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

Protocol Amendment 9 Date: 02 March 2016

*Any inconsistent numbering or deletion of pages is due to the removal of a full protocol due to its summary of changes being supplied.

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 Endometriosis

Original Protocol: July 18, 2012

SPONSOR:

Repros Therapeutics Inc.®
2408 Timberloch Place, B-7
The Woodlands, TX 77380

IND 76,631

[redacted]

Confidentiality Statement
The confidential information in this document is provided to you as a Principal Investigator or consultant for review by you, your staff and the applicable Institutional Review Board / Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor, Repros Therapeutics Inc.®

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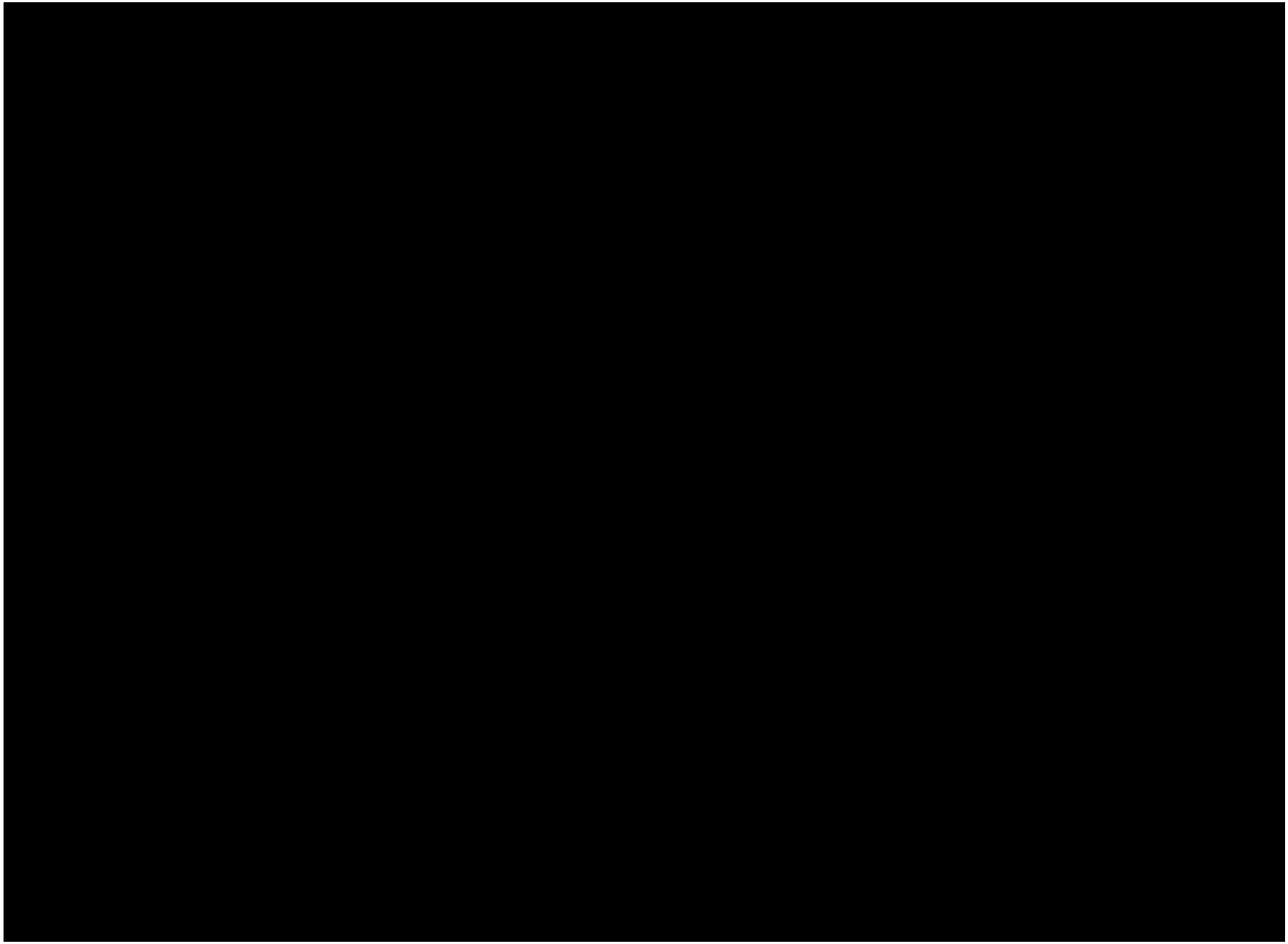
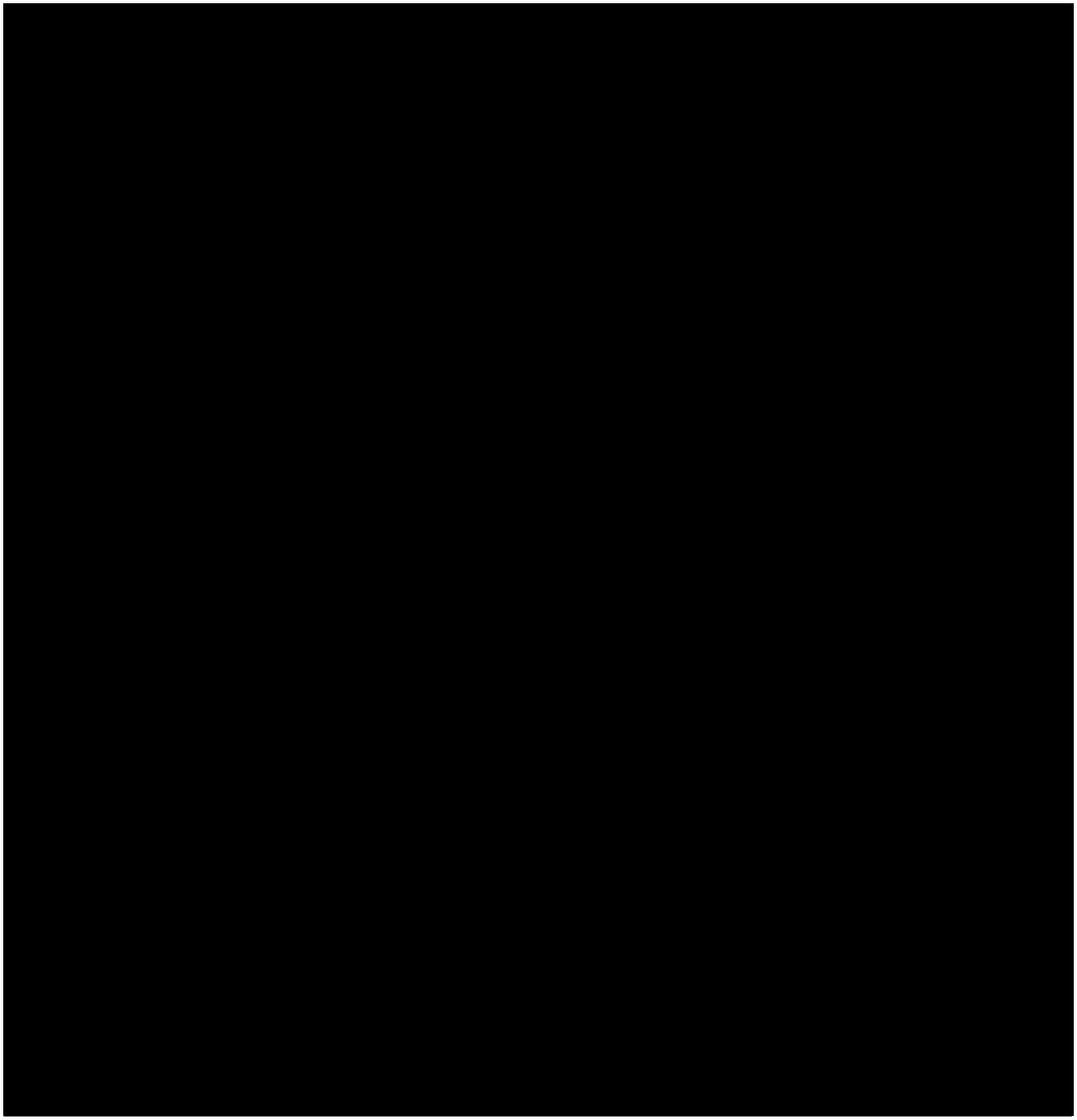
3. PROTOCOL SYNOPSIS

Test Drugs:	Proellex® (Telapristone Acetate): 6 and 12 mg gelatin capsules and matching placebo
Protocol Number:	ZPE-202
Study Purpose:	To determine the safety and efficacy of two doses of Proellex in premenopausal women with pelvic pain in confirmed endometriosis patients.
Study Design and Duration Of Treatment:	This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in two stages. In the first stage, women will receive daily single blind dosing with placebo, for at least one full menstrual cycle. Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications and vaginal bleeding intensity will be recorded using an electronic diary. Following the placebo run-in phase, subjects will be randomized into one of 3 arms in a 1-1-1 fashion weighted by a combined BBSS and analgesic score. The start of the 18 week dosing period in the double-blind phase should commence as soon after ovulation as possible, after which subjects will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the electronic diary. The final follow-up visit should be scheduled after blood flow has stopped. [redacted]
Subject Population:	The study will enroll healthy adult, non-obese pre-menopausal women with surgically confirmed endometriosis.
Number of Subjects:	Up to 60 female subjects, 20 per dose arm
Number of Sites	Approximately 10 sites in the US
Study Duration:	Total participation in the study is approximately 6-7 months.
[redacted]	[redacted]

	[redacted]
Study Endpoints	• The primary efficacy endpoint will be percent change in daily average combined BBSS patient reported scores comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18) • The secondary endpoints will be ➢ Change in daily average use of analgesics from the baseline menstrual cycle to the matching end-of- study period ➢ Change in BBSS score incorporating the two physician reported scores ➢ Change in the individual BBSS scores of the three patient reported outcomes ➢ Change in number of days and intensity of menstrual or non-menstrual vaginal bleeding. [redacted]
Statistical Methods:	Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. All summaries will be prepared for each treatment group. Summaries will be prepared for each treatment group of subject accountability, baseline demographic, and medical history data. The primary efficacy variable is the change in the subject reported outcomes of the BBSS from the baseline period to a comparable period leading up to the end of dosing. An overall comparison among the 3 treatment groups will be performed. The secondary efficacy variables will be treated similarly. [redacted]





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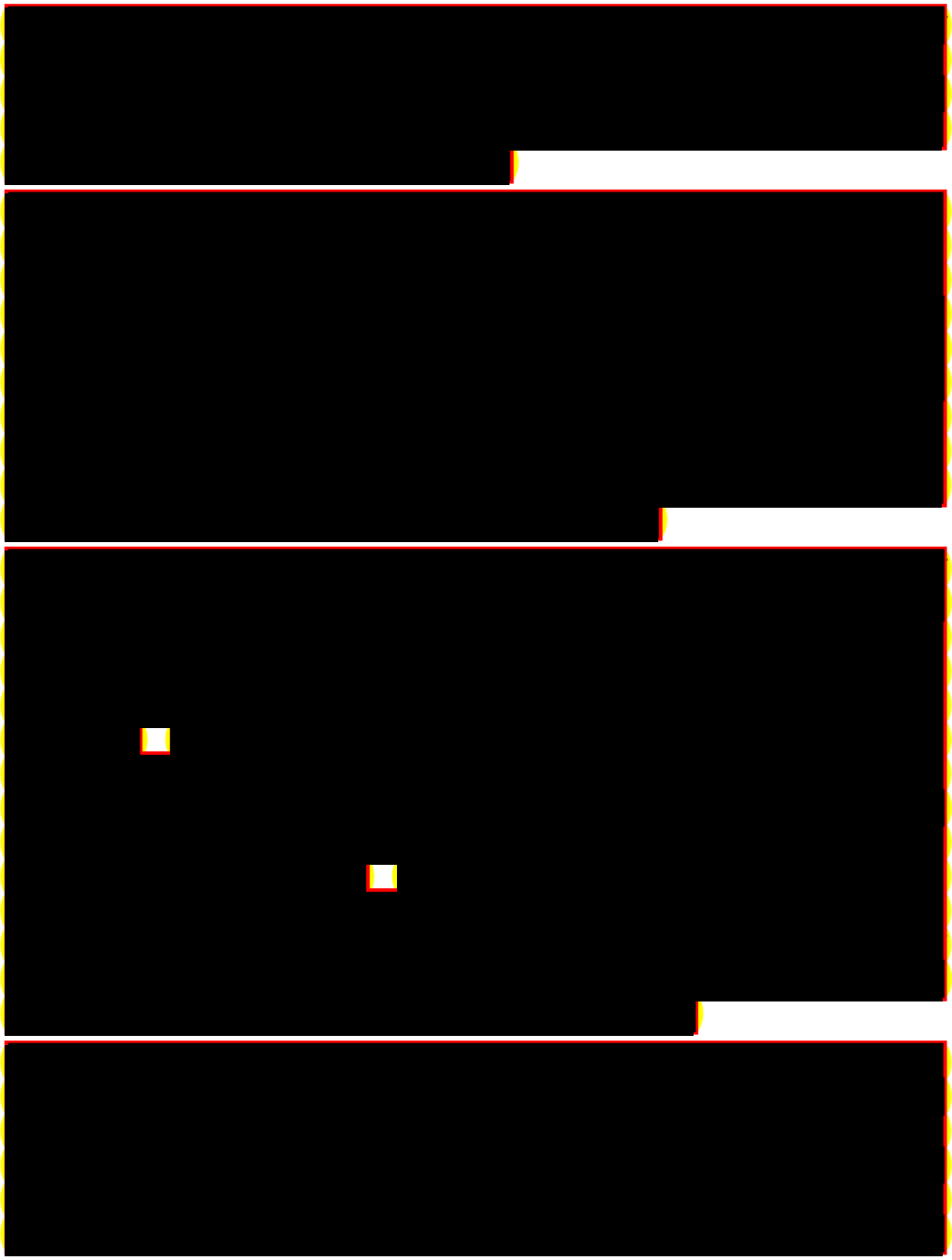
5. LIST OF ABBREVIATIONS

AE	Adverse event
PBAC	Pictorial Bleeding Assessment Chart
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
m	Meters
mg	Milligram(s)
mL	Milliliter
ng	Nanograms
PCOS	Polycystic Ovarian Syndrome
PK	Pharmacokinetic
PRL	Prolactin
PSA	Prostate specific antigen
RBC	Red blood cell
SAE	Serious adverse event
SHBG	Sex hormone binding globulin
TT	Total testosterone
UFSQOL	Uterine Fibroid Symptoms Quality of Life Questionnaire
WBC	White blood cell

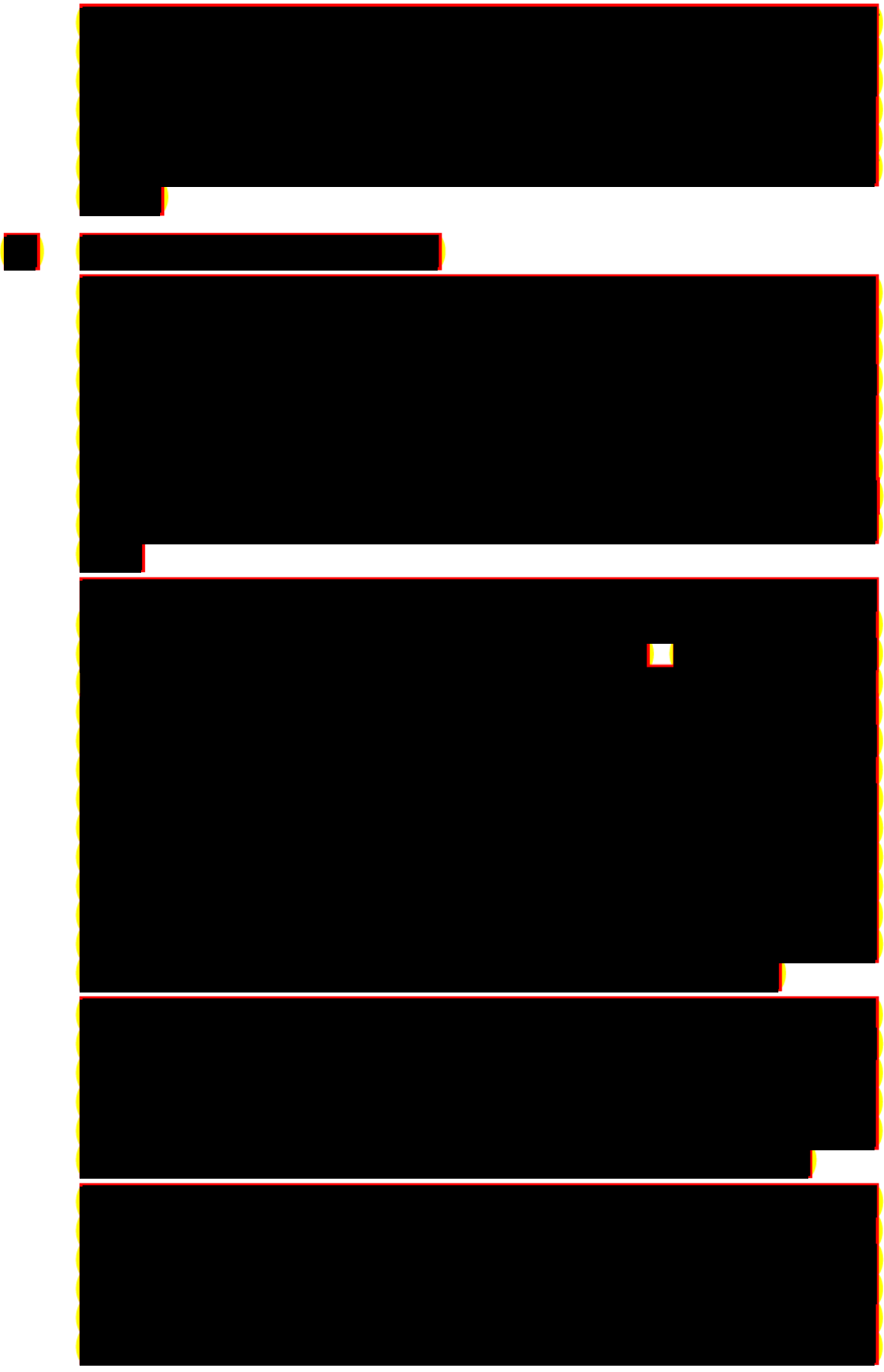
6. BACKGROUND INFORMATION

6.1 Rationale for Current Study

Repros believes telapristone offers the potential to provide significant symptomatic relief to women that suffer from a variety of reproductive disorders in which progesterone may be implicated. Most notably the sponsor has seen significant clinically relevant impact on the symptoms of both uterine fibroids and endometriosis.



sponsor believes there is a direct correlation of symptomatic relief for uterine



[redacted]

FDA Guidance For Liver Enzyme Elevation Characterization as SAE

- 1. LFTs ≥ 8 x ULN
- 2. LFTs ≥ 5 x ULN for 2 consecutive weeks
- 3. LFTs ≥ 3 x ULN + Bilirubin 2 x ULN
- 4. LFTs ≥ 3 x ULN + clinical signs or symptoms (nausea; jaundice; etc.)

[redacted]

[redacted]

[redacted]

6.5 Ethical Conduct of the Study

This trial will be conducted in strict compliance with the protocol and all applicable FDA regulations and GCP guidelines to insure Good Clinical Practice standards. The Institutional Review Board (IRB) for this study is IntegReview, 3001 S. Lamar Blvd., Suite 210, Austin, Texas 78704.

6.6 [redacted]

7. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered for 18 weeks to premenopausal women with confirmed endometriosis.

8. TRIAL DESIGN

8.1 Study Endpoints

The Primary endpoint will be:

- Percent change in daily average combined BBSS patient reported scores comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18)

The Secondary endpoints will be:

- Change in daily average use of analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change in BBSS score incorporating the two physician reported scores
- Change in the individual BBSS scores of the three patient reported outcomes
- Change in number of days and intensity of menstrual or vaginal bleeding

8.2 Study Design

8.2.1 Overview of Study Design

This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in 2 stages. In the first stage, women will receive a daily single-blind placebo. This stage will last as long as it takes to record at least one full menstrual cycle (ovulation until ovulation). Daily patient reported scores for the three elements of endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia will be recorded using an electronic diary with prompts replicating a modified Biberoglu and Behrman symptom severity score

(BBSS). [redacted] Following the run-in phase, 60 subjects will be randomized into one of 3 arms in a 1-1-1 fashion weighted by a combined BBSS and analgesic score. [redacted] The start of dosing in the double-blind phase should commence as soon as possible after ovulation following the end of the previous menstrual event. Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within 35 days or less). The follow-up visit should be scheduled after blood flow has stopped. During the follow-up period subjects will continue to record study information in the electronic diary.

