NCT01728454

Study ID: ZPE-202

Title: A Phase 2, Multi-Center, Parallel Design, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of 6 and 12 mg Proellex® (Telapristone Acetate) Administered Vaginally in the Treatment of Premenopausal Women with Confirmed Symptomatic Uterine Fibroids

Statistical Analysis Plan Date: 30 August 2016

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Statistical Analysis Plan
Stage 2

Protocol Number: ZPE-202

A Phase 2, Multi-Center, Three-Arm, Parallel Design, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of 6 and 12 mg Proellex® (Telapristone Acetate) Administered Orally in the Treatment of Premenopausal Women with Confirmed Symptomatic Endometriosis

Version Date: August 30, 2016

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List of Abbreviations and Definitions

AE	Adverse event
BBSS	Biberoglu Behrman symptom severity scale
C_{avg}	Average concentration
C_{max}	Maximum concentration
CRF	Case report form
DHEA	Dehydroepiandrosterone
dL	Deciliter
ECG	Electrocardiogram
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotrophin releasing hormone
g	Grams
hCG	Human chorionic gonadotrophin
ICH	International Conference on Harmonization
IGF-1	Insulin-like growth factor-1
IRB	Institutional Review Board
IND	Investigational new drug
IUD	Intra-uterine device
kg	Kilogram(s)
LD_{50}	Median lethal dose
LH	Luteinizing hormone
LOCF	Last observation carried forward
m	Meters
mg	Milligram(s)
mL	Milliliter
ng	Nanograms
NRS	Numerical Rating Scale
ODI	Off-Drug Interval
PCOS	Polycystic Ovarian Syndrome
PK	Pharmacokinetic
RBC	Red blood cell
SAE	Serious adverse event
VAS	Visual Analog Scale
WBC	White blood cell

1. INTRODUCTION

This statistical analysis plan (SAP) describes the data analysis specifications for stage 2 of study ZPE-202, entitled "A Phase 2, Multi-Center, Three-Arm, Parallel Design, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of 6 and 12 mg Proellex® (Telapristone Acetate) Administered Orally in the Treatment of Premenopausal Women with Confirmed Endometriosis". The preparation of this version of the SAP adheres to Amendment 9 of the ZPE-202 protocol.

Two separate analyses are planned. The first analysis will occur once all subjects have completed the placebo-controlled (stage 2) portion of the study, and will only include data from the placebo-controlled (stage 2) and baseline assessment (stage 1) portions of the study. The second analysis will occur once all subjects have completed the active treatment portion of the study (stage 3), and will include all data collected during the study.

This SAP will focus on analyses for stage 2. Another SAP will focus on analyses for stage 3.

2. STUDY OBJECTIVES

The purpose of this study is to determine the safety and efficacy of two doses of Proellex in premenopausal women with pelvic pain associated with endometriosis confirmed within the last seven years and using prescription analgesics for symptomatic pain.

3. STUDY DESIGN

3.1 OVERVIEW AND LENGTH OF STUDY

ZPE-202 is a phase 2, 3-arm study with an 18 week active dosing period and an option to extend treatment for 2 additional cycles. The study will be conducted in three stages.

In the first stage, women will undergo a baseline assessment period with placebo or no study medication until their second ovulation event. Endometriosis pain, dysmenorrhea, non-

[redacted]

In the second stage (placebo-controlled), following the baseline assessment period, subjects will be randomized into one of 3 arms (placebo, 6 mg Proellex, 12 mg Proellex) in a 1-1-1 fashion. The start of the 18 week dosing period for the first cycle of treatment should commence as soon after ovulation as possible, after which subjects will be followed until menses returns. Subjects who do not wish to receive additional cycles of treatment after stage 2 will have their last visit scheduled after blood flow has stopped. During this off-drug interval subjects will continue to record study information in the daily diaries.

After completing a minimum of 28 days of treatment in the second stage of the study, subjects may discontinue the study and still be eligible to qualify for 2 additional treatment cycles.

