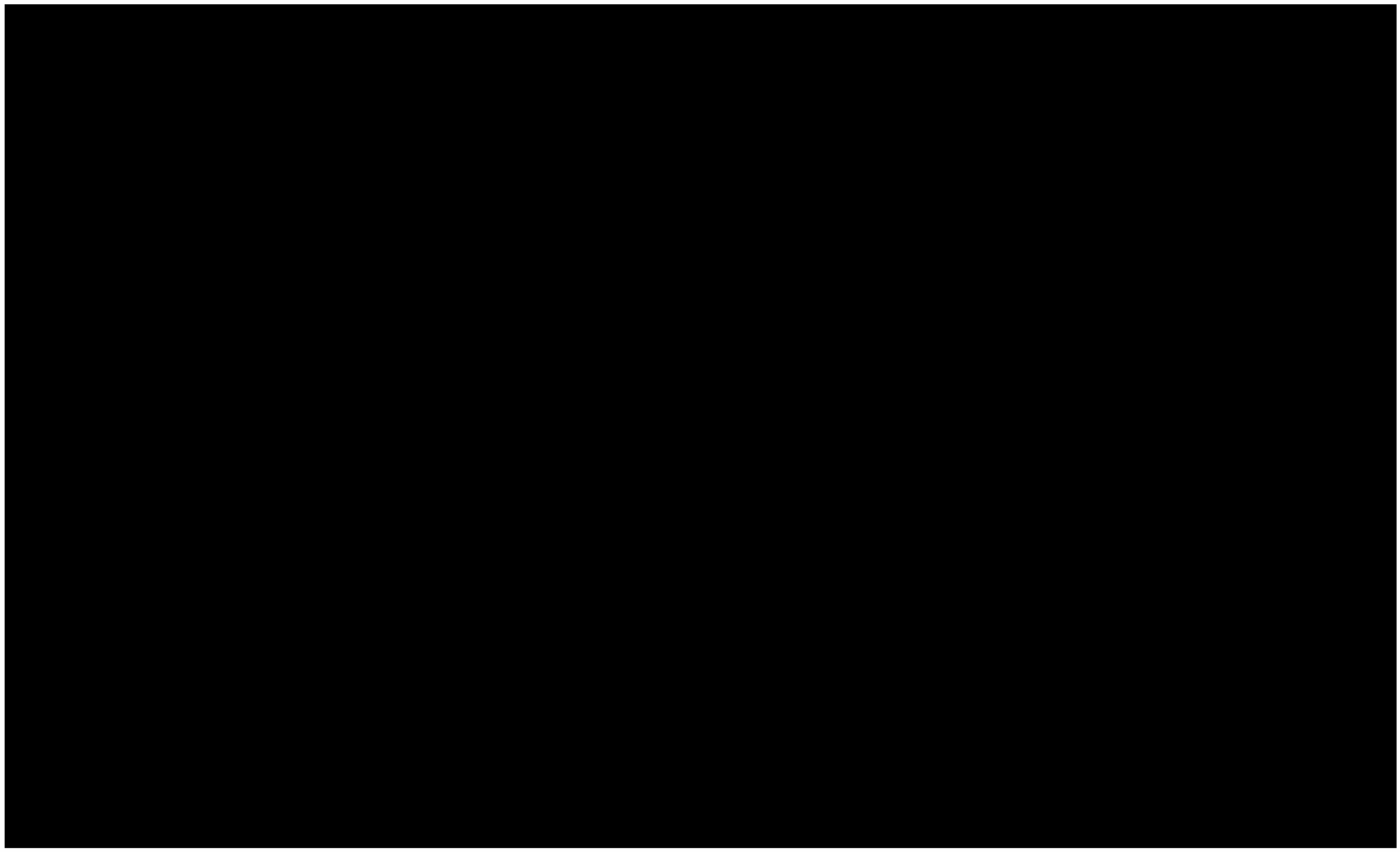

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g	grams
GCP	Good Clinical Practice
HbA1c	hemoglobin A1c
hCG	human chorionic gonadotrophin
Hct	hematocrit
Hgb	hemoglobin
HOMA-IR	Homeostasis Model of Assessment – Insulin Resistance
ICH	International Conference on Harmonization
IWQOL-LITE	Impact of Weight on Quality of Life
IND	investigational new drug
IRB	Institutional Review Board
kg	kilogram(s)
LBM	lean body mass
LH	luteinizing hormone
m	meters
mg	milligram(s)
mL	milliliter
ng	nanograms
TE	thromboembolic
PSA	prostate specific antigen
RBC	red blood cell
SAE	serious adverse event
SHBG	sex hormone binding globulin
SF-36	Rand 36-Item Short Form Health Survey
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