[redacted]

8.2.2 Study Drug Accountability

The designee assigned by the Principal Investigator at each site will maintain accurate records of receipt of all study drugs, including dates of receipt. Reasons for deviation from the expected dispensing regimen must also be recorded. A Drug Dispensing Form will be provided for this purpose. To satisfy regulatory requirements regarding drug accountability and destruction, the Principal Investigator at each site will return all used or unused empty and partially used study medication with dispensing records to the Sponsor for final accountability and disposal, after accountability has been verified by the study monitor.

8.2.3 Randomization and Blinding

All subjects will receive placebo from Visit 1 until Visit 3. At Visit 3, subjects will be randomized to treatment in Arms 1, 2, or 3 and will be treated with one capsule daily of 6 mg or 12 mg of Proellex, or placebo, which will be administered for 18 weeks. Blinded treatments kits will be randomized and distributed by the packaging company.

8.2.4 Study Medication

All study drugs will be supplied by Repros Therapeutics Inc. Test drug, Proellex, [redacted] and will be

packaged by a clinical supplies contract vendor designated by Repros Therapeutics Inc. The placebo [redacted] and will be packaged by the same clinical supplies contract vendor. Active and matching placebo capsules will be bottled in identical packaging. Each bottle will have a label containing bottle number, number of capsules, expiration date, clinical use only and instructions to take 1 capsule daily in the morning approximately one hour before breakfast. Subjects will take one capsule with approximately 8 ounces of water and study medication should be taken roughly at the same time every day. Subjects will record study medication date and time on subject electronic drug diary cards. [redacted]

8.3 Selection and Withdrawal of Subjects

Subjects for the study will be selected during screening based on the inclusion and exclusion criteria and clinical assessments listed below. Subjects will be discontinued from the study prematurely if:

- Unacceptable adverse events occur considered by the investigator to be associated with use of the study drug
- The subject requests to be withdrawn from the study
- LFT elevation >3 times upper limit of normal
- ALT > upper limit of normal for 3 successive weeks
- A need arises for concomitant medication prohibited by the protocol
- The Principal Investigator decides that it is in the subject's best interest
- The subject is noncompliant with the protocol
- Any subject who develops an endometrial thickness ≥ 20 mm and experiences heavy bleeding for 7 days or more will be discontinued from the study. Appropriate follow up treatment will be provided as deemed necessary by the investigator.

8.3.1 Inclusion Criteria

Subjects must meet the following criteria:

- Healthy adult females between 18 and 47 years of age with surgically confirmed diagnosis of endometriosis (within-10 years). A laparoscopic diagnosis is acceptable.
- Normal or abnormal but non-clinically significant transvaginal ultrasound
- History of menstrual events occurring in regular cycles

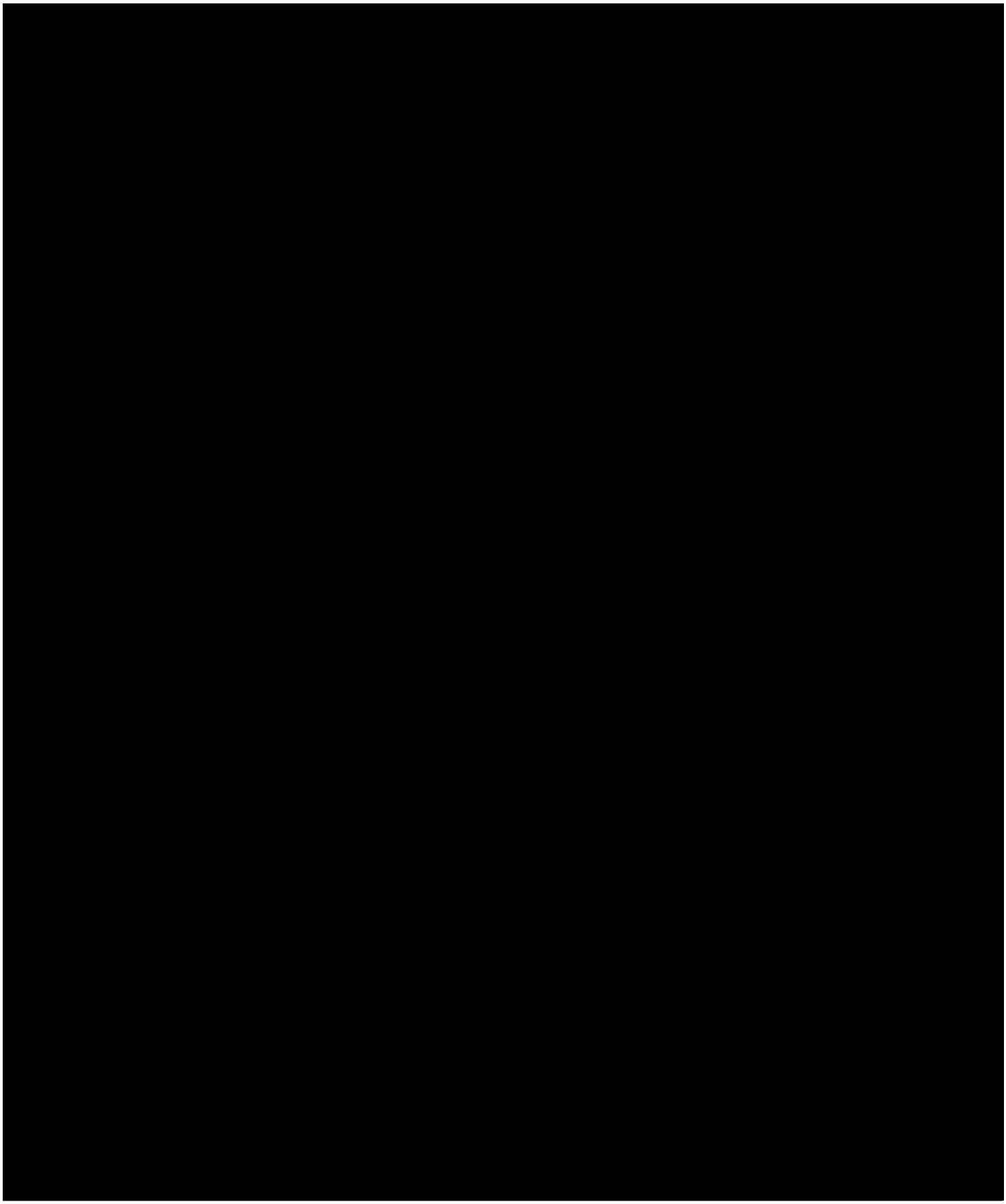
- Agreement not to attempt to become pregnant during the trial
- Agreement to limit alcohol consumption to no more than 2 drinks per week and to avoid alcohol consumption within 48 hours before each visit
- Ability to complete a daily electronic subject diary and study procedures in compliance with the protocol
- Agrees to use a double-barrier contraceptive over the course of the study
- Has a negative pregnancy test at the Screening and Baseline visits, and subsequent study visits
- A Body Mass Index (BMI) between 18 and 39 inclusive
- Is available for all treatment and follow-up visits

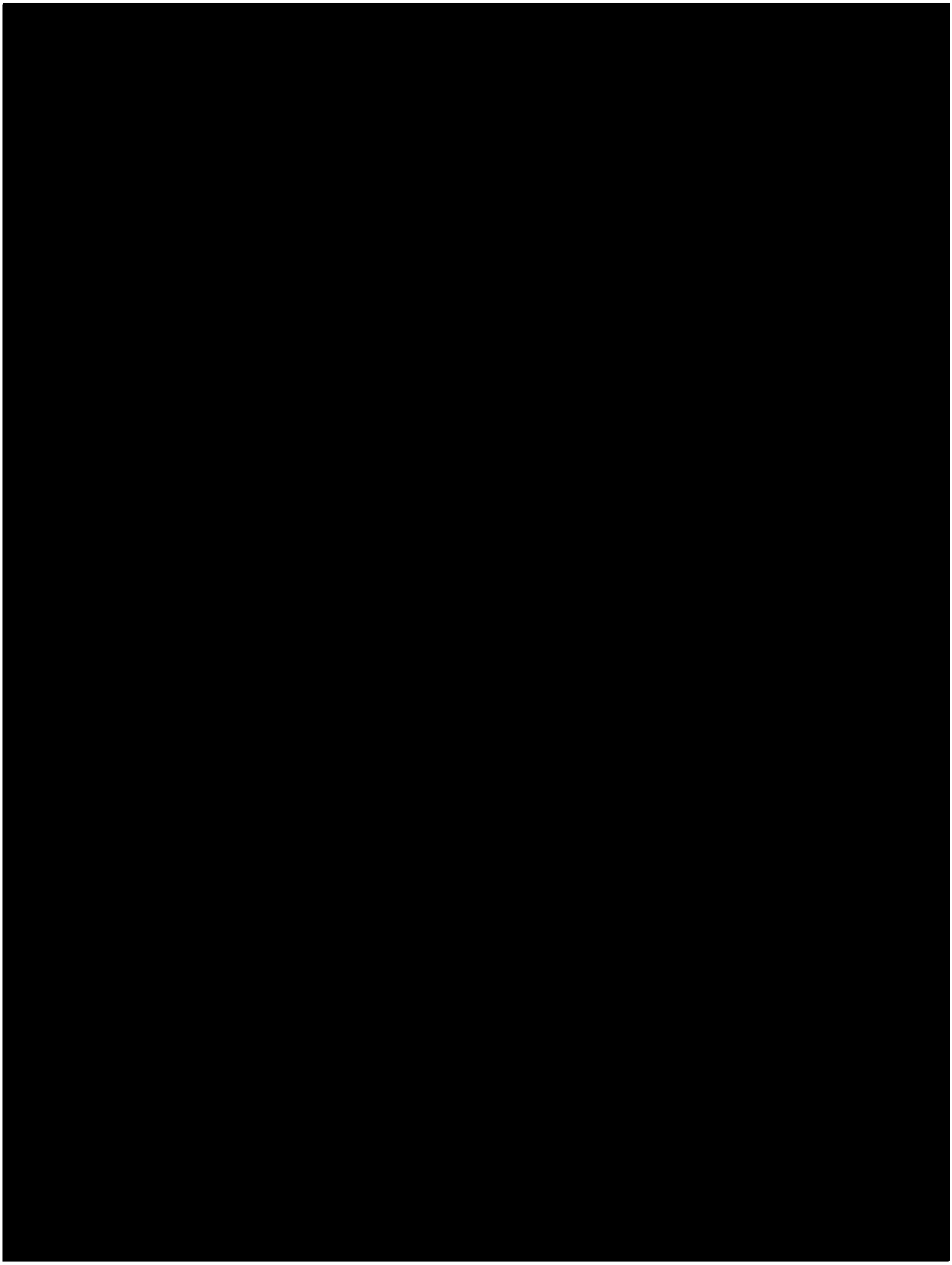
8.3.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

- Subject is a post-menopausal woman, defined as either; six (6) months or more (immediately prior to screening visit) without a menstrual period, or prior hysterectomy and/or oophorectomy.
- Subject is pregnant or lactating or is attempting or expecting to become pregnant [redacted]
- Women with abnormally high liver enzymes or liver disease. (ALT or AST exceeding 1.5x ULN AND total bilirubin exceeding 1.5xULN at screening and confirmed on repeat).
- Received an investigational drug in the 30 days prior to the screening for this study
- Women with a history of PCOS
- Concurrent use of any testosterone, progestin, androgen, estrogen, anabolic steroids, DHEA or hormonal products for at least 2 weeks prior to screening and during the study.
- Use of oral contraceptives in the preceding 30 days. Use of Depo-Provera® in the preceding [redacted]
- Use of GnRHas (e.g. Lupron Depot) within 3 months of the first dose of study drug (Lupron Depot must have a wash-out period of 3 months after the period of duration of the Lupron dose).

- Has an IUD in place
- Presence of intramural fibroids that impact the endometrial stripe, submucosal fibroids (any size), or endometrial polyps. Subserosal and intramural fibroids with no impact on the endometrial stripe are acceptable.
- Present history or condition that causes non-endometriosis related dyspareunia (e.g. vulvar vestibulitis).
- Past or present history of thrombophlebitis or thromboembolic disorders.
- Known or suspected carcinoma of the breast or reproductive organs.
- History of abnormal ECG that, in the opinion of the investigator, is clinically significant and will prevent the subject from completing the study, including a QTc of greater than 450 ms.
- Cervical dysplasia classified as Atypical Squamous Cells of Undetermined Significance (ASCUS) associated with high-risk human papilloma virus (HPV) or Low/High Grade Squamous Intraepithelial Lesion (LGSIL or HGSIL).
- History of abnormal endometrial biopsy including the presence of EIN.
- Recent history (within past 6 months) of alcoholism or drug abuse.
- Known active infection with HIV, Hepatitis A, B or C.
- Previous history of auto-immune disease and/or positive antinuclear antigen (ANA).
- Endometrial stripe ≥18 mm in thickness at Visit 1.
- Women currently taking cimetidine or spironolactone.
- Clinically significant abnormal findings on screening examination and laboratory assessments or any condition which in the opinion of the investigator would interfere with the participant's ability to comply with the study instructions or endanger the participant if she took part in the study..





10. ASSESSMENT OF EFFICACY

10.1 Primary Endpoint

The Primary endpoint will be:

- The percent change in daily average combined BBSS patient reported scores comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18)

10.2 Secondary Endpoints

The Secondary endpoints will be:

- Change in daily average use of analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change in BBSS score incorporating the two physician reported scores
- Change in the individual BBSS scores of the three patient reported outcomes
- Change in number of days and intensity of menstrual or vaginal bleeding.

[redacted]

11.1 Adverse Events

11.1.1 Reporting Adverse Experiences

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this investigational drug, whether or not considered related to the investigational product, shall be documented on the CRF. All AEs reported by the subject or observed by the Principal Investigator will be individually listed. The signs and symptoms, time of onset (24-hour clock), duration, action taken and follow-up procedures will be reported.

11.1.2 Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) – An adverse drug experience that results in any of the following outcomes: death, a life-threatening experience, requires or prolongs subject hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

Unexpected Adverse Event: Any adverse event that is not identified in nature, severity, or frequency in the current Investigator's Brochure.

Additionally, the Principal Investigator will evaluate all AEs as follows:

Action taken: whether or not the AE caused the subject/patient to discontinue the study medication.

Intensity, to be graded as:

DEGREE	DESCRIPTION
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent daily activity
Severe	Unable to carry out usual activity

Relationship to study medication, to be graded as:

DEGREE	DESCRIPTION
Definitely	There is evidence of exposure to the study drug, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the medication is reasonable; the AE is most likely to be explained by the treatment than by another cause; the AE shows a pattern consistent with previous knowledge of the treatment.
Probably	There is evidence of exposure to the study drug; the temporal sequence of the AE onset relative to medication administration is reasonable; the AE is more likely explained by the treatment than by another cause.
Possibly	There is evidence of exposure to the study drug; the temporal sequence of the AE relative to the medication administration is reasonable; the AE could have been due to another equally likely cause.
Probably not	There is evidence of exposure to the study drug; there is another more likely cause of the AE.
Definitely not	The subject/patient did not receive the study drug; or temporal sequence of the AE onset relative to administration of the study drug is not reasonable; or there is another obvious cause of the AE.

11.1.3 Serious Adverse Events (SAEs)

The Principal Investigator shall document all SAEs in a subject receiving study drug [redacted] and must be reported to the Repros Therapeutics Inc. Safety Monitor within 24 hours by Fax or telephone, even if the SAE does not appear to be drug-related. This report should include all available information at the time of notification. This notification should be followed with submitting a SAE Report Form provided by Repros Therapeutics Inc. All additional follow-up reports must be reported to the Repros Therapeutic Inc monitor as soon as available.

12. CONCOMITANT MEDICATIONS

Any prescription or over-the-counter medication taken during the study will be recorded in the appropriate section of the CRF. Subject must be on a stable dosage of approved concomitant medications at least 48 hours prior to drug administration.

13. STATISTICAL METHODS

13.1 Determination of Sample Size

The sample size determination was not based on statistical considerations. Up to 60 female subjects, 20 per dose arm, meeting the inclusion/exclusion criteria will be randomized in a 1-1-1 fashion weighted by a combined BBSS and analgesic score. [redacted]

Adequate data are not available for estimating the sample size necessary to detect statistical differences between treatment groups with reasonable statistical power. The planned number of patients (20 per dose arm) should provide sufficient data to assist with the design of future studies. While the sample size was not based on statistical considerations, hypothesis testing will be performed for exploratory purposes.

13.2 Statistical and Analytical Plan

13.2.1 Demographics and Subject Characteristics

For all subjects included in this study, subject accountability, baseline demographic and medical history data will be summarized for each treatment group. Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. No statistical testing will be performed to compare these factors between treatment groups.

13.2.2 Efficacy Analyses

Efficacy analyses will be conducted in the modified Intent-to-Treat population, which will consist of all subjects who are randomized, who receive study drug, and who have some post-baseline efficacy data.

13.2.2.1 BBSS Patient Reported Scores

The primary efficacy variable is percent change in daily average combined BBSS patient-reported scores comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. For each treatment group the mean change from baseline will be assessed for statistical significance using a paired t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the

interim visits. [redacted]

13.2.2.2 Analgesic Usage

The change in daily average use of analgesics comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18) will be summarized for each treatment group. An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. For each treatment group the mean change from baseline will be assessed for statistical significance using a paired t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

13.2.2.3 BBSS Patient and Physician Reported Scores

The BBSS score incorporating the two physician-reported scores will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. For each treatment group the mean change from baseline will be assessed for statistical significance using a paired t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. [redacted]

13.2.2.4 Patient Reported Outcomes

Each of the three patient reported outcomes will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18). An overall comparison among the 3 treatment groups will be performed on each patient reported outcome score using a one-way Analysis of Variance. For each treatment group the mean change from baseline will be assessed for statistical significance using a paired t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

13.2.2.5 Menstrual or Non-menstrual Vaginal Bleeding

The number of days and intensity of menstrual and non-menstrual vaginal bleeding will be summarized from the diary data. The total number of days and average intensity will be summarized from the days preceding each visit. An overall comparison among the 3 treatment groups will be performed on both the total number of days and average intensity using a one-way Analysis of Variance. For each treatment group the mean change from baseline will be assessed for statistical significance using a paired t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

[redacted]

13.3 General Statistical Issues

[redacted] Statistical significance will be declared if the two-sided p-value is ≤ 0.05. Since the study was not powered for efficacy assessments based on statistical

hypotheses, the p-values reported at the conclusion of the study are being reported to quantify the difference in the treatment effect between treatment groups. [redacted]

14. ETHICS

14.1 Subject Information and Consent

A properly executed, written informed consent in compliance with Food and Drug Administration (FDA) regulations and Good Clinical Practice (GCP) guidelines will be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure that involve a risk to the subject. The Principal Investigator will submit a copy of the informed consent document to the Institutional Review Board for review and approval before research subjects are enrolled. The Principal Investigator will provide a copy of the signed informed consent to the subject and the original will be maintained in the subject's medical record.

14.2 Institutional Review Board

The Principal Investigator will provide the Institutional Review Board with all requisite material, including a copy of the informed consent. The study will not be initiated until the IRB provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Principal Investigator and copies received by the Sponsor. Appropriate reports on the progress of this study by the Principal Investigator will be made to the Institutional Review Board and the Sponsor in accordance with the applicable government regulations and in agreement with the policy established by the Sponsor.

14.3 Monitoring Case Report Forms

Repros Therapeutics Inc. or their designee will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable federal regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

14.4 Study Record Retention

In accordance with FDA regulations and GCP guidelines, all study-related documentation shall be retained by the Principal Investigator for a minimum of 2 years after FDA approval of telapristone acetate or clinical development has been terminated. At that time, the Principal Investigator will contact Repros Therapeutics Inc. regarding further disposition of the study records and comply with instructions.

14.5 Data Quality Assurance

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing. The Principal Investigator will be responsible for the following:

1. Monitoring study conduct to ensure that the rights of subjects are protected;
2. Monitoring study conduct to ensure trial compliance with GCP guidelines; and
3. Monitoring accuracy, completion and verification from source documents of study data.

14.6 Confidentiality

All information provided to the Principal Investigator by Repros Therapeutics Inc. or their designees including non-clinical data, protocols, CRFs and verbal and written information will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be released in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Repros Therapeutics Inc. or their designees or in confidence to the IRB, except if required by law.

14.7 Publications

Following completion of the study, the data from the entire study or from subsets of the study may be considered for reporting at a scientific meeting or for publication in a scientific journal, in which case Repros Therapeutics Inc. will be responsible for these activities and will work with the Principal Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues.