In the third stage (active treatment), subjects who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled to start dosing in their next course 21 days (+/- 2 days) after the start of bleeding, following the first menses after the end of

their first course of treatment (off-drug interval). Subjects will receive 2 courses of additional active treatment separated by an off-drug interval (ODI), after which they will continue to record study information in the daily diary. Subjects randomized to placebo in the second stage will receive 12 mg of Proellex in this stage. Those randomized to Proellex in the second stage will retain their current dose level for the duration of this stage. The final follow-up visit will be scheduled after blood flow has stopped.

3.2 Sample Size Calculation/Justification

Up to 60 female subjects, 20 per dose arm, meeting the inclusion/exclusion criteria will be randomized in a 1-1-1 fashion. The sample size was powered based on the two-sample t-test that will be used to make pairwise comparisons between treatment groups. It is anticipated that

[redacted]

4. ANALYSIS SETS

4.1 Intent-to-Treat Population

The ITT population will consist of all patients who are randomized and receive study drug.

4.2 Safety Population

The Safety population will consist of all patients who are randomized, receive study drug, and have some post-baseline safety data.

5. ENDPOINTS

Efficacy endpoints will be:

[redacted]

- Changes in patient and physician reported BBSS scores
- Number of subjects becoming amenorrheic
- Changes in pain assessments
- Changes in analgesic use

[redacted]

6. STATISTICAL METHODOLOGY AND ANALYSES

6.1 General Considerations

Standard statistical methods will be employed to analyze all data. It is anticipated that 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. 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 Adjustment for Multiple Comparisons

No adjustments for multiple comparisons will be made.

6.3 Extent of Exposure

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

6.4 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 using the Intent-to-Treat population.

6.5 Deviations

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

6.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the Intent-to-Treat population. Results will be presented for each treatment group.

6.7 Efficacy Analyses

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

[redacted]

[redacted]

[redacted]

6.7.3 Analgesic Use

Analgesic use (number of pills) and change/percentage change from baseline will be summarized from patient diaries. Non-prescription, prescription, and total analgesic use will be analyzed.

[redacted]

The statistical significance of the change/percentage change from baseline within treatment groups will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate. The change/percentage change from baseline will be compared between groups using a t-test or Wilcoxon rank-sum test, as appropriate.

6.7.4 Patient Reported Daily Endometriosis Pain and Sexual Avoidance Scores

Patient reported daily endometriosis pain and sexual avoidance scores and the change from baseline in each will be summarized from patient diaries.

[redacted]

[redacted]

The statistical significance of the change from baseline within treatment groups will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate. The change from baseline will be compared between groups using a t-test or Wilcoxon rank-sum test, as appropriate.

6.7.5 BBSS Patient Reported Scores

Patient reported daily BBSS component scores (dysmenorrhea, pelvic pain, dyspareunia) and total score and the change from baseline in each will be summarized from patient diaries.

[redacted]

The statistical significance of the change from baseline within treatment groups will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate. The change from baseline will be compared between groups using a t-test or Wilcoxon rank-sum test, as appropriate.

6.7.6 BBSS Physician Reported Scores

Physician reported BBSS component scores (pelvic tenderness and induration) and total score and the change from baseline in each will be summarized.

[redacted]

[redacted]

The statistical significance of the change from baseline within treatment groups will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate. The change from baseline will be compared between groups using a t-test or Wilcoxon rank-sum test, as appropriate.

6.7.7 VAS

VAS pain assessment scores and the percentage change from baseline will be summarized.

[redacted]

[redacted]

The statistical significance of the percentage change from baseline within treatment groups will be based on a paired t-test or Wilcoxon signed-rank test, as appropriate. The percentage change from baseline will be compared between groups using a t-test or Wilcoxon rank-sum test, as appropriate.

6.8 SAFETY ANALYSES

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

6.8.1 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 in stage 2, 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 included in the Safety population. Each subject will contribute at most one count per summarization category.