15. INVESTIGATOR'S STATEMENT

I have reviewed the ZPE-202 protocol and Investigator Brochure and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

_____ _____

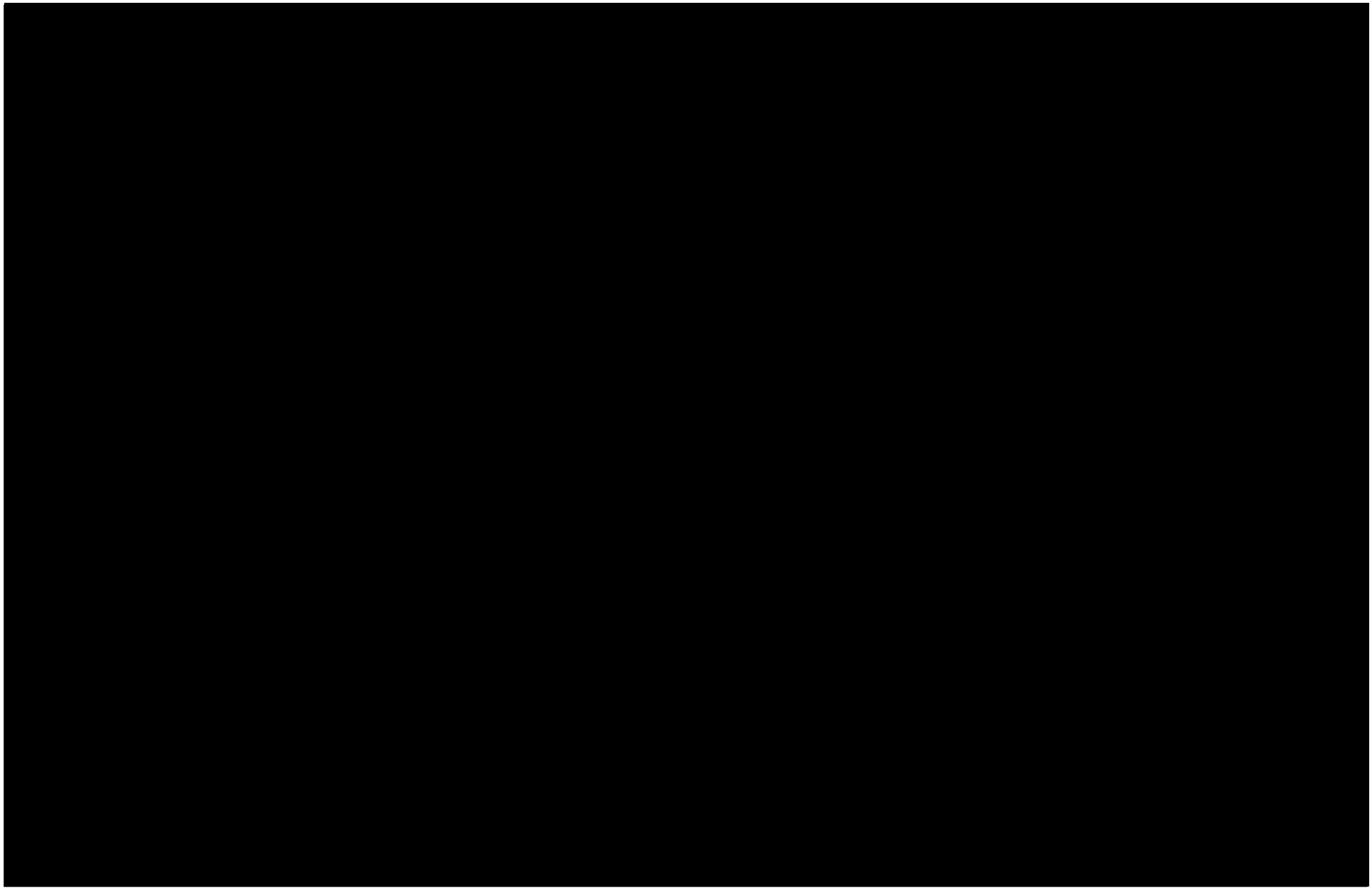
Investigator Date

_____

Printed name

[redacted]

[redacted]



Repros THERAPEUTICS INC.

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 Endometriosis Confirmed Within the Last Five Years and Who are Currently Using Narcotics for Control of Symptomatic Pain

Original Protocol: July 18, 2012
Amendment 1: August 31, 2012

SPONSOR:

Repros Therapeutics Inc.®
2408 Timberloch Place, B-7
The Woodlands, TX 77380

IND 76,631

[redacted]

Confidentiality Statement
The confidential information in this document is provided to you as a Principal Investigator or consultant for review by you, your staff and the applicable Institutional

Review Board / Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor, Repros Therapeutics Inc.®

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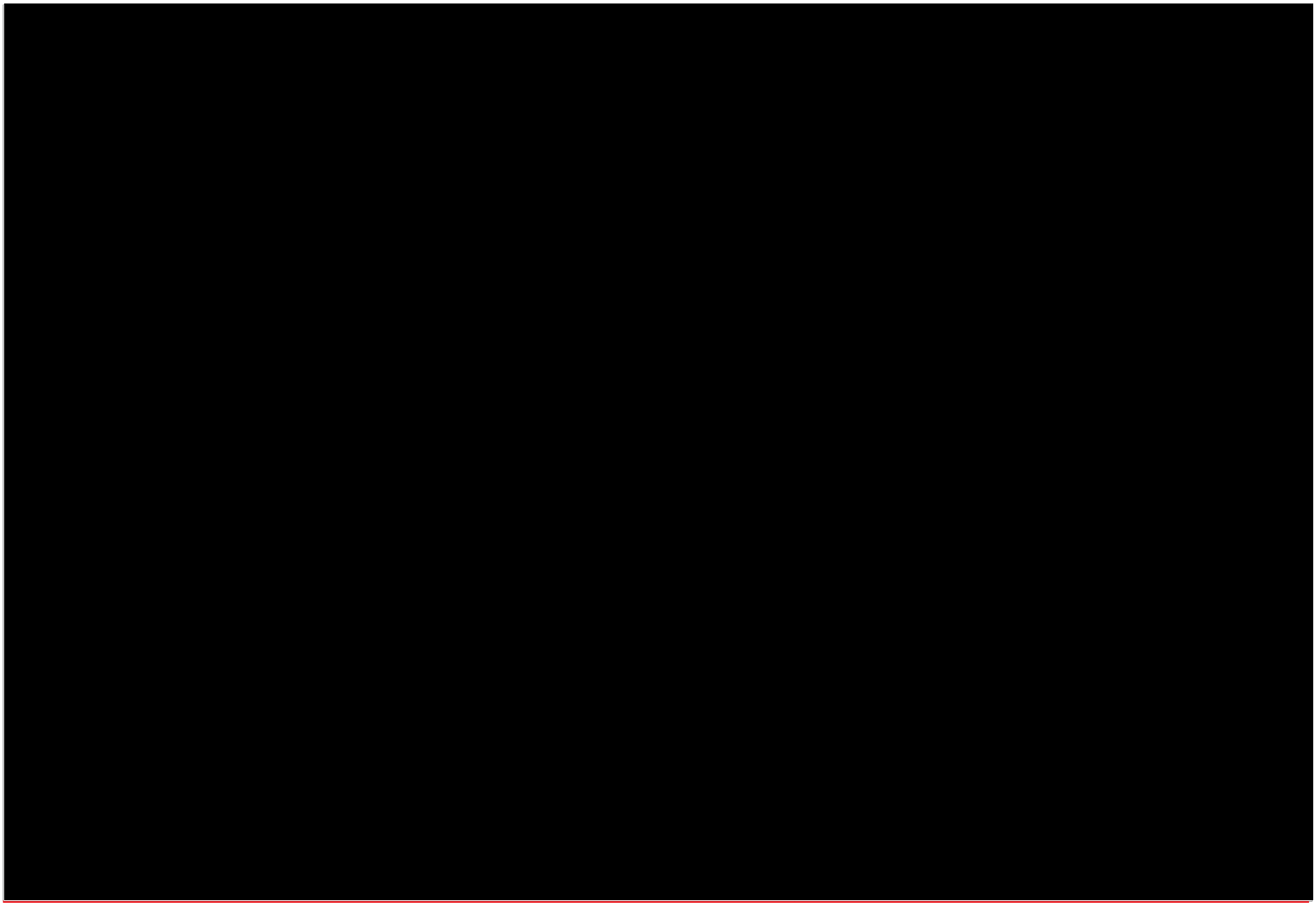
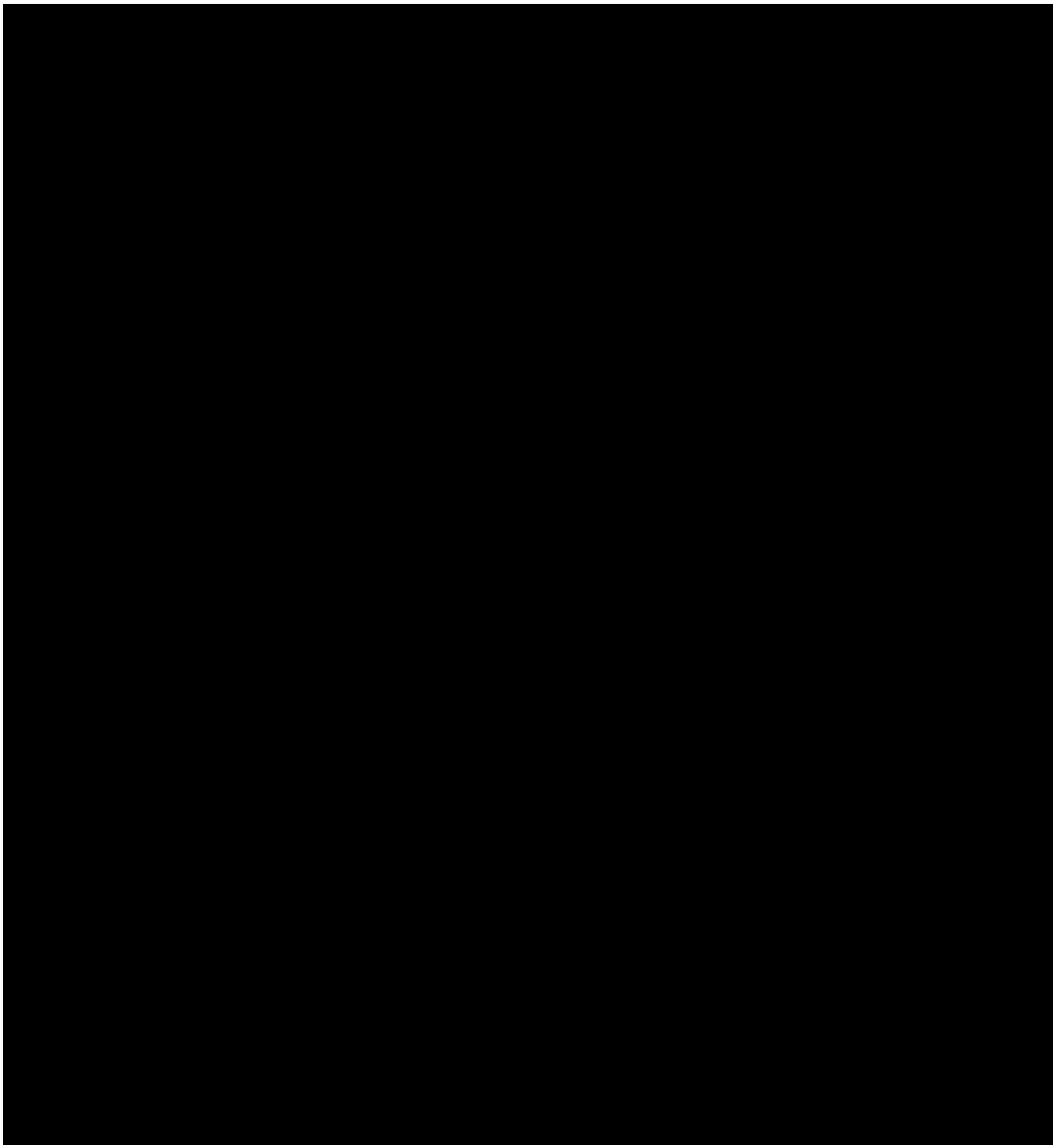
Study Design and Duration Of Treatment:	This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in two stages. In the first stage, women will receive daily single blind dosing with placebo, for at least one full menstrual cycle. Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications, vaginal bleeding intensity and alcohol use will be recorded using an electronic diary. Following the placebo run-in phase, subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of the 18 week dosing period in the double-blind phase should commence as soon after ovulation as possible, after which subjects will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the electronic diary. The final follow-up visit should be scheduled after blood flow has stopped. [redacted]
Subject Population:	The study will enroll healthy adult, non-obese pre-menopausal women with surgically confirmed endometriosis using narcotic analgesics for their endometriosis pain.
Number of Subjects:	Up to 90 female subjects, 30 per dose arm
Number of Sites	Approximately 10 sites in the US
Study Duration:	Total participation in the study is approximately 6-7 months.
[redacted]	[redacted]

	[redacted]
Study Endpoints	• The primary efficacy endpoint will be percent change from baseline in use of narcotic analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18). It is anticipated that subjects randomized to active treatment will stop menstruating. • The secondary endpoints will be ➢ Change in daily average use and percent change of non-narcotic prescription analgesics from the baseline menstrual cycle to the matching end-of- study period ➢ Change in daily average use of narcotic prescription analgesics from the baseline menstrual cycle to the matching end-of- study period ➢ Change in daily average use and percent change over the counter analgesics from the baseline menstrual cycle to the matching end-of- study period ➢ Change and percent change in BBSS score incorporating the two physician reported scores ➢ Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) • [redacted]
Statistical Methods:	Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries

	for categorical variables include the number and percent of patients for each outcome. All summaries will be prepared for each treatment group. Summaries will be prepared for each treatment group of subject accountability, baseline demographic, and medical history data. The primary efficacy variable will be percent change from baseline in use of narcotic analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18). An overall comparison among the 3 treatment groups will be performed using an Analysis of Covariance, including the baseline narcotic analgesic usage and treatment in the model. Pairwise comparisons between treatment groups will be made using a two-sample t-test. The secondary efficacy variables will be treated similarly. [redacted]





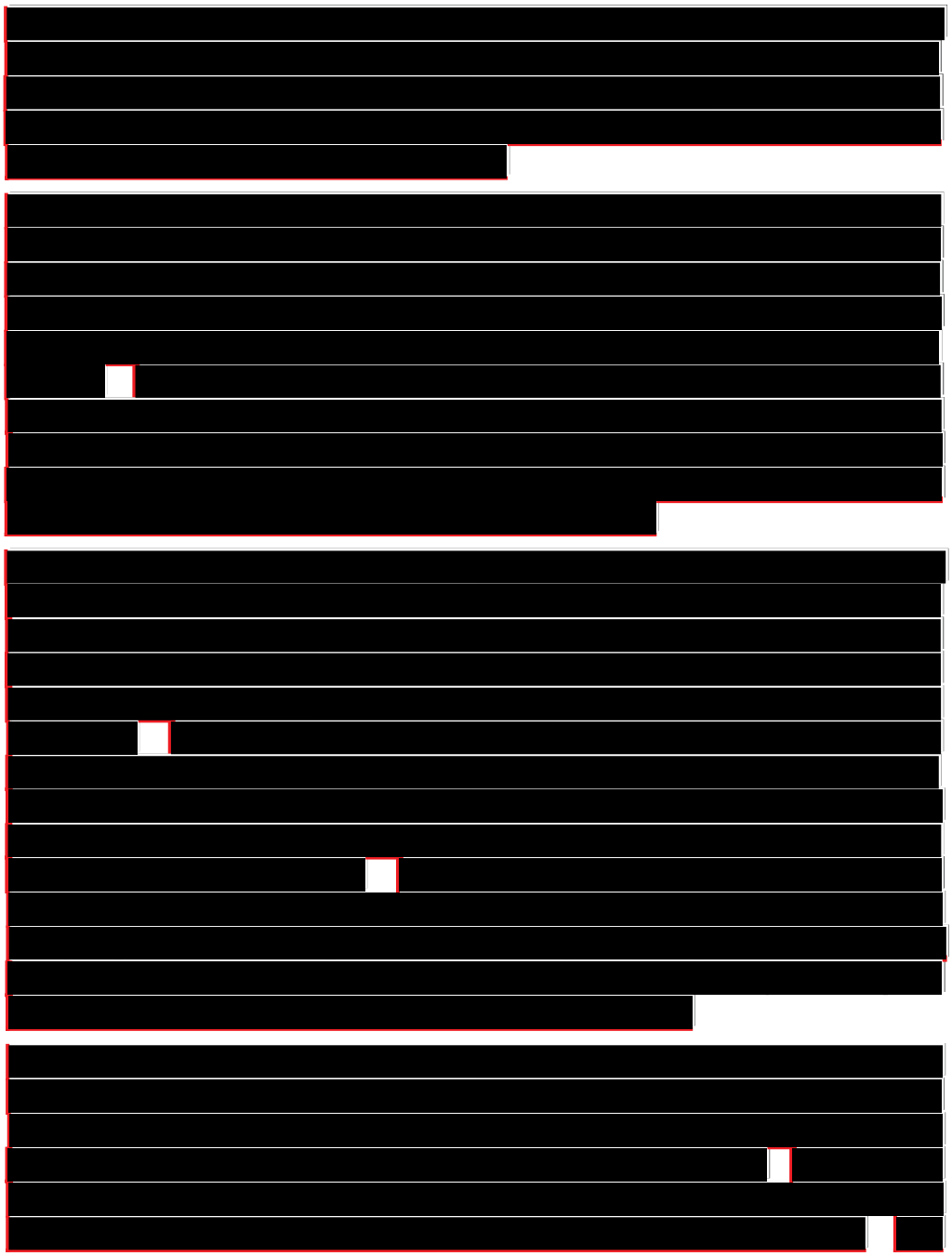
5. LIST OF ABBREVIATIONS

AE	Adverse event
PBAC	Pictorial Bleeding Assessment Chart
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
m	Meters
mg	Milligram(s)
mL	Milliliter
ng	Nanograms
PCOS	Polycystic Ovarian Syndrome
PK	Pharmacokinetic
PRL	Prolactin
PSA	Prostate specific antigen
RBC	Red blood cell
SAE	Serious adverse event
SHBG	Sex hormone binding globulin
TT	Total testosterone
UFSQOL	Uterine Fibroid Symptoms Quality of Life Questionnaire
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Rationale for Current Study

Repros believes telapristone offers the potential to provide significant symptomatic relief to women that suffer from a variety of reproductive disorders in which progesterone may be implicated. Most notably the sponsor has seen significant clinically relevant impact on the symptoms of both uterine fibroids and endometriosis.



[redacted]

[redacted]

6.2 [redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

6.3 Clinical Data/Human Experience

[redacted]

[redacted]

6.4 [redacted]

[redacted]

FDA Guidance For Liver Enzyme Elevation Characterization as SAE

1. LFTs ≥ 8 x ULN
2. LFTs ≥ 5 x ULN for 2 consecutive weeks
3. LFTs ≥ 3 x ULN + Bilirubin 2 x ULN
4. LFTs ≥ 3 x ULN + clinical signs or symptoms (nausea; jaundice; etc.)

[redacted]

[redacted]

6.5 Ethical Conduct of the Study

This trial will be conducted in strict compliance with the protocol and all applicable FDA regulations and GCP guidelines to insure Good Clinical Practice standards. The Institutional Review Board (IRB) for this study is IntegReview, 3001 S. Lamar Blvd., Suite 210, Austin, Texas 78704.

6.6 [redacted]

[redacted]

7. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered for 18 weeks to premenopausal women with pelvic pain in endometriosis confirmed within the last five years and using narcotics for symptomatic pain.

8. TRIAL DESIGN

8.1 Study Endpoints

The Primary endpoint will be:

- Percent change from baseline in use of narcotic analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18)

The Secondary endpoints will be:

- Change in daily average use of non-narcotic prescription analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change in daily average use and percent change of narcotic prescription analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change in daily average use of over the counter analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change in BBSS score incorporating the two physician reported scores
- Change in the individual BBSS scores of the three patient reported outcomes: dysmenorrhea, dyspareunia and non-menstrual pelvic pain

8.2 Study Design

8.2.1 Overview of Study Design

This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in 2 stages. In the first stage, women will receive a daily single-blind placebo. This stage will last as long as it takes to record at least one full menstrual cycle (ovulation until ovulation). Daily patient reported scores for the three elements of endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia will be recorded using an electronic diary with prompts replicating a modified Biberoglu and Behrman symptom severity score (BBSS). [redacted]

Following the run-in phase, 90 subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of dosing in the double-blind phase should commence as soon as possible after ovulation following the end of the previous menstrual event. Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within 35 days or less). The follow-up visit should be scheduled after blood flow has stopped. During the follow-up period subjects will continue to record study information in the electronic diary.

[redacted]

8.2.2 Study Drug Accountability

The designee assigned by the Principal Investigator at each site will maintain accurate records of receipt of all study drugs, including dates of receipt. Reasons for deviation from the expected dispensing regimen must also be recorded. A Drug Dispensing Form will be provided for this purpose. To satisfy regulatory requirements regarding drug accountability and destruction, the Principal Investigator at each site will return all used or unused empty and partially used study medication with dispensing records to the Sponsor for final accountability and disposal, after accountability has been verified by the study monitor.

8.2.3 Randomization and Blinding

All subjects will receive placebo from Visit 1 until Visit 3. At Visit 3, subjects will be randomized to treatment in Arms 1, 2, or 3 and will be treated with one capsule daily of 6 mg or 12 mg of Proellex, or

placebo, which will be administered for 18 weeks. Blinded treatments kits will be randomized and distributed by the packaging company.

8.2.4 Study Medication

All study drugs will be supplied by Repros Therapeutics Inc. Test drug, Proellex, will be [redacted] and will be packaged by a clinical supplies contract vendor designated by Repros Therapeutics Inc. [redacted] and will be packaged by the same clinical supplies contract vendor. Active and matching placebo capsules will be bottled in identical packaging. Each bottle will have a label containing bottle number, number of capsules, expiration date, clinical use only and instructions to take 1 capsule daily in the morning approximately one hour before breakfast. Subjects will take one capsule with approximately 8 ounces of water and study medication should be taken roughly at the same time every day. Subjects will record study medication date and time on subject electronic drug diary cards. [redacted]

8.3 Selection and Withdrawal of Subjects

Subjects for the study will be selected during screening based on the inclusion and exclusion criteria and clinical assessments listed below. Subjects will be discontinued from the study prematurely if:

- Unacceptable adverse events occur considered by the investigator to be associated with use of the study drug
- The subject requests to be withdrawn from the study
- LFT elevation >3 times upper limit of normal
- ALT > upper limit of normal for 3 successive weeks
- A need arises for concomitant medication prohibited by the protocol
- The Principal Investigator decides that it is in the subject's best interest
- The subject is noncompliant with the protocol
- Any subject who develops an endometrial thickness ≥ 20 mm and experiences heavy bleeding for 7 days or more will be discontinued from the study. Appropriate follow up treatment will be provided as deemed necessary by the investigator.

8.3.1 Inclusion Criteria

Subjects must meet the following criteria:

- Healthy adult females between 18 and 47 years of age using narcotic analgesics for their endometriosis related pain
- Endometriosis diagnosis must have been surgically confirmed within 5 years. A laparoscopic diagnosis is acceptable.
- Subjects must have a history of at least 3 regular menstrual cycles in which symptoms of endometriosis occurred immediately prior to screening
- Normal or abnormal but non-clinically significant transvaginal ultrasound
- History of menstrual events occurring in regular cycles
- Agreement not to attempt to become pregnant during the trial
- Agreement to limit alcohol consumption to no more than 2 drinks per week and to avoid alcohol consumption within 48 hours before each visit
- Ability to complete a daily electronic subject diary and study procedures in compliance with the protocol
- Women of child-bearing potential must be willing to use double-barrier contraception during the study and for 30 days after discontinuation of study medication. Acceptable double-barrier methods are: male condom with spermicide; male condom with diaphragm; diaphragm containing spermicide plus additional intra-vaginal spermicide
- Has a negative pregnancy test at the Screening and Baseline visits, and subsequent study visits
- A Body Mass Index (BMI) between 18 and 39 inclusive
- Is available for all treatment and follow-up visits

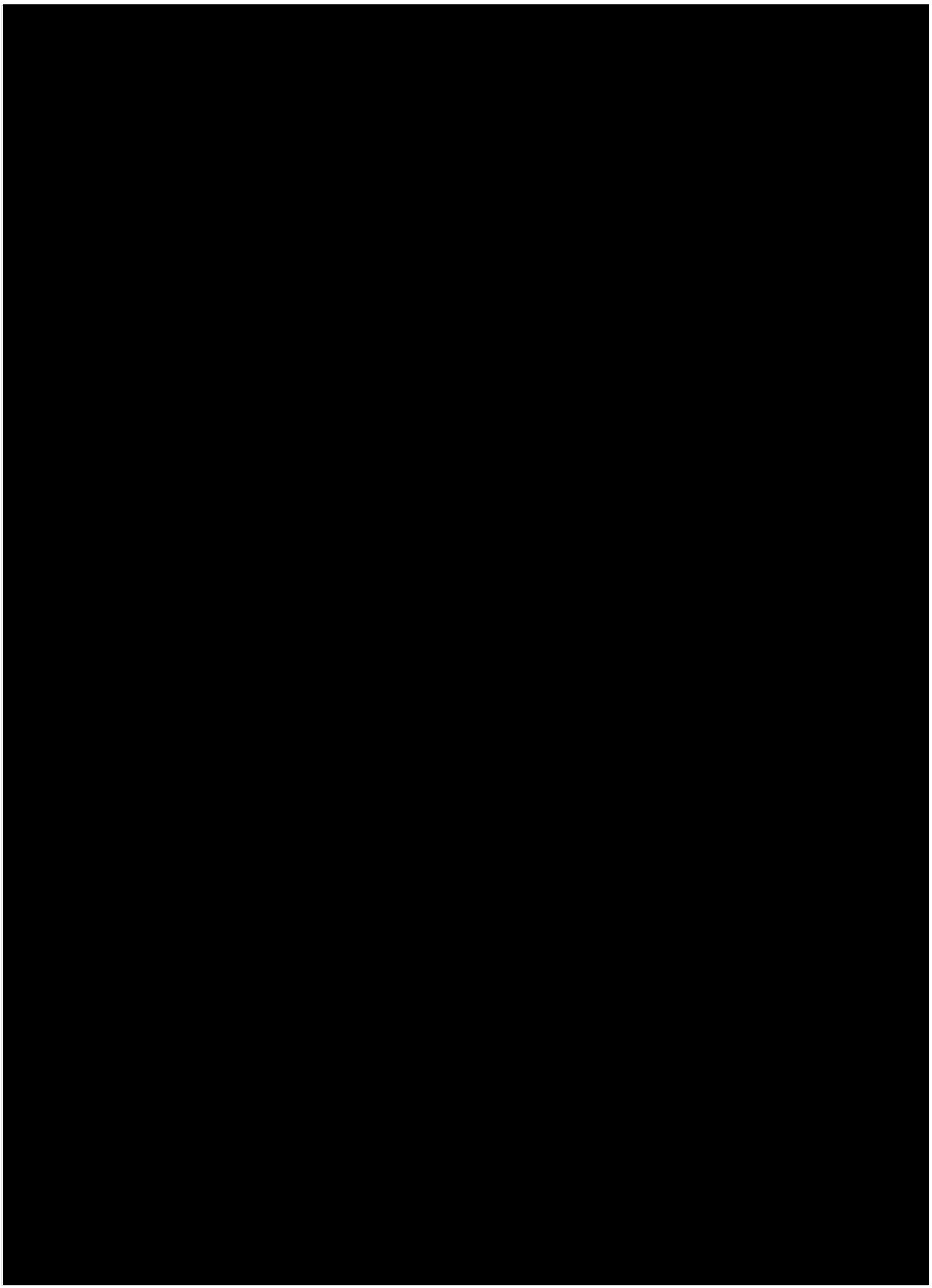
8.3.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

- Subject is a post-menopausal woman, defined as either; six (6) months or more (immediately prior to screening visit) without a menstrual period, or prior hysterectomy and/or oophorectomy.

- Subject is pregnant or lactating or is attempting or expecting to become pregnant [redacted]
- [redacted]
- Women with abnormally high liver enzymes or liver disease. (ALT or AST exceeding 2 x ULN AND total bilirubin exceeding 1.5xULN at screening and confirmed on repeat).
- Received an investigational drug in the 30 days prior to the screening for this study
- Women with a history of PCOS
- Concurrent use of any testosterone, progestin, androgen, estrogen, anabolic steroids, DHEA or hormonal products for at least 2 weeks prior to screening and during the study.
- Use of oral contraceptives in the preceding 30 days. Use of Depo-Provera® in the preceding [redacted]
- Use of GnRHas (e.g. Lupron Depot) within 3 months of the first dose of study drug (Lupron Depot must have a wash-out period of 3 months after the period of duration of the Lupron dose).
- Has an IUD in place
- Presence of intramural fibroids that impact the endometrial stripe, submucosal fibroids (any size), or endometrial polyps. Subserosal and intramural fibroids with no impact on the endometrial stripe are acceptable.
- Presence of endometrioma(s)
- Present history or condition that causes non-endometriosis related dyspareunia (e.g. vulvar vestibulitis).
- Past or present history of thrombophlebitis or thromboembolic disorders.
- Known or suspected carcinoma of the breast or reproductive organs.
- History of abnormal ECG that, in the opinion of the investigator, is clinically significant and will prevent the subject from completing the study, including a QTc of greater than 450 ms.
- Cervical dysplasia classified as Atypical Squamous Cells of Undetermined Significance (ASCUS) associated with high-risk human papilloma virus (HPV) or Low/High Grade Squamous Intraepithelial Lesion (LGSIL or HGSIL).

- History of abnormal endometrial biopsy including the presence of EIN.
- Recent history (within past 6 months) of alcoholism or drug abuse.
- Known active infection with HIV, Hepatitis A, B or C.
- Previous history of auto-immune disease and/or positive antinuclear antigen (ANA).
- Endometrial stripe ≥18 mm in thickness at Visit 1.
- Women currently taking cimetidine or spironolactone.
- Clinically significant abnormal findings on screening examination and laboratory assessments or any condition which in the opinion of the investigator would interfere with the participant's ability to comply with the study instructions or endanger the participant if she took part in the study..



[redacted]

[redacted]

10. ASSESSMENT OF EFFICACY

10.1 Primary Endpoint

The Primary endpoint will be:

- The percent change from baseline in use of narcotic analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18)

10.2 Secondary Endpoints

The Secondary endpoints will be:

- Change in daily average use and percent change of non-narcotic prescription analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change in daily average use of narcotic prescription analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching end-of- study period
- Change and percent change in BBSS score incorporating the two physician reported scores
- Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain)

[redacted]

11.1 Adverse Events

11.1.1 Reporting Adverse Experiences

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this investigational drug, whether or not considered related to the investigational product, shall be documented on the CRF. All AEs reported by the subject or observed by the Principal Investigator will be individually listed. The signs and symptoms, time of onset (24-hour clock), duration, action taken and follow-up procedures will be reported.

11.1.2 Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) – An adverse drug experience that results in any of the following outcomes: death, a life-threatening experience, requires or prolongs subject hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

Unexpected Adverse Event: Any adverse event that is not identified in nature, severity, or frequency in the current Investigator's Brochure.

Additionally, the Principal Investigator will evaluate all AEs as follows:

Action taken: whether or not the AE caused the subject/patient to discontinue the study medication.

Intensity, to be graded as:

DEGREE	DESCRIPTION
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent daily activity
Severe	Unable to carry out usual activity

Relationship to study medication, to be graded as:

DEGREE	DESCRIPTION
Definitely	There is evidence of exposure to the study drug, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the medication is reasonable; the AE is most likely to be explained by the treatment than by another cause; the AE shows a pattern consistent with previous knowledge of the treatment.
Probably	There is evidence of exposure to the study drug; the temporal sequence of the AE onset relative to medication administration is reasonable; the AE is more likely explained by the treatment than by another cause.
Possibly	There is evidence of exposure to the study drug; the temporal sequence of the AE relative to the medication administration is reasonable; the AE could have been due to another equally likely cause.
Probably not	There is evidence of exposure to the study drug; there is another more likely cause of the AE.
Definitely not	The subject/patient did not receive the study drug; or temporal sequence of the AE onset relative to administration of the study drug is not reasonable; or there is another obvious cause of the AE.

11.1.3 Serious Adverse Events (SAEs)

The Principal Investigator shall document all SAEs in a subject receiving study drug [redacted] and must be reported to the Repros Therapeutics Inc. Safety Monitor within 24 hours by Fax or telephone, even if the SAE does not appear to be drug-related. This report should include all available information at the time of notification. This notification should be followed with submitting a SAE Report Form provided by Repros Therapeutics Inc. All additional follow-up reports must be reported to the Repros Therapeutic Inc monitor as soon as available.

12. CONCOMITANT MEDICATIONS

Any prescription or over-the-counter medication taken during the study will be recorded in the appropriate section of the CRF. Subject must be on a stable dosage of approved concomitant medications at least 48 hours prior to drug administration.

13. STATISTICAL METHODS

13.1 Determination of Sample Size

Up to 90 female subjects, 30 per dose arm, meeting the inclusion/exclusion criteria will be randomized in a 1-1-1 fashion. [redacted]

13.2 Statistical and Analytical Plan

13.2.1 Demographics and Subject Characteristics

For all subjects included in this study, subject accountability, baseline demographic and medical history data will be summarized for each treatment group. Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. No statistical testing will be performed to compare these factors between treatment groups.

13.2.2 Efficacy Analyses

Efficacy analyses will be conducted in the modified Intent-to-Treat population, which will consist of all subjects who are randomized, who receive study drug, and who have some post-baseline efficacy data.

13.2.2.1 Narcotic Analgesic Usage

The primary efficacy variable is the percent change in daily average use of narcotic analgesics comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing (Week 18), and will be summarized for each treatment group. For each subject, the total number of doses of narcotic analgesics during each 28 day menstrual cycle will be calculated, and the daily average use of narcotic analgesics will be determined by dividing the total number of doses of narcotic analgesics by the number of days in the menstrual cycle (number of doses per day). The percent change from baseline in the narcotic analgesic usage will be determined by

subtracting the baseline narcotic analgesic usage from the narcotic analgesic usage during each menstrual cycle, dividing by the baseline narcotic analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline narcotic analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. [redacted]

13.2.2.2 Non-narcotic Prescription Analgesic Usage

The change in daily average use of non-narcotic prescription analgesics comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18) will be summarized for each treatment group. For each subject, the total number of doses of non-narcotic prescription analgesics during each menstrual cycle will be calculated, and the daily average use of non-narcotic prescription analgesics will be determined by dividing the total number of doses of non-narcotic prescription analgesics by the number of days in the menstrual cycle (number of doses per day). The percent change from baseline in the non-narcotic prescription analgesic usage will be determined by subtracting the baseline non-narcotic prescription analgesic usage from the non-narcotic prescription analgesic usage during each menstrual cycle, dividing by the baseline non-narcotic prescription analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline non-narcotic prescription analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. [redacted]

13.2.2.3 Over the Counter Analgesic Usage

The change in daily average use of over the counter analgesics comparing the baseline menstrual cycle to a similar period

leading up to the last day of dosing (Week 18) will be summarized for each treatment group. For each subject, the total number of doses of over the counter analgesics during each menstrual cycle will be calculated, and the daily average use of over the counter analgesics will be determined by dividing the total number of doses of over the counter analgesics by the number of days in the menstrual cycle (number of doses per day). The percent change from baseline in the over the counter analgesic usage will be determined by subtracting the baseline over the counter analgesic usage from the over the counter analgesic usage during each menstrual cycle, dividing by the baseline over the counter analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline over the counter analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

13.2.2.4 BBSS Patient and Physician Reported Scores

The BBSS score incorporating the two physician-reported scores will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including baseline BBSS score and treatment in the model. Pairwise comparisons of the treatment groups will be made using a paired t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. [redacted]

13.2.2.5 BBSS Patient Reported Scores

The percent change from baseline in each of the daily average combined BBSS patient-reported scores (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including baseline

BBSS score and treatment in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

13.2.2.5 Menstrual or Non-menstrual Vaginal Bleeding

The number of days and intensity of menstrual and non-menstrual vaginal bleeding will be summarized from the diary data. The total number of days and average intensity will be summarized from the days preceding each visit. An overall comparison among the 3 treatment groups will be performed on both the total number of days and average intensity using a one-way Analysis of Covariance, including the baseline score (number of days or average intensity) and treatment in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the interim visits and visit post-recovery menses. [redacted]

[redacted]

treatment group. No formal hypothesis testing will be performed to compare the treatment groups.

13.3 General Statistical Issues

[redacted] Statistical significance will be declared if the two-sided p-value is ≤ 0.05. Since the study was not powered for efficacy assessments based on statistical hypotheses, the p-values reported at the conclusion of the study are being reported to quantify the difference in the treatment effect between treatment groups. [redacted]

14. ETHICS

14.1 Subject Information and Consent

A properly executed, written informed consent in compliance with Food and Drug Administration (FDA) regulations and Good Clinical Practice (GCP) guidelines will be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure that involve a risk to the subject. The Principal Investigator will submit a copy of the informed consent document to the Institutional Review Board for review and approval before research subjects are enrolled. The Principal Investigator will provide a copy of the signed informed consent to the subject and the original will be maintained in the subject's medical record.

14.2 Institutional Review Board

The Principal Investigator will provide the Institutional Review Board with all requisite material, including a copy of the informed consent. The study will not be initiated until the IRB provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Principal Investigator and copies received by the Sponsor. Appropriate reports on the progress of this study by the Principal Investigator will be made to the Institutional Review Board and the Sponsor in accordance with the applicable government regulations and in agreement with the policy established by the Sponsor.

14.3 Monitoring Case Report Forms

Repros Therapeutics Inc. or their designee will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable federal regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

14.4 Study Record Retention

In accordance with FDA regulations and GCP guidelines, all study-related documentation shall be retained by the Principal Investigator for a minimum of 2 years after FDA approval of telapristone acetate or clinical development has been terminated. At that time, the Principal Investigator will contact Repros Therapeutics Inc. regarding further disposition of the study records and comply with instructions.

14.5 Data Quality Assurance

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing. The Principal Investigator will be responsible for the following:

1. Monitoring study conduct to ensure that the rights of subjects are protected;
2. Monitoring study conduct to ensure trial compliance with GCP guidelines; and
3. Monitoring accuracy, completion and verification from source documents of study data.

14.6 Confidentiality

All information provided to the Principal Investigator by Repros Therapeutics Inc. or their designees including non-clinical data, protocols, CRFs and verbal and written information will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be released in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Repros Therapeutics Inc. or their designees or in confidence to the IRB, except if required by law.

14.7 Publications

Following completion of the study, the data from the entire study or from subsets of the study may be considered for reporting at a scientific meeting or for publication in a scientific journal, in which case Repros Therapeutics Inc. will be responsible for these activities and will work with the Principal Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues.

15. INVESTIGATOR'S STATEMENT

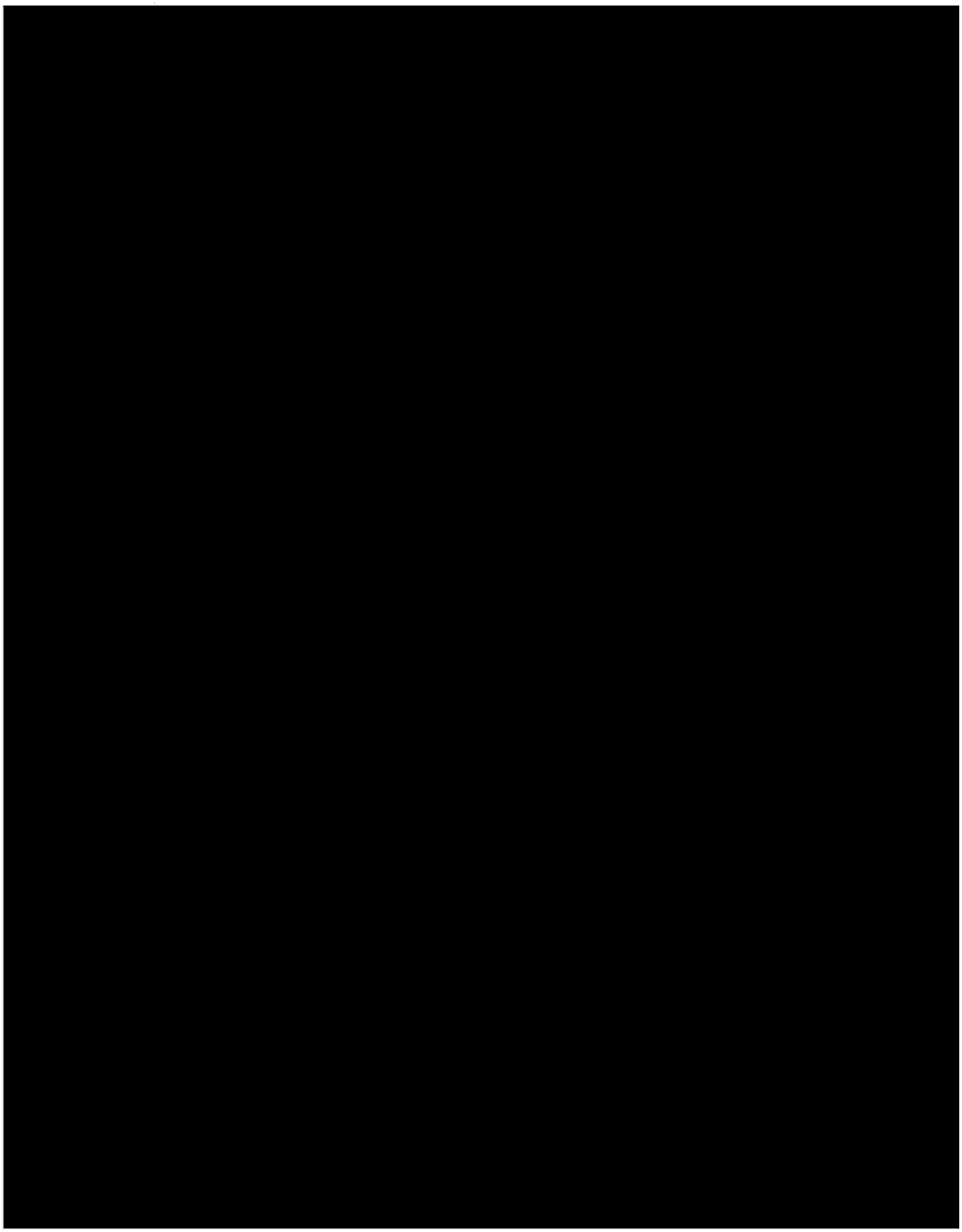
I have reviewed the ZPE-202 protocol and Investigator Brochure and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