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. 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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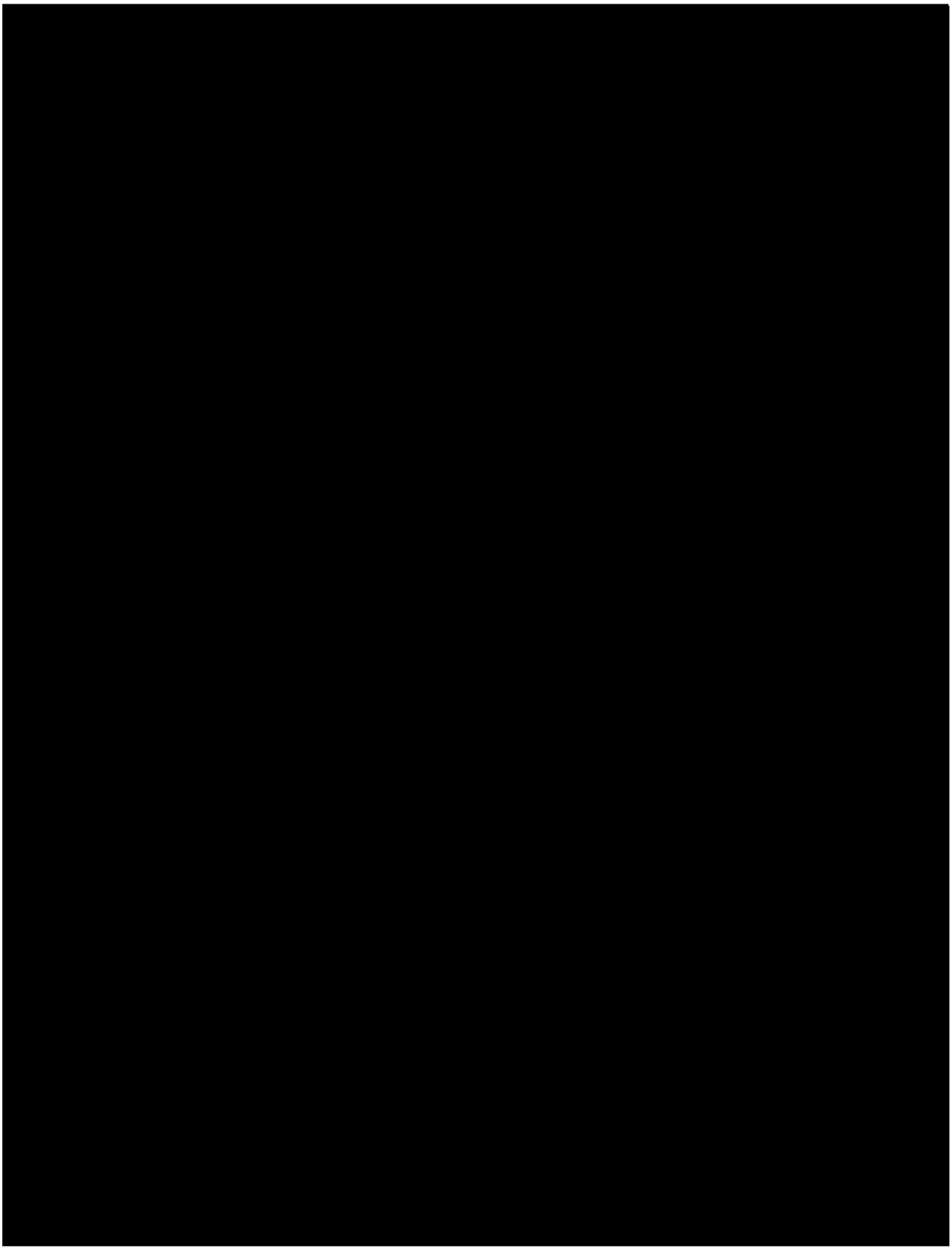