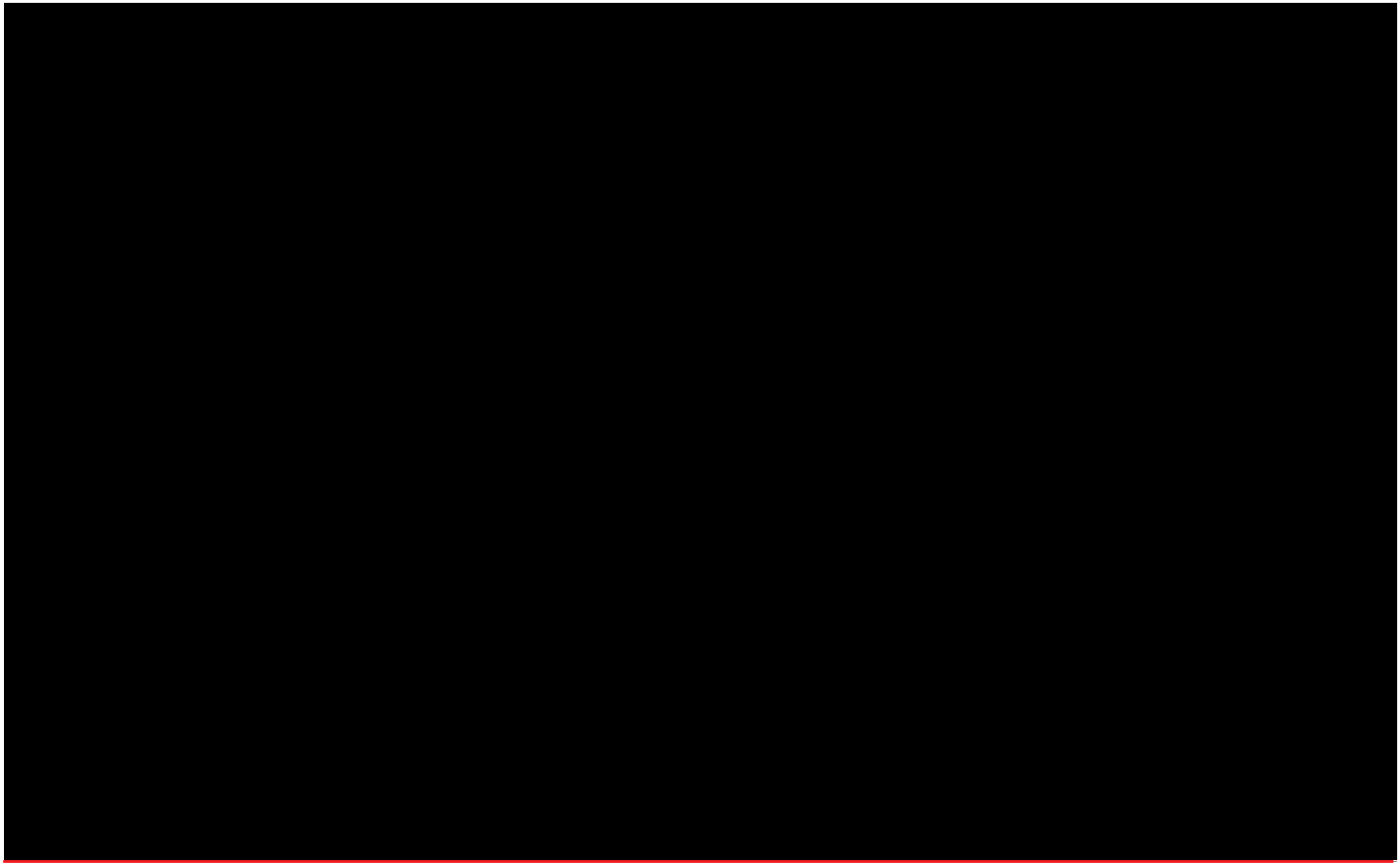
_____ _____

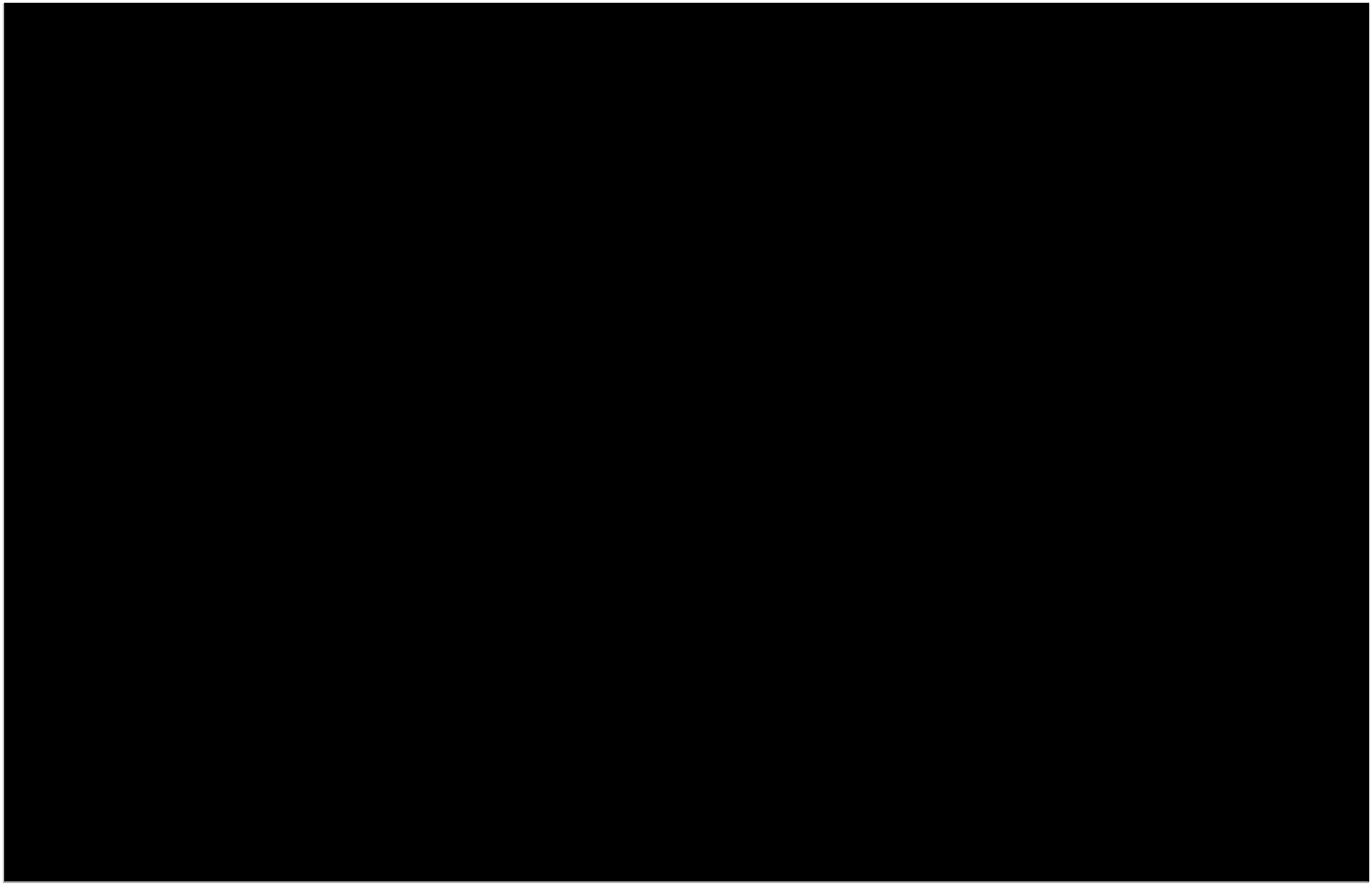
Investigator Date

_____

Printed name







ZPE-202 Protocol Summary of Changes

Protocol Title: 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

Changes From: Protocol Amendment 2 dated October 24, 2012 **To:** Protocol Amendment 3 dated April 23, 2013

Reason for Amendment: Change in required meds to prescription analgesics and addition of pain scores as inclusion and change in pain score as an endpoint

Changes to Protocol: Significant changes to the protocol are listed below. All references to narcotic analgesics were changed to prescription analgesics. Alcohol breath tests were removed.

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
COVER PAGE AND HEADERS	Amendment ~~2: October 24, 2012~~	Amendment **3: April 23, 2013**	Administrative
3. PROTOCOL SYNOPSIS: Study Purpose	To determine the safety and efficacy of two doses of Proellex in premenopausal women with pelvic pain in endometriosis confirmed within the last ~~five~~ years and using ~~narcotics~~ for symptomatic pain.	To determine the safety and efficacy of two doses of Proellex in premenopausal women with pelvic pain in endometriosis confirmed within the last **seven** years and using **prescription analgesics** for symptomatic pain.	Administrative
PROTOCOL SYNOPSIS Study Design and Duration of Treatment:	This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in two stages. In the first stage, women will receive daily single blind dosing with placebo, ~~for at least one full menstrual cycle.~~ Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications, vaginal bleeding intensity and alcohol use will	This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in two stages. In the first stage, women will receive daily single blind dosing with placebo **prior to enrollment, until their second ovulation event.** Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications, vaginal bleeding intensity and alcohol use will be recorded	Clarification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	be recorded using an electronic diary. Following the placebo run-in phase, subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of the 18 week dosing period in the double-blind phase should commence as soon after ovulation as possible, after which subjects will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the electronic diary. The final follow-up visit should be scheduled after blood flow has stopped.	using an electronic diary **and Visual Analog Scale (VAS) pain assessment will be utilized.** Following the placebo run-in phase, subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of the 18 week dosing period in the double-blind phase should commence as soon after ovulation as possible, after which subjects will be followed until menses has returned. **After completing a minimum of 28 days of treatment in this stage of the study, subjects may discontinue the study and still be eligible to qualify for the open-label extension study.** **Subjects will be treated for 18 weeks, after which subjects will be followed until menses has returned.** During the follow-up period subjects will continue to record study information in the electronic diary. The final follow-up visit will be scheduled after blood flow has stopped.	New assessment Clarification Clarification
PROTOCOL SYNOPSIS Study Population:	The study will enroll healthy adult, non-obese pre-menopausal women with surgically confirmed endometriosis using ~~narcotic~~ analgesics for their endometriosis pain.	The study will enroll healthy adult, non-obese pre-menopausal women with surgically confirmed endometriosis using **prescription** analgesics for their endometriosis pain.	All references to narcotic analgesics changed to prescription analgesics
PROTOCOL SYNOPSIS Number of Sites:	Approximately 10 sites ~~in the US~~	Approximately 10-20 sites	Clarification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
PROTOCOL SYNOPSIS **Study Endpoints:**	The ~~primary efficacy~~ endpoint will be percent change from baseline in use of ~~narcotic~~ analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18). It is anticipated that subjects randomized to active treatment will stop menstruating. ~~The secondary endpoints will be:~~ • Change in daily average use and percent change of ~~non-narcotic~~ prescription analgesics from the baseline menstrual cycle to the matching end-of- study period calculated based on days with reported values • ~~Change in daily average use of narcotic prescription analgesics from the baseline menstrual cycle to the matching end of study period~~	The **study** endpoints will be: • Percent change from baseline in use of **prescription** analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18). It is anticipated that subjects randomized to active treatment will stop menstruating • Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching end-of- study period calculated based on days with reported values • **Change from baseline in pain assessed using a Visual Analog Scale (VAS)** [redacted]	Administrative New assessment [redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	~~calculated based on days with reported values~~	[redacted]	[redacted]
PROTOCOL SYNOPSIS **Statistical Methods:**	~~The primary efficacy variable will be~~ percent change from baseline in use of ~~narcotic~~ analgesics ~~comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18). An overall comparison among the 3 treatment groups will be performed using an Analysis of Covariance, including the baseline narcotic analgesic usage and treatment in the model.~~ Pairwise comparisons between treatment groups will be made using a two-sample t-test. ~~The secondary~~ efficacy variables will be treated similarly. [redacted]	**A Statistical Analysis Plan (SAP) will be developed prior to unblinding of the data that will outline all planned analyses and analysis populations.** **Continuous efficacy endpoints, such as the** percentage change from baseline in the use of **prescription** analgesics, **will assess treatment effect using an Analysis of Covariance, including the baseline prescription analgesic usage and treatment in the model.** Pairwise comparisons between treatment groups will be made using a two-sample t-test. **Other continuous** efficacy variables will be treated similarly. [redacted]	Clarification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
5. List of Abbreviations		**VAS-Visual Analog Scale**	
7. TRIAL OBJECTIVES AND PURPOSE	The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered for 18 weeks to premenopausal women with pelvic pain in endometriosis confirmed within the last ~~five~~ years and using ~~narcotics~~ for symptomatic pain.	The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered for 18 weeks to premenopausal women with pelvic pain in endometriosis confirmed within the last **seven** years and using **prescription** analgesics for symptomatic pain.	Administrative
8. TRIAL DESIGN **8.1 Study Endpoints**	8.1 Study Endpoints ~~The Primary endpoint will be:~~ • Percent change from baseline in use of ~~narcotic~~ analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18) ~~The Secondary endpoints will be:~~ • Change in daily average use of ~~non-narcotic~~ prescription analgesics from the baseline menstrual cycle to the matching end-of- study period	8.1 Study Endpoints • Percent change from baseline in use of **prescription** analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18) • Change in daily average use of prescription analgesics from the baseline menstrual cycle to the matching end-of- study period • Change in daily average use of over the counter analgesics from the baseline menstrual cycle to the matching end-of-study period calculated based on days	Administrative

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	• ~~Change in daily average use and percent change of narcotic prescription analgesics from the baseline menstrual cycle to the matching end of study period calculated based on days with reported values~~ • Change in daily average use of over the counter analgesics from the baseline menstrual cycle to the matching end-of- study period calculated based on days with reported values	with reported values • **Change from baseline in pain assessed using a Visual Analog Scale (VAS)** [redacted]	New assessment Assessment added as endpoint
8.2 Study Design **8.2.1 Overview of Study Design**	Data must be entered ~~within 24 hours of a given timepoint~~.	Data must be entered **daily**. **Subjects who complete at least 28 days after visit 3 and wish to exit the study due to lack of efficacy will be eligible to enter an open-label extension study. Subjects who discontinue the study prior to this date will not be eligible for enrollment in the extension study.**	Administrative Clarification
8.3.1 Inclusion Criteria	• Healthy adult females between 18 and 47 years of age using ~~an average of at least 6 and no more than 36 doses of narcotic analgesics in a 28 day period for their endometriosis related pain~~ • Endometriosis diagnosis must have been surgically confirmed within ~~5~~	• Healthy adult females between 18 and 47 years of age using **prescription analgesics for endometriosis pain and with a BBSS score ≥7 at screening (assessed over the previous 28 days, see Appendix 2).** • Endometriosis diagnosis must have been surgically confirmed within **7**	New assessment (pain score) Change in eligibility criterion

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	years. A laparoscopic diagnosis is acceptable.	years. A laparoscopic diagnosis is acceptable.	
8.3.2 Exclusion Criteria	• ~~Abnormal DEXA scan (baseline T score < 1.0STD or Z score ≤ 1.50SRD) or diagnosis of osteopenia~~ • Has an IUD in place • History of abnormal ECG that, …	• Has an IUD in place. **Copper IUDs (non-hormone containing will be permitted)** • **Known** history of abnormal ECG that …	Change in Exclusion criterion Clarification Clarification
[redacted]	[redacted]	[redacted]	[redacted]

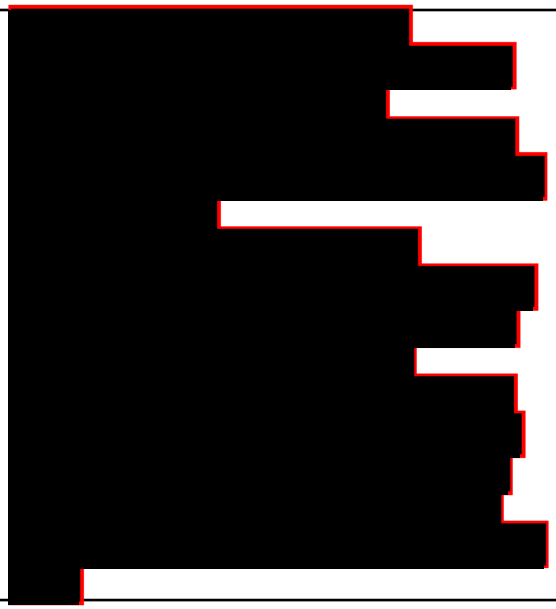
SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted]	[redacted]	[redacted]
10. ASSESSMENT OF EFFICACY **10.1 Study Endpoints**	ASSESSMENT OF EFFICACY 10.1 ~~Primary Endpoint~~ ~~The Primary endpoint will be:~~ The percent change from baseline in use of ~~narcotic~~ analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18) ~~10.2 Secondary Endpoints~~ ~~The Secondary endpoints will be:~~ • Change in daily average use and percent change of ~~non-narcotic~~ prescription analgesics from the baseline menstrual cycle to the matching end-of- study period • ~~Change in daily average use of narcotic prescription analgesics from the baseline menstrual cycle to the matching end-of- study period calculated based on days with reported values~~ [redacted]	ASSESSMENT OF EFFICACY 10.1 Study Endpoints • The percent change from baseline in use of prescription analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18) • Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching end-of- study period • **Change from baseline in pain assessed using a Visual Analog Scale (VAS)** [redacted]	Administrative New assessment (pain score) [redacted]
[redacted]		[redacted]	

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		[redacted]	
12. Concomitant Medications **12.1 Prescription Analgesics Permitted During the Study**	12.1 Analgesics Permitted During the Study Subjects should not take any analgesics during the study unless necessary for pain. In the event that a subject needs to use ~~narcotic~~ analgesics for endometriosis-related pain, one of the following regimens should be prescribed: Any deviation from this list requires pre-approval by Repros. All narcotic and non-narcotic medication will be recorded in the appropriate section of the CRF.	12.1 **Prescription** Analgesics Permitted During the Study Subjects should not take any analgesics during the study unless necessary for pain. In the event that a subject needs to use **prescription** analgesics for endometriosis-related pain, one of the following regimens should be prescribed: • **Ponstel (mefenamic acid) (500 mg initial dose, then 250 mg every 6 hours)** • **Ibuprofen/Hydrocodone: 1-2 tabs every 6-8 hrs prn** Any deviation from this list requires pre-approval by Repros. All narcotic, non-narcotic and **over–the-counter** medication will be recorded in the appropriate section of the CRF.	Change in study design Allowed medications added Administrative
13. STATISTICAL METHODS		All references to narcotics changed to prescription	
13.2.2.1 Prescription Analgesic Usage		Reference to primary endpoint removed Reference to narcotic changed to prescription	
13.2.2.2 Non-Narcotic Prescription Analgesic Usage Removed		Section removed	
13.2.2.6 VAS Assessment of Pain		**The percentage change from baseline VAS pain score will be analyzed within**	New assessment added

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		treatment group and between treatment groups. An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. Pairwise comparisons of the treatment groups will be made using t-test or non-parametric test as appropriate. While the primary assessment will be based on scores at Visit 12 (after 18 weeks of treatment), summaries will also be prepared for each of the interim visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.	
[redacted]		[redacted]	
			[redacted]
		[redacted]	[redacted]
		[redacted]	
		[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
			

[redacted]

ZPE-202 Protocol Summary of Changes

[redacted]tocol Title: 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

[redacted]anges From: Protocol Amendment 3 dated April 23, 2013 To: Protocol Amendment 4 dated June 12, 2013

[redacted]n for Amendment: To clarify: pelvic exam is required for investigator BBSS assessment, DEXA requirements, inclusion criteria for analgesic use, LFTs on Visits 1, 6 and 12.

[redacted]ges to Protocol: Significant changes to the protocol are listed below.

SECTIONS CHANGED	CHANGES MADE	REASON FOR CHANGE
[redacted]TRIAL OBJECTIVES AND [redacted]POSE [redacted]NCLUSION CRITERIA	Healthy adult females between 18 and 47 years of age ~~using~~ **prescribed** prescription analgesics **(see section 12.1)** for endometriosis pain and with a BBSS score ≥7 at screening (assessed over the previous 28 days, see Appendix 2). **Note: it is required that subjects have been prescribed analgesics, but not that they have actually taken them, provided they score ≥7 on the screening BBSS assessment.**	Inclusion Clarification
12 [redacted]NCOMITANT MEDICATIONS [redacted]SCRIPTION ANALGESICS [redacted]TED DURING THE STUDY	Any deviation from this list requires pre-approval by Repros. **Note: Over-the-counter medications (e.g. ibuprofen, naproxen) do not qualify as prescription medications for entrance into the study, even if a prescription has been written for the specific medication.**	Inclusion Clarification
[redacted]	[redacted]	[redacted]

HAN	CHANGES MADE	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

ZPE-202 Protocol Summary of Changes

Protocol Title: 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

Changes From: Protocol Amendment 4 dated June 12, 2013 **To:** Protocol Amendment 6 dated January 7, 2014

Reason for Amendment: Addition of up to 2 additional (optional) cycles of treatment

Changes to Protocol: Significant changes to the protocol are listed below.

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
SYNOPSIS: Study Purpose:	To determine the safety and efficacy of two doses of Proellex in premenopausal women with pelvic pain in endometriosis confirmed within the last seven years and using prescription analgesics for symptomatic pain.	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.	Administrative change
SYNOPSIS: Study Design and Duration Of Treatment	This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in ~~two~~ stages. Following the placebo run-in phase, subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of the 18 week dosing period in the double-blind phase should commence as soon after ovulation as possible, after which subjects will be followed until menses has returned. [redacted] Subjects will be treated for 18 weeks, after which subjects will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the electronic diary. The final follow-up visit will be scheduled after blood flow has stopped.	This study is a phase 2, 3-arm-study with an 18 week active dosing period **and an option to extend treatment for 2 additional cycles (US sites only).** The study will be conducted in **three** stages. **In the second stage,** following the placebo run-in phase, subjects will be randomized into one of 3 arms 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 electronic diary.** After completing a minimum of 28 days of treatment in this stage of the study, subjects may discontinue the study and still be eligible to qualify for up to 2 additional treatment cycles **(stage 3, US sites only).** In the third stage, subjects (US only) who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled within a week before	Additional stage added

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		the next expected menses (+/- 2 days), following the off-drug interval. Subjects will receive 2 cycles of additional treatment separated by an off-drug interval (ODI), after which they will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the electronic diary. The final follow-up visit will be scheduled after blood flow has stopped.	
SYNOPSIS: Study Duration	Total participation in the study is approximately ~~6-7~~ months.	Total participation in the study is approximately **18** months.	Extended due to additional cycles
[redacted]	[redacted]	[redacted]	[redacted]
SYNOPSIS Section 8.1 and Section 10.1 Study Endpoints	➢ Percent change from baseline in use of prescription analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to the last day of dosing (Week 18). ~~It is anticipated that subjects randomized to active treatment will stop menstruating~~ ➢ Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching ~~end~~	• **The** percent change from baseline in use of prescription analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to Week 18, the last day of dosing of the first cycle of treatment • Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching **period leading up to Week 18, the last day of dosing of the first cycle of treatment**	Administrative Clarification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	~~of study period calculated based on days with reported values~~ ➢ Change in daily average use and percent change over the counter analgesics from the baseline menstrual cycle to the matching ~~end of study period~~ ➢ Change and percent change in BBSS score incorporating the two physician reported scores	• Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching period **leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.** • Change and percent change in BBSS score incorporating the two physician reported scores **by study visit and treatment cycle.**	Clarification Clarification
Study Endpoints (cont)	➢ Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) ➢ Change from baseline in pain assessed using a Visual Analog Scale (VAS) [redacted]	• Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) **by study visit and treatment cycle.** • Change from baseline in pain assessed using a Visual Analog Scale (VAS) **by study visit and treatment cycle.** [redacted]	Clarification Clarification [redacted]
SYNOPSIS: Statistical Methods	A Statistical Analysis Plan (SAP) will be developed prior to unblinding of the data that will outline all planned analyses and analysis populations.	A Statistical Analysis Plan (SAP) will be developed prior to unblinding of the data that will outline all planned analyses and analysis populations. **The first efficacy analysis will be conducted when all subjects complete the first cycle of treatment. A second analysis will summarize the subject's additional treatment cycles which will be conducted after all subjects complete study treatment and follow-up.**	Amended to account for additional on drug cycles
5. LIST OF ABBREVIATIONS		**ODI Off drug interval added**	Administrative

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
7. TRIAL OBJECTIVES AND PURPOSE	The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered ~~for 18 weeks~~ to premenopausal women with pelvic pain ~~in~~ endometriosis confirmed within the last seven years and using prescription analgesics for symptomatic pain.	The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered to premenopausal women with pelvic pain **associated with e**ndometriosis confirmed within the last seven years and using prescription analgesics for symptomatic pain. **Proellex will be administered for up to 3 cycles (18 or 16 weeks in duration), each separated by an Off-Drug Interval (ODI).**	Administrative Additional on drug cycles added
8. TRIAL DESIGN 8.1 Study Endpoints		See study endpoint changes in synopsis	
[redacted]		[redacted]	
8.2 Study Design 8.2.1 Overview of Study Design	This study is a phase 2, 3-arm-study with an 18 week active dosing period. The study will be conducted in ~~2~~ stages. Following the run-in stage, at Visit 3, 90 subjects will be randomized into one of 3 arms in a 1-1-1 fashion. Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within 35 days or less). The follow-up visit should be scheduled after blood flow has stopped. During the follow-up period subjects will continue to record study information in the electronic diary.	This study is a phase 2, 3-arm-study with an 18 week active dosing period **and an option for subjects (US sites only) to receive 2 additional 16-week cycles of active treatment at their randomized dose (6 mg or 12 mg/day). Placebo subjects who elect additional treatment will receive treatment at 12 mg/day. The treatment dose will remain double-blind.** The study will be conducted in **3** stages. **For stage 2,** following the run-in stage, at Visit 3, 90 subjects will be randomized into one of 3 arms in a 1-1-1 fashion. Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within 35 days or less). **At US sites only, subjects may elect to receive up to 2 additional cycles of treatment at their randomized dose (6 mg or 12 mg/day), placebo-treated subjects will receive treatment at 12 mg/day. In stage 3 all subjects will receive active treatment but the treatment dose will remain double-blind. For subjects who do not choose additional treatment cycles, their final** follow-up visit should be scheduled after blood flow has stopped. During the follow-up period subjects will continue to record study information in the electronic diary.	Additional on drug cycles added Administrative Additional on drug cycles added

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
8.2.1 Overview of Study Design (Cont)		**For stage 3, subjects who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled within a week before the next expected menses (+/- 2 days), following the off-drug interval. Only subjects at US sites will be eligible for additional courses of treatment. Subjects will receive 2 cycles of treatment separated by an off-drug interval (ODI), after which they will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the electronic diary. The final follow-up visit will be scheduled after blood flow has stopped.**	Additional on drug cycles added
	In addition to the diary information, endometrial thickness will be recorded at screening and every month thereafter. Assessment of trough levels of drug will be determined at every office visit during the 18 week dosing period.	In addition to the diary information, endometrial thickness will be recorded at screening and every month thereafter. Assessment of trough levels of drug will be determined at every office visit during the **first** 18 week dosing period.	Clarification
	Subjects who complete at least 28 days after visit 3 and wish to ~~exit the study~~ due to lack of efficacy will be eligible to ~~enter an~~ open-label ~~extension study~~. Subjects who discontinue the study prior to this date will not be eligible for ~~enrollment in the extension study~~.	Subjects who complete at least 28 days after visit 3 and wish to **discontinue treatment** due to lack of efficacy will be eligible to **start active treatment (stage 3).** Subjects who discontinue the study prior to this date will not be eligible for **additional treatment**.	Clarification
8.2.3 Randomization and Blinding	All subjects will receive placebo from Visit 1 until Visit 3. At Visit 3, subjects will be randomized to treatment in Arms 1, 2, or 3. Subjects will be treated with one capsule daily of 6 mg or 12 mg of Proellex, or placebo, which will be administered for 18 weeks. Blinded treatments kits will be randomized and distributed by the packaging company.	All subjects will receive placebo from Visit 1 until Visit 3. At Visit 3, subjects will be randomized to treatment in Arms 1, 2, or 3. Subjects will be treated with one capsule daily of 6 mg or 12 mg of Proellex, or placebo, which will be administered for 18 weeks. **Subjects who elect to receive additional treatment cycles will be treated at their previously randomized dose level. Subjects randomized to placebo treatment will receive treatment at 12 mg/day. Each 18-week treatment cycle will be separated by an ODI.** Blinded treatments kits will be randomized and distributed by the packaging company.	Additional on drug cycles added
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
12.2 Prohibited Medications		**The following medications are prohibited during the study:** • **Testosterone** • **Progestin** • **Androgen** • **Estrogen** • **Anabolic steroids** • **DHEA** • **Other hormonal products**	New section added
13.2 Statistical and Analytical Plan		**An analysis will be conducted once Stage 2, the first cycle of treatment, has been completed. A later analysis will focus on the data collected from the active treatment stage of the study, Stage 3.**	Amended to account for additional treatment cycles
13.2.2 Efficacy Analyses	Efficacy analyses will be conducted in the Intent-to-Treat population, which will consist of all subjects who are randomized and who receive study drug.	Efficacy analyses **of the cycle of treatment** will be conducted in the Intent-to-Treat population, which will consist of all subjects who are randomized and who receive study drug.	Clarification
13.2.2.1 Prescription Analgesic Usage and 13.2.2.2 Over the Counter Analgesic Usage	The percent change in daily average use of prescription analgesics comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing (Week 18), and will be summarized for each treatment group.	The **change and** percent change in daily average use of prescription analgesics comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing **in Cycle 1** (Week 18) will be summarized for each treatment group. Changes in prescription analgesic use during the **active treatment stage of the study (Stage 3) will also be summarized.**	Clarification Additional on drug cycles added
13.2.2.3 BBSS Patient and Physician Reported Scores AND	The BBSS score incorporating the two physician-reported scores will be analyzed to compare the baseline menstrual cycle to a similar period	The percent change from baseline in each of the daily average combined BBSS patient-reported scores (dysmenorrhea, dyspareunia and non-menstrual pelvic pain)	Clarification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
13.2.2.4 BBSS Patient Reported Scores	leading up to the last day of dosing (Week 18).	will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing **in Cycle 1** (Week 18). **The BBSS patient and physician scores during the active treatment stage of the study (Stage 3) will also be summarized.**	Additional on drug cycles added
13.2.2.5 Menstrual or Non-menstrual Vaginal Bleeding		[redacted]	Additional on drug cycles added
13.2.2.6 VAS Assessment of Pain		**The VAS pain scores collected during the active treatment stage of the study (Stage 3) will also be summarized.**	Additional on drug cycles added
13.3 General Statistical Issues		**A Statistical Analysis Plan (SAP) will be developed prior to the analyses of the first cycle of treatment. Two analyses will be conducted. The first analysis will occur when all subjects have completed the first cycle of treatment (Week 18) and the second with be conducted once all subjects have completed the active treatment stage of the study (Stage 3).**	Amended to account for additional on drug cycles
[redacted]		[redacted]	[redacted]

[redacted]

ZPE-202 Protocol Summary of Changes

Protocol Title: 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

Changes From: Protocol Amendment 6 dated January 7, 2014 **To:** Protocol Amendment 7 dated March 12, 2014

Reason for Amendment: Addition of up to 2 additional (optional) cycles of treatment

Changes to Protocol: Significant changes to the protocol are listed below.

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
SYNOPSIS: Study Design and Duration Of Treatment	Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications, vaginal bleeding intensity and alcohol use will be recorded using an electronic diary and Visual Analog Scale (VAS) pain assessment will be utilized.	Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications, vaginal bleeding intensity and alcohol use will be recorded using a daily electronic **or paper** diary. **Daily subject ratings of dysmennorhea and non-menstrual pelvic pain will be captured using an 11-point numerical rating scale (NRS)** and Visual Analog Scale (VAS) pain assessment will be utilized.	Addition of paper diary for some/all sites Addition of NRS to study assessments
SYNOPSIS: Number of Subjects	Up to ~~90~~ female subjects, ~~30~~ per dose arm	Up to **60** female subjects, **20** per dose arm.	Change in sample size
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted]	[redacted]	[redacted]
SYNOPSIS Section 8.1 and Section 10.1 Study Endpoints	• ~~The percent change from baseline in use of prescription analgesics comparing the baseline nominal 28-day menstrual cycle (including menstrual event) to a similar period leading up to Week 18, the last day of dosing of the first cycle of treatment~~ • Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment • Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values. • Change and percent change in BBSS score incorporating the two physician reported scores by study visit and treatment cycle. • Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle. • Change from baseline in pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle.	*Primary Endpoint* • Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle. *Secondary Endpoints* • Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment. • Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values. • **Change in daily average use and percent change of overall analgesic use, prescription and over the counter, from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.** • Change and percent change in BBSS score incorporating the two physician reported scores by study visit and treatment cycle. • Change from baseline in pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle. • **Change from baseline in daily average dysmenorrhea and non-menstrual pelvic pain using an 11-point**	Endpoints re-ordered to reflect possible Phase 3 study design New endpoint added New endpoint added

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		numerical rating scale (NRS) by study visit and treatment cycle. [redacted]	[redacted]
[redacted]		[redacted]	[redacted]
5. LIST OF ABBREVIATIONS		Added: **NRS Numerical Rating Scale**	New study procedure
8. TRIAL DESIGN 8.2.1 Overview of Study design	[redacted] For stage 2, following the run-in stage, at Visit 3, 690 subjects will be randomized into one of 3 arms in a 1-1-1 fashion. Assessment of trough levels of drug will be determined at every office visit ~~during the first 18 week dosing period.~~	[redacted] For stage 2, following the run-in stage, at Visit 3, **60** subjects will be randomized into one of 3 arms in a 1-1-1 fashion. Assessment of trough levels of drug will be determined at every **on-drug** office visit.	[redacted] Change in sample size Clarification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
8.2 Study Design 8.2.3 Randomization and Blinding	Subjects randomized to placebo treatment will receive treatment at 12 mg/day. Each 18-week treatment cycle will be separated by an ODI. Blinded treatments kits will be randomized and distributed by the packaging company.	Subjects randomized to placebo treatment will receive treatment at 12 mg/day. **In stage 3 all subjects will receive active treatment but the treatment dose will remain double-blind.** Each 18-week treatment cycle will be separated by an ODI. Blinded treatments kits will be randomized and distributed by the packaging company. **For the statistical analysis at Week 18, only statistical staff will be unblinded once the acute portion of the study database is locked. All clinical operations staff and staff at investigative sites will remain blinded until completion of the study.**	Clarification Clarification
8.2.4 Study Medication		Statement added: **Subjects will not be provided with analgesic medications by Repros Therapeutics Inc.**	Clarification
8.3 Selection and Withdrawal of Subjects	• Any subject who develops an endometrial thickness ≥ ~~20~~ mm ~~and~~ experiences heavy bleeding for 7 days or more will be discontinued from the study Appropriate follow up treatment will be provided as deemed necessary by the investigator.	• Any subject who develops an endometrial thickness ≥ **18** mm or experiences **suspicious or unusually** heavy bleeding for 7 days **or** more will be discontinued from the study **and undergo endometrial biopsy. Women with such findings will not be eligible for extension of treatment.** Appropriate follow up treatment will be provided as deemed necessary by the investigator.	New study requirement
8.3.2 Exclusion Criteria	• Has an IUD in place. Copper IUDs (non-hormone containing) will be permitted	• Has an IUD in place. Copper IUDs (non-hormone containing) will be permitted **provided subjects agree to keep them in place for the duration of the study (unless a medical need to remove it arises)**	New study requirement
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
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SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
11.1.2 Definitions Serious Adverse Event (SAE) 11.1.3 Serious Adverse Events (SAEs)		Statement added: **Cases of liver transaminases that increase above 3 times the upper limit of normal must be reported as SAEs regardless of whether the above defined SAE criteria are met.**	New safety requirement
12 CONCOMITANT MEDICATIONS 12.1 Prescription Analgesics Permitted During the Study	• Acetaminophen/Hydrocodone: 1-2 tabs every 4-6 hours prn • Ibuprofen/Hydrocodone: 1-2 tabs every 6-8 hrs prn All narcotic, non-narcotic and over–the-counter medication will be recorded in the appropriate section of the CRF.	• Acetaminophen/Hydrocodone: **5-10 mg/325 -750 mg**, 1-2 tabs every 4-6 hours prn • Ibuprofen/Hydrocodone: **7.5/200 mg,** 1-2 tabs every 6-8 hrs prn All narcotic, non-narcotic and over–the-counter medication **for endometriosis-related pain will be captured in the subjects' daily diary.** **All narcotic, non-narcotic and over–the-counter medications for non-endometriosis-related pain** will be recorded in the appropriate section of the CRF. **Analgesic medications will not be provided by Repros Therapeutics Inc.**	Clarification Clarification Clarification Clarification
12.2 Prohibited Medications		Statement added: • **CYP3A4 inhibitors, e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin.**	New safety requirement added
13. STATISTICAL METHODS 13.1 Determination of Sample Size	Up to ~~90~~ female subjects, 230 per dose arm, meeting the inclusion/exclusion criteria will be randomized in a 1-1-1 fashion. ~~Although the primary analysis for each endpoint in this study will be an Analysis of Covariance~~, the sample size was powered based on the two-sample t-tests that will be used to make pairwise comparisons between treatment groups. [redacted]	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. [redacted]	Change in sample size and justification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted]	[redacted] **a sample of 18 subjects per group would provide 80% power to detect a statistically significant difference between the treatment groups.**	
13.2 Statistical and Analytical Plan		New statement added: **A statistical analysis will be conducted once all subjects have completed the placebo-controlled portion of the study, Stages 1 and 2. A Statistical Analysis Plan will be developed that outlines in detail all planned analyses. This document will be completed prior to unblinding study data for the placebo-controlled portion of the study.** **A separate analysis and reporting will occur once all subjects have completed all study treatment. A separate Statistical Analysis Plan will describe these analyses. This summary will focus on the results noted in Stage 3 of the study.**	Clarification
13.2.2 Efficacy Analyses 13.2.2.3 Overall Analgesic Use		**The change and percent change in daily average use of all analgesics (prescription and over the counter) comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing in Cycle 1 (Week 18) will be summarized for each treatment group. For each subject, the total number of pills or tablets of analgesics taken during each 28 day menstrual cycle will be calculated, and the daily average use of prescription analgesics will be determined by dividing the total number of pills/tablets of analgesics taken during the 28 day nominal period by 28. The percent change from baseline in the analgesic usage will be determined by subtracting the baseline analgesic usage from the**	New endpoint added

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		analgesic usage during the last nominal 28 day menstrual cycle, dividing by the baseline analgesic usage, and multiplying by 100%. **An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.** **Changes in analgesic use during the active treatment stage of the study (Stage 3) will also be summarized.**	
13.2.2.1 Prescription Analgesic Usage and 13.2.2.2 Over the Counter Analgesic Usage	The percent change in daily average use of prescription analgesics comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing (Week 18), and will be summarized for each treatment group.	The **change and** percent change in daily average use of prescription analgesics comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing **in Cycle 1** (Week 18) will be summarized for each treatment group. Changes in prescription analgesic use during the **active treatment stage of the study (Stage 3) will also be summarized.**	Clarification Clarification
13.2.2.8 Assessment of Pain Using the NRS		New statement added: **The average daily assessment will be calculated separately for dysmenorrhea and pelvic pain within each key 28-day baseline and treatment periods. The percentage change from baseline NRS pain score will be analyzed within treatment group and between treatment groups. An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. Pairwise comparisons of the treatment groups will be made using t-test or non-parametric test as appropriate. While the primary assessment will be based on scores during the 28-day period prior to Visit 12 (after 18 weeks of treatment), summaries will also be prepared for each of the other visits.**	New endpoint added

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		The average daily assessment of dysmenorrhea and pelvic pain scores collected during the active treatment stage of the study (Stage 3) will also be summarized.	
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	
[redacted]		[redacted]	

ZPE-202 Protocol Summary of Changes

Protocol Title: 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

Changes From: Protocol Amendment 7 dated March 12, 2014 **To:** Protocol Amendment 8US dated March 31, 2015

Reason for Amendment: Run in period changed from placebo to no treatment

Changes to Protocol: Significant changes to the protocol are listed below.