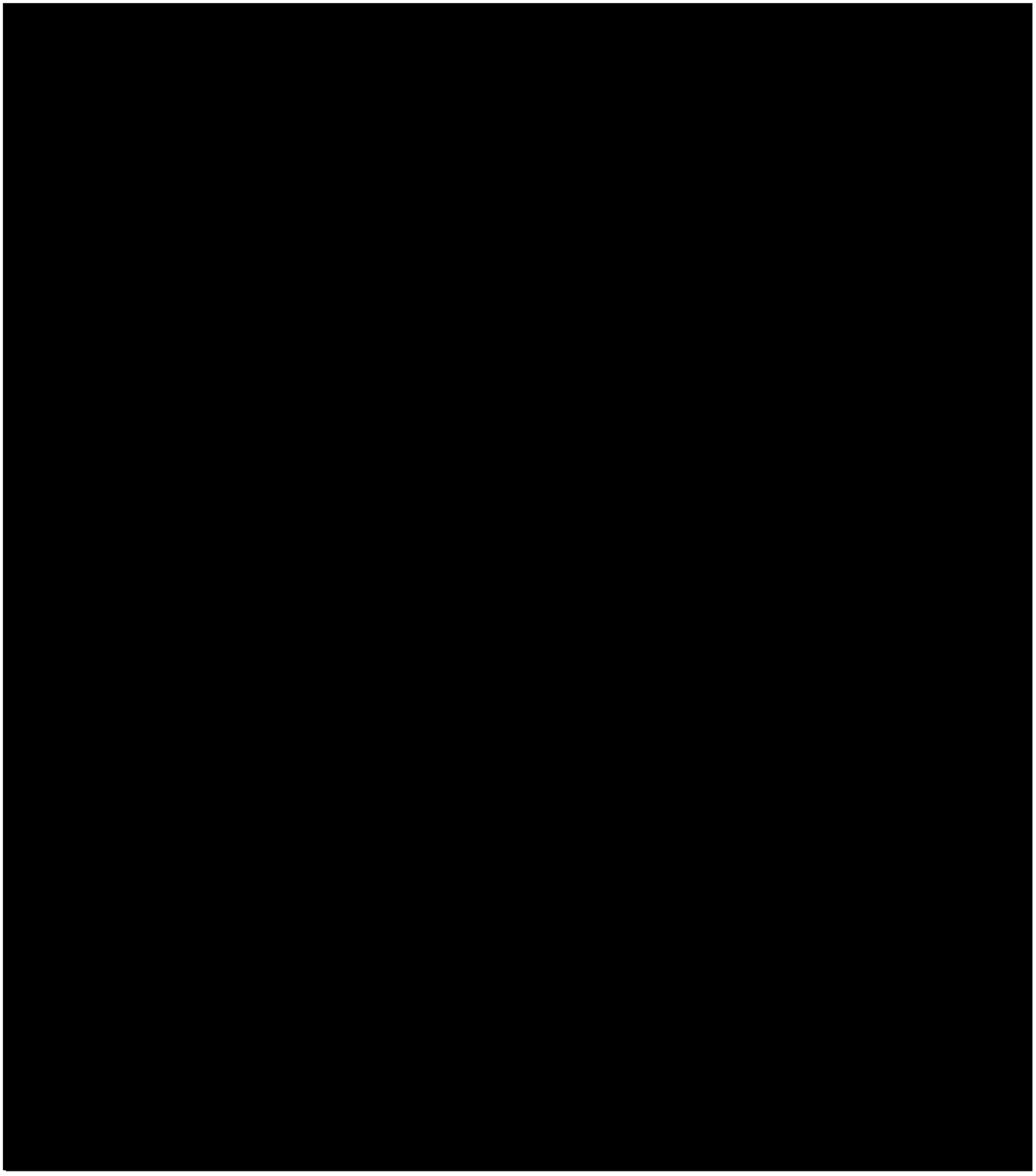

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