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
Throughout document	References to "US sites only" have been removed as the protocol is now only for US sites References to an electronic diary have been deleted as the study is now using only paper diaries [redacted]		
SYNOPSIS: Study Design and Duration Of Treatment	In the first stage, women will receive daily single blind dosing with placebo prior to enrollment, until their second ovulation event.	**In the first stage, women** will undergo a baseline assessment period with no treatment, until their second ovulation event.	Change in study design
	In the second stage, following the ~~placebo run-in phase~~	In the second stage, following the **baseline assessment period**,	Change in study design
	In the third stage, subjects ~~(US only)~~ who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled ~~within a week before the second expected menses~~ (+/- 2 days), following the off-drug interval). Subjects will receive 2 ~~cycles~~ of additional treatment separated by an off-drug interval (ODI), after which they will be followed until menses has returned.	In the third stage, 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 end of their first course of treatment** (off-drug interval). Subjects will receive 2 **courses** of additional treatment separated by an off-drug interval (ODI), after which they will be followed until menses has returned.	Change in study design
	[redacted]		Establishment of DSMB for all Proellex studies

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	Change in study design
	[redacted]	[redacted]	Clarification
[redacted]			
6. BACKGROUND INFORMATION 6.6 DSMB	[redacted]	[redacted]	[redacted]
8. TRIAL DESIGN 8.2.1 Overview of Study design	The study will be conducted in 3 stages. In the first stage, women will ~~receive a daily single blind placebo~~	The study will be conducted in 3 stages. In the first stage, women will **undergo a baseline assessment period with no treatment**.	Change in study design
	The daily number of doses	The daily number of doses **and dosages**	Clarification
	For stage 2, following the ~~run in stage~~	For stage 2, following the **baseline assessment period**,	
	Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within ~~35~~ days or less).	Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within **21** days or less).	Correction
	For subjects who do not choose additional treatment cycles, their final follow-up visit ~~should be scheduled after blood flow has stopped.~~	For subjects who do not choose additional treatment cycles, **this will be** their final follow-up visit	Clarification
	For stage 3, subjects who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled within a week before the second expected menses (+/- 2 days), following the off-drug interval. ~~Only subjects at US sites will be eligible for additional~~	For stage 3, subjects who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled **at 21 ± 2 days after start of bleeding in their first menses after Visit 12 (recovery menses)**.	Correction

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	~~courses of treatment.~~ [redacted]	[redacted]	Correction
8.2 Study Design 8.2.3 Randomization and Blinding	All subjects will receive ~~placebo~~ treatment from Visit 1 until Visit 3	All subjects will receive **no** treatment from Visit 1 until Visit 3	Change in study design
8.3 Selection and Withdrawal of Subjects		• **The decision to withdraw from the study because of an adverse event, including pain from endometriosis or from another condition, is decided by the subject and the investigator or her personal physician. The event, and any treatment should be recorded in the study records.**	Clarification
8.3.2 Exclusion Criteria	• Has an IUD in place. ~~Copper IUDs (non hormone containing) will be permitted provided subjects agree to keep them in place for the duration of the study (unless a medical need arises to remove it).~~	• Has an IUD in place. • Previous use of telapristone acetate or participation in a Repros clinical study	Additional safety criterion Clarification
[redacted]	[redacted]		[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	[redacted]
12 CONCOMITANT MEDICATIONS 12.1 Prescription Analgesics Permitted During the Study		**12.1.1 Treatment of Endometriosis-Related Pain** **12.1.2 Treatment of Non-Endometriosis–Related Pain** **If the subject experiences pain (not related to endometriosis), she should be treated as medically appropriate. The choice of drug will depend on the medical condition. Dosage forms and route of administration should be as per product specifications.**	Formatting changed for clarity Clarification
12.2 Prohibited Medications		• **St. John's Wort** • **Spironolactone** • **Cimetidine**	Additional prohibited medications added
13. STATISTICAL METHODS 13.2 SAP	A statistical analysis will be conducted once all subjects have completed the placebo-controlled portion of the study, Stages ~~1 and~~ 2	A statistical analysis will be conducted once all subjects have completed the placebo-controlled portion of the study, Stage 2	Change in study design
[redacted]	[redacted]	[redacted]	[redacted]

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

Original Protocol: July 18, 2012
Amendment 1: August 31, 2012
Amendment 2: October 24, 2012
Amendment 3: April 23, 2013
Amendment 4: June 12, 2013
Amendment 5: January 06, 2014
Amendment 6: January 7, 2014
Amendment 7: March 12, 2014
Amendment 8US: March 31, 2015

SPONSOR:

Repros Therapeutics Inc.®
2408 Timberloch Place, B-7
The Woodlands, TX 77380

IND 76,631

[redacted]

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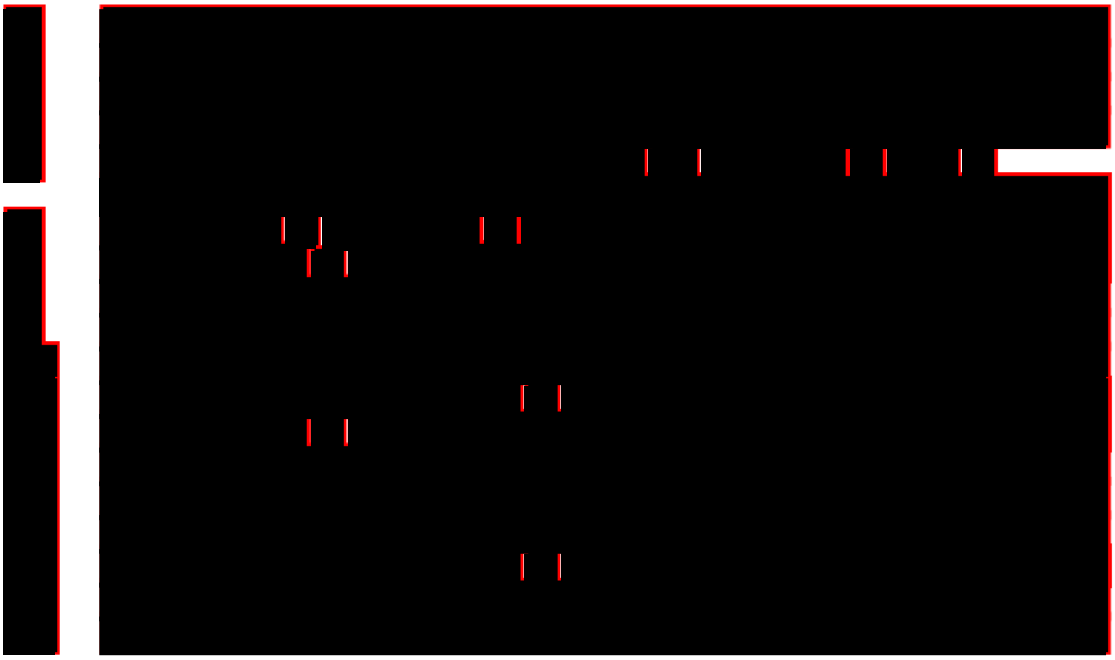
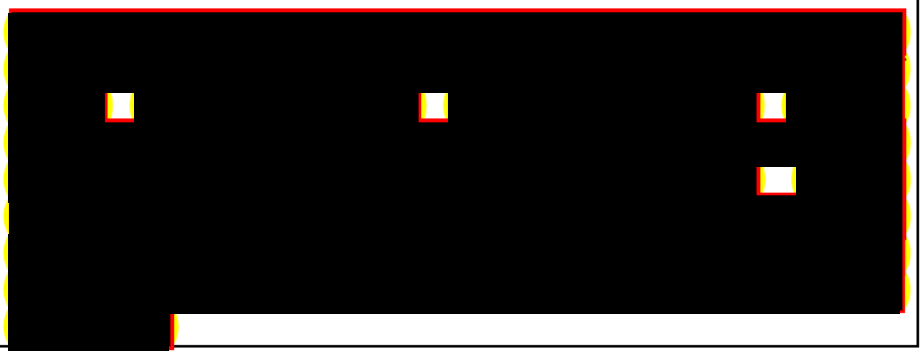


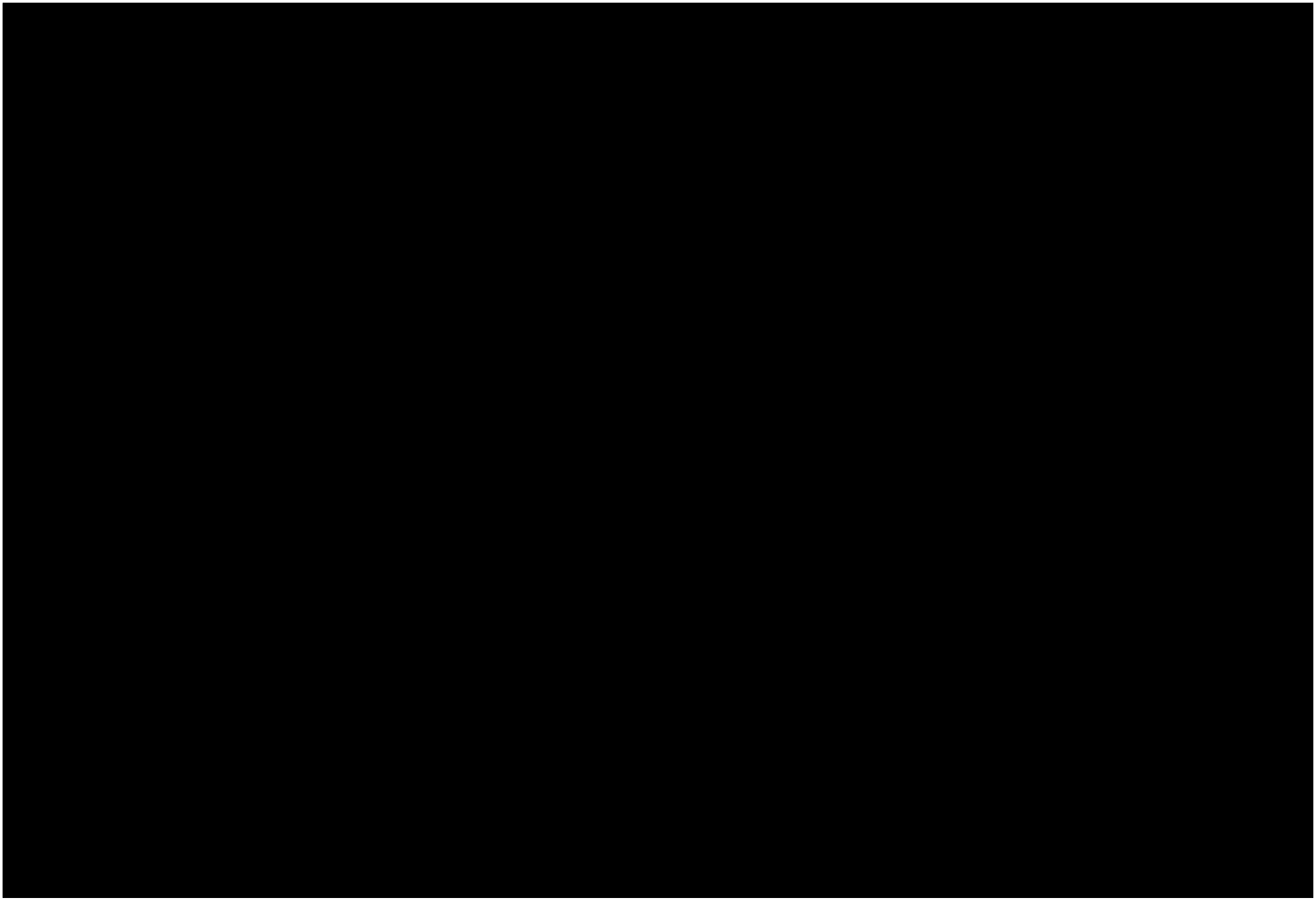
3. PROTOCOL SYNOPSIS

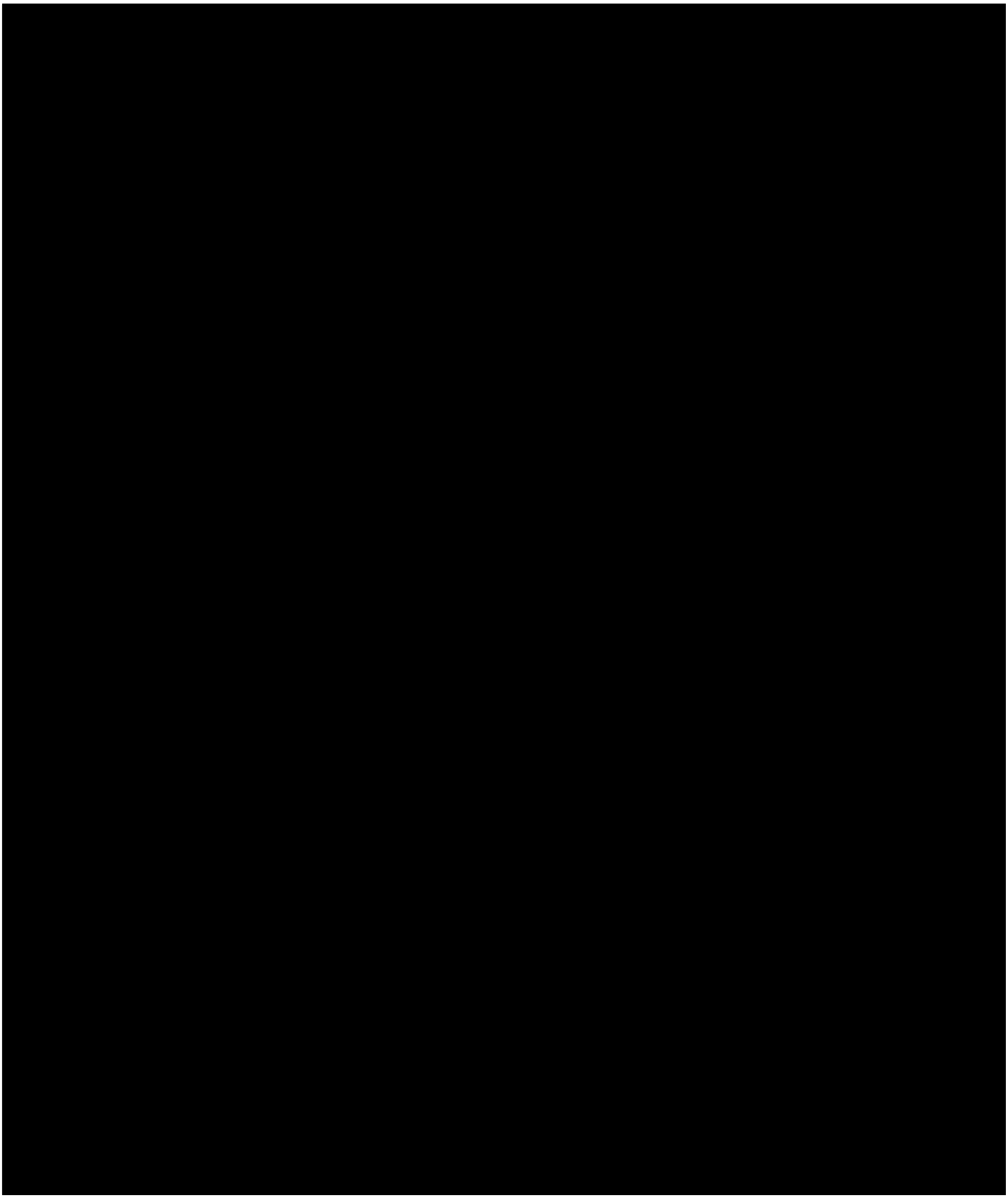
Test Drugs:	Proellex® (Telapristone Acetate): 6 and 12 mg gelatin capsules and matching placebo
Protocol Number:	ZPE-202
Study Purpose:	To determine the safety and efficacy of two doses of Proellex in premenopausal women with pelvic pain associated with endometriosis confirmed within the last seven years and using prescription analgesics for symptomatic pain.
Study Design and Duration Of Treatment:	This study 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 no treatment until their second ovulation event. Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications, vaginal bleeding intensity and alcohol use will be recorded using a daily diary. Daily subject ratings of dysmenorrhea and non-menstrual pelvic pain will be captured using an 11-point numerical rating scale (NRS) and Visual Analog Scale (VAS) pain assessment will be utilized. In the second stage, following the baseline assessment period, subjects will be randomized into one of 3 arms 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 this stage of the study, subjects may discontinue the study and still be eligible to qualify for up to 2 additional treatment cycles. In the third stage, 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 end of their first course of treatment (off-drug interval). Subjects will receive 2 courses of additional treatment separated by an off-drug interval (ODI), after which they will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the daily diary. The final follow-up visit will be scheduled after blood flow has stopped. [redacted]

	[redacted]
Subject Population:	The study will enroll healthy adult, non-obese pre-menopausal women with surgically confirmed endometriosis using prescription analgesics for their endometriosis pain.
Number of Subjects:	Up to 60 female subjects, 20 per dose arm (US and Argentina)
Number of Sites	Approximately 10-20 sites
Study Duration:	Total participation in the study is approximately 18 months.
[redacted]	[redacted]

Study Endpoints	The study endpoints will be: *Primary Endpoint* • Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle. *Secondary Endpoints* • Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment. • Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values. • Change in daily average use and percent change of overall analgesic use, prescription and over the counter, from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values. • Change and percent change in BBSS score incorporating the two physician reported scores by study visit and treatment cycle. • Change from baseline in pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle. • Change from baseline in daily average dysmenorrhea and non-menstrual pelvic pain using an 11-point numerical rating scale (NRS) by study visit and treatment cycle. 
Statistical Methods:	A Statistical Analysis Plan (SAP) will be developed prior to unblinding of the data that will outline all planned analyses and

	analysis populations. The first efficacy analysis will be conducted when all subjects complete the first cycle of treatment. A second analysis will summarize the subject's additional treatment cycles which will be conducted after all subjects complete study treatment and follow-up. Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. All summaries will be prepared for each treatment group. Summaries will be prepared for each treatment group of subject accountability, baseline demographic, and medical history data. Continuous efficacy endpoints, such as the percentage change from baseline in the use of prescription analgesics, will assess treatment effect using an Analysis of Covariance, including the baseline prescription analgesic usage and treatment in the model. Pairwise comparisons between treatment groups will be made using a two-sample t-test. Other continuous efficacy variables will be treated similarly. 





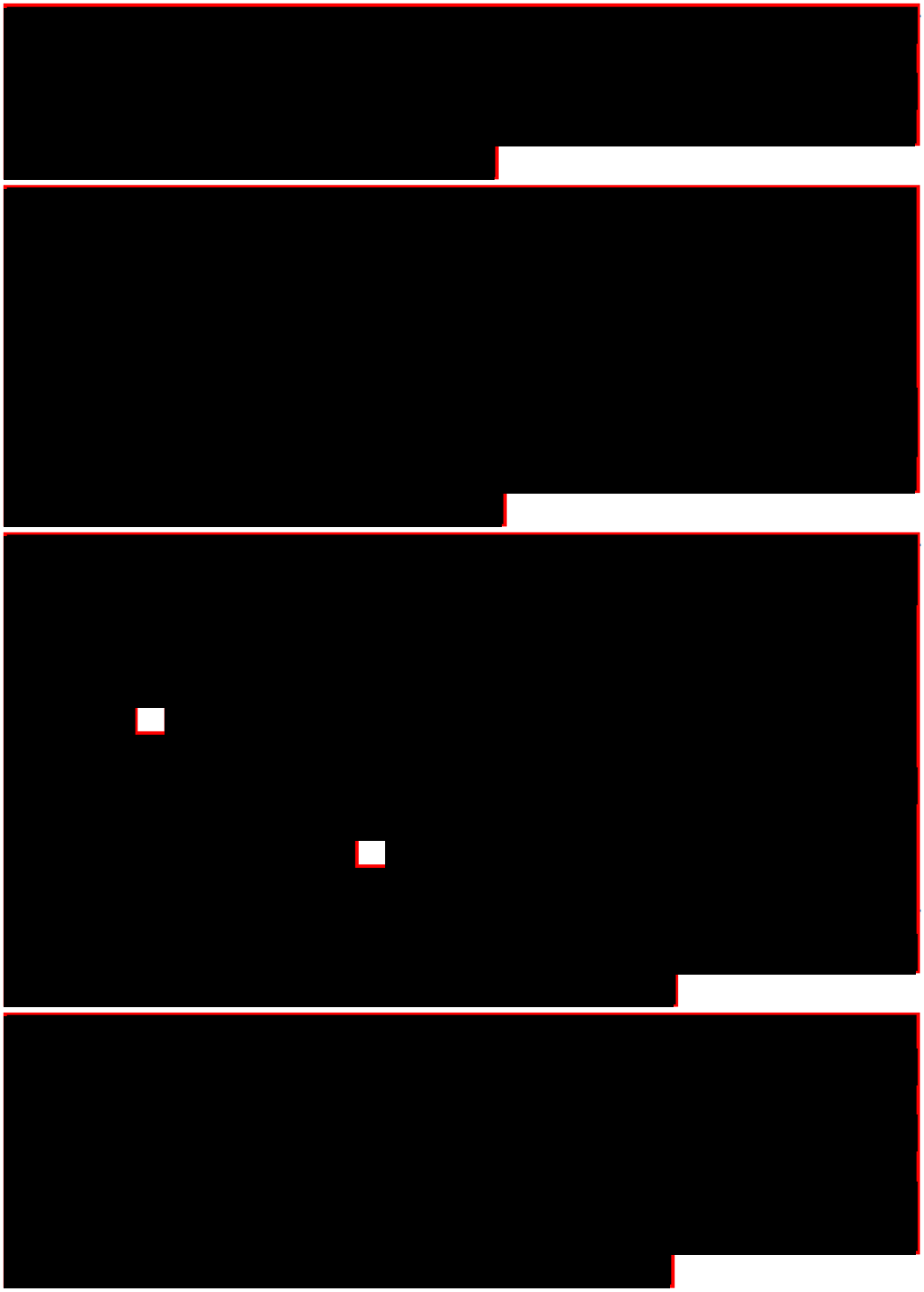
5. LIST OF ABBREVIATIONS

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
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

6. BACKGROUND INFORMATION

6.1 Rationale for Current Study

Repros believes telapristone offers the potential to provide significant symptomatic relief to women that suffer from a variety of reproductive disorders in which progesterone may be implicated. Most notably the sponsor has seen significant clinically relevant impact on the symptoms of both uterine fibroids and endometriosis.



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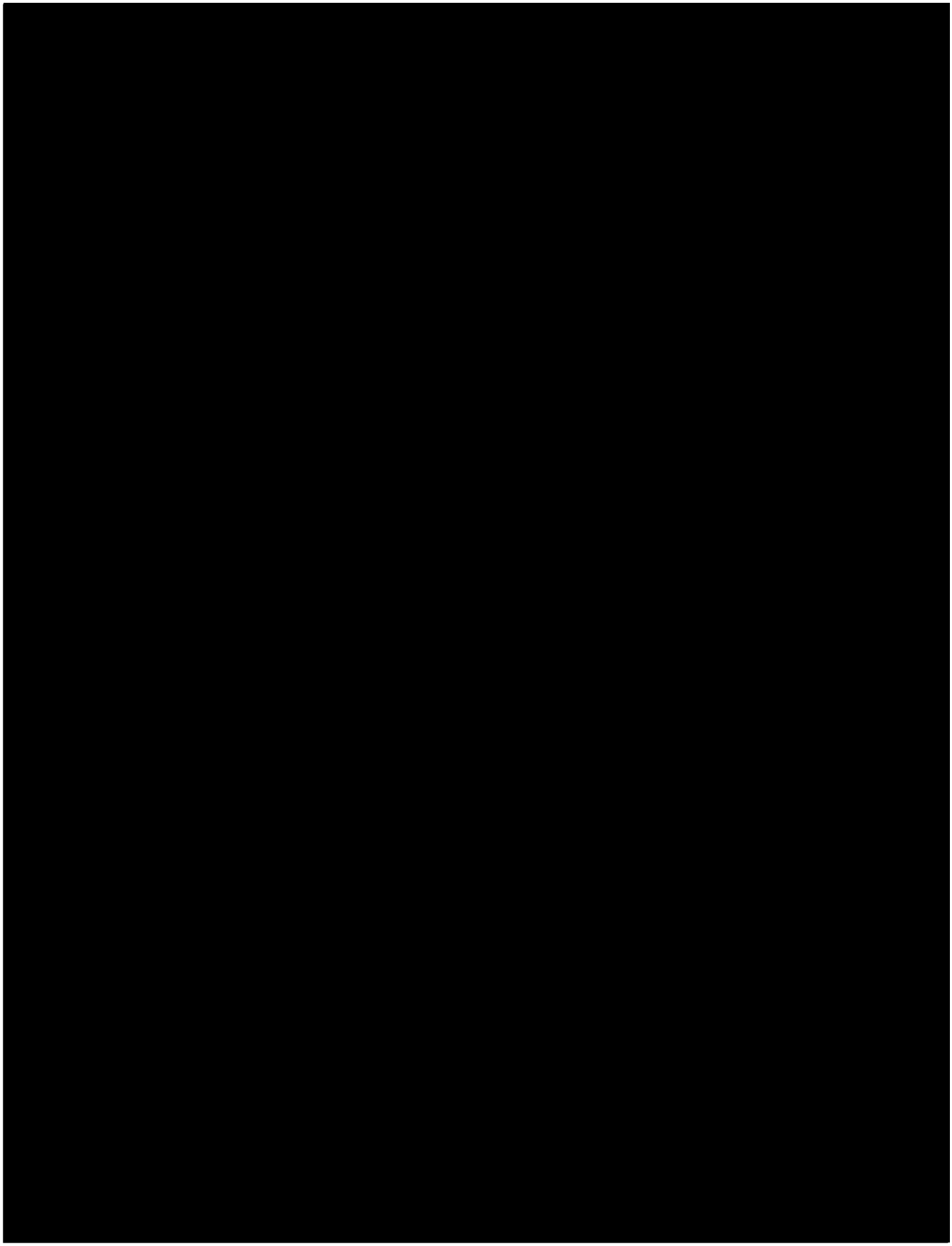
Overall, findings were favorable to the Proellex treatments, in particular the

[redacted]

[redacted]

FDA Guidance For Liver Enzyme Elevation Characterization as SAE

- 1. LFTs ≥ 8 x ULN
- 2. LFTs ≥ 5 x ULN for 2 consecutive weeks
- 3. LFTs ≥ 3 x ULN + Bilirubin 2 x ULN
- 4. LFTs ≥ 3 x ULN + clinical signs or symptoms (nausea; jaundice; etc.)



[redacted]

6.5 Ethical Conduct of the Study

This trial will be conducted in strict compliance with the protocol and all applicable FDA regulations and GCP guidelines to insure Good Clinical Practice standards. The Institutional Review Board (IRB) for this study is IntegReview, 3001 S. Lamar Blvd., Suite 210, Austin, Texas 78704.

[redacted]

7. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered to premenopausal women with pelvic pain associated with endometriosis confirmed within the last seven years and using prescription analgesics for symptomatic pain. Proellex will be administered for up to 3 cycles (18 or 16 weeks in duration), each separated by an Off-Drug Interval (ODI).

8. TRIAL DESIGN

8.1 Study Endpoints

Primary Endpoint

- Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle

Secondary Endpoints

- Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment.
- Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change in daily average use and percent change of overall analgesic use, prescription and over the counter, from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change and percent change in BBSS score incorporating the two physician-reported scores by study visit and treatment cycle.
- Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle.
- Change from baseline in pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle.
- Change from baseline in daily average dysmenorrhea and non-menstrual pelvic pain using an 11-point numerical rating scale (NRS) by study visit and treatment cycle.

[redacted]

8.2 Study Design

8.2.1 Overview of Study Design

This study is a phase 2, 3-arm-study with an 18 week active dosing period and an option for subjects to receive 2 additional 16-week cycles of active treatment at their randomized dose (6 mg or 12 mg/day). Placebo subjects who elect additional treatment will receive treatment at 12 mg/day. The treatment dose will remain double-blind. The study will be conducted in 3 stages. In the first stage, women will undergo a baseline assessment period with no treatment. This stage will last as long as it takes to record at least one full menstrual cycle (ovulation until ovulation).

Subjects will be provided with a daily diary with which to record patient reported scores for the three elements of endometriosis pain: dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS). [redacted]

For stage 2, following the baseline assessment period, at Visit 3, 60 subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of dosing should commence as soon as possible after ovulation following the end of the previous menstrual event.

Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within 21 days or less). Subjects may elect to receive up to 2 additional cycles of treatment at their randomized dose (6 mg or 12 mg/day), placebo-treated subjects will receive treatment at 12 mg/day. In stage 3 all subjects will receive active treatment but the treatment dose will remain double-blind. For subjects who do not choose additional treatment cycles, this will be their final follow-up visit. During the follow-up period subjects will continue to record study information in the daily diary.

For stage 3, subjects who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled at 21 ± 2 days after start of bleeding in their first menses after Visit 12 (recovery menses). Subjects will receive 2 cycles of treatment separated by an off-drug interval (ODI), after which they will be followed until menses has returned. During the follow-up period

subjects will continue to record study information in the daily diary. The final follow-up visit will be scheduled after blood flow has stopped.

Subjects who complete at least 28 days after Visit 3 and wish to discontinue treatment due to lack of efficacy will be eligible to start active treatment (stage 3). Subjects who discontinue the study prior to this date will not be eligible for additional treatment.

8.2.2 Study Drug Accountability

The designee assigned by the Principal Investigator at each site will maintain accurate records of receipt of all study drugs, including dates of receipt. Reasons for deviation from the expected dispensing regimen must also be recorded. A Drug Dispensing Form will be provided for this purpose. To satisfy regulatory requirements regarding drug accountability and destruction, the Principal Investigator at each site will return all used, unused, or empty and partially used study medication with dispensing records to the Sponsor for final accountability and disposal, after accountability has been verified by the study monitor.

8.2.3 Randomization and Blinding

All subjects will receive no treatment from Visit 1 until Visit 3. At Visit 3, subjects will be randomized to treatment in Arms 1, 2, or 3. Subjects will be treated with one capsule daily of 6 mg or 12 mg of Proellex, or placebo, which will be administered for 18 weeks. Subjects who elect to receive additional treatment cycles will be treated at their previously randomized dose level. Subjects randomized to placebo treatment will receive treatment at 12 mg/day. In stage 3 all subjects will receive active treatment but the treatment dose will remain double-blind. Each treatment cycle will be separated by an ODI. Blinded treatments kits will be randomized and distributed by the packaging company.

For the statistical analysis at Week 18, only statistical staff will be unblinded once the acute portion of the study database is locked. All

clinical operations staff and staff at investigative sites will remain blinded until completion of the study.

8.2.4 Study Medication

All study drugs will be supplied by Repros Therapeutics Inc. Test drug, Proellex, will be [redacted] and will be packaged by a clinical supplies contract vendor designated by Repros Therapeutics Inc. The placebo [redacted] and will be packaged by the same clinical supplies contract vendor. Active and matching placebo capsules will be bottled in identical packaging. Each bottle will have a label containing bottle number, number of capsules, expiration date, a statement "Caution: New Drug – Limited by Federal Law (US) to Investigational use" and instructions to take 1 capsule daily in the morning before breakfast. Subjects will take one capsule with approximately 8 ounces of water and study medication should be taken roughly at the same time every day. Subjects will record study medication date and time on subject drug diary cards. [redacted]

Subjects will not be provided with analgesic medications by Repros Therapeutics Inc.

8.3 Selection and Withdrawal of Subjects

Subjects for the study will be selected during screening based on the inclusion and exclusion criteria and clinical assessments listed below. Subjects will be discontinued from the study prematurely if:

- Unacceptable adverse events occur considered by the investigator to be associated with use of the study drug
- The subject requests to be withdrawn from the study
- Any of the following occur:
  - ALT or AST >8xULN
  - ALT or AST >5xULN for more than 2 weeks
  - ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
  - ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)
- A need arises for concomitant medication prohibited by the protocol
- The Principal Investigator decides that it is in the subject's best interest
- The subject is noncompliant with the protocol

- Any subject who develops an endometrial thickness ≥ 18 mm or experiences suspicious or unusually heavy bleeding for 7 days or more will be discontinued from the study and undergo endometrial biopsy. Women with such findings will not be eligible for extension of treatment. Appropriate follow up treatment will be provided as deemed necessary by the investigator.
- The decision to withdraw from the study because of an adverse event, including pain from endometriosis or from another condition, is decided by the subject and the investigator or her personal physician. The event, and any treatment should be recorded in the study records.

8.3.1 Inclusion Criteria

Subjects must meet the following criteria:

- Healthy adult females between 18 and 47 years of age (inclusive) prescribed prescription analgesics (see section 12.1) for endometriosis pain and with a BBSS score ≥7 at screening (assessed over the previous 28 days, [redacted]
- Endometriosis diagnosis must have been surgically confirmed within 7 years. A laparoscopic diagnosis is acceptable.
- Subjects must have a history of at least 3 regular menstrual cycles in which symptoms of endometriosis occurred immediately prior to screening
- Normal or abnormal but non-clinically significant transvaginal ultrasound
- History of menstrual events occurring in regular cycles
- Agreement not to attempt to become pregnant during the trial
- Agreement to limit alcohol consumption to no more than 2 drinks per week and to avoid alcohol consumption within 48 hours before each visit
- Ability to complete a daily subject diary and study procedures in compliance with the protocol
- Women of child-bearing potential must be willing to use double-barrier contraception during the study and for 30 days after discontinuation of study medication. Acceptable double-barrier methods are: male condom with spermicide; male condom with diaphragm; diaphragm containing spermicide plus additional intra-vaginal spermicide

- Has a negative pregnancy test at the Screening and Baseline visits, and subsequent study visits
- A Body Mass Index (BMI) between 18 and 39 inclusive
- Is available for all treatment and follow-up visits

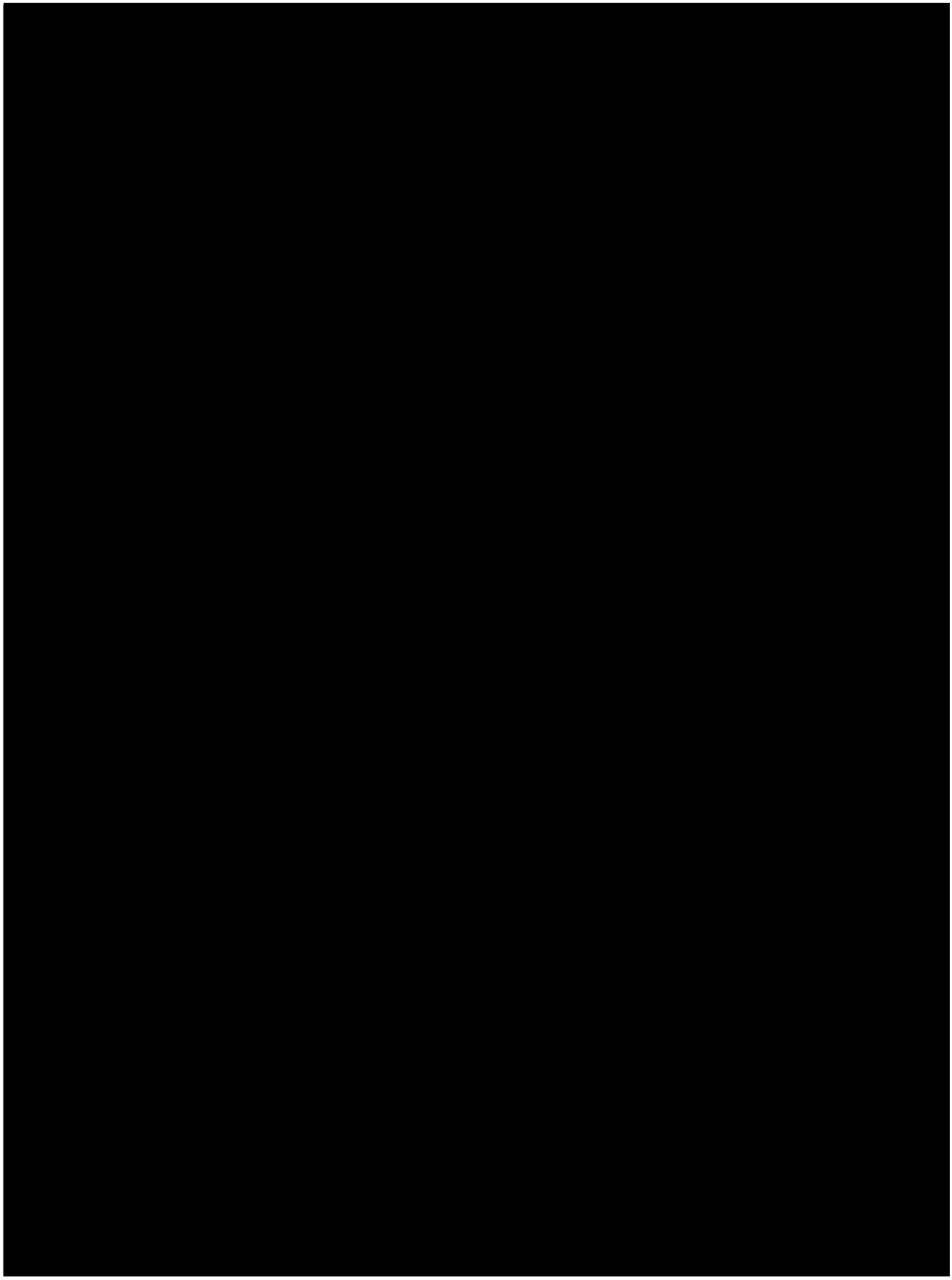
8.3.2 Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from the study:

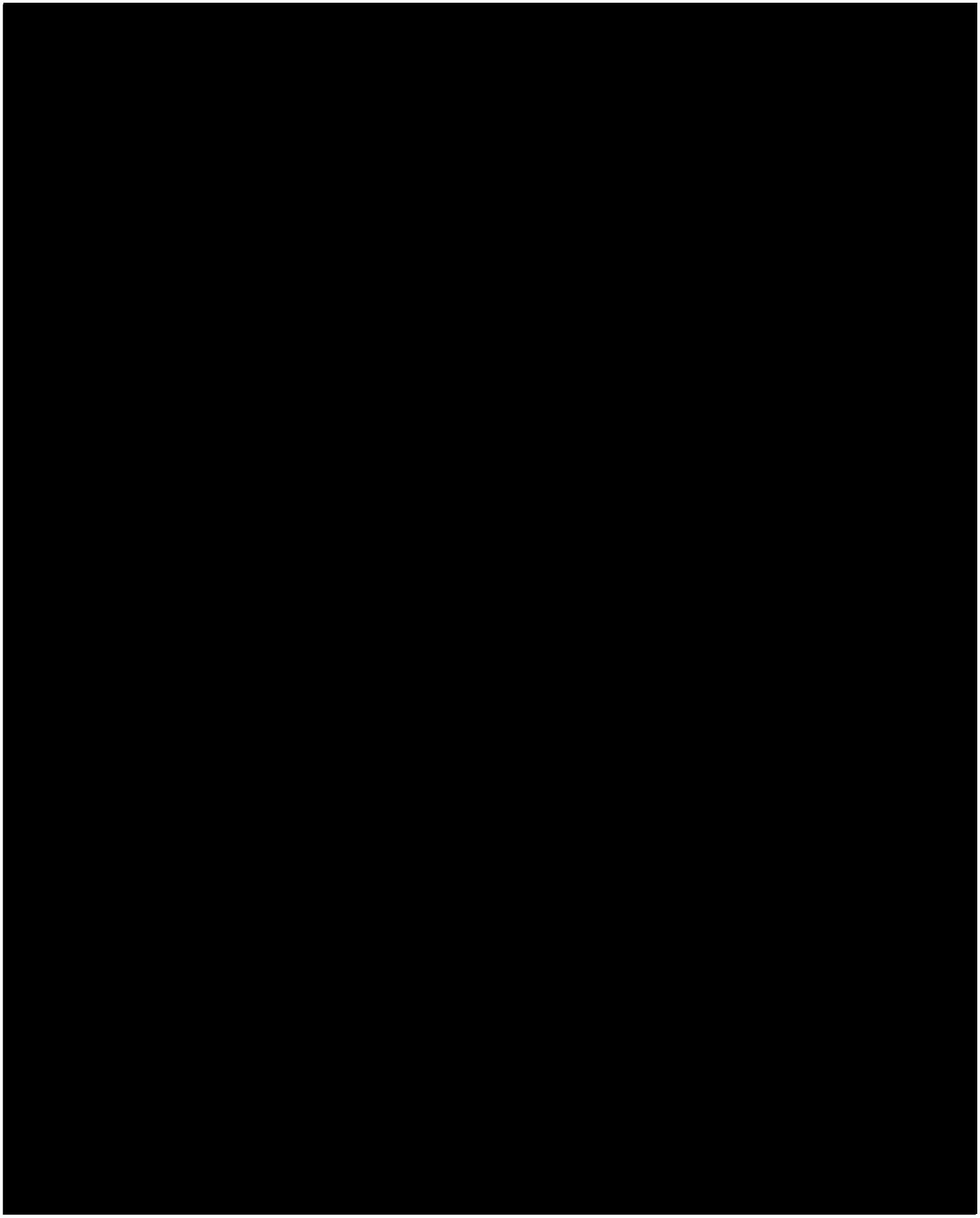
- Subject is a post-menopausal woman, defined as either; six (6) months or more (immediately prior to screening visit) without a menstrual period, or prior hysterectomy and/or oophorectomy.
- Subject is pregnant or lactating or is attempting or expecting to become pregnant during participation in the study
- Subjects with abnormally high liver enzymes or liver disease. (ALT or AST exceeding 2 x ULN AND total bilirubin exceeding 1.5xULN at screening and confirmed on repeat).
- Received an investigational drug in the 30 days prior to the screening for this study
- Subject has a history of PCOS
- Concurrent use of any testosterone, progestin, androgen, estrogen, anabolic steroids, DHEA or hormonal products for at least 2 weeks prior to screening and during the study.
- Use of oral contraceptives in the preceding 30 days. Use of Depo-Provera® in the preceding 10 months.
- Use of GnRHas (e.g. Lupron Depot) within 3 months of the first dose of study drug (Lupron Depot must have a wash-out period of 3 months after the period of duration of the Lupron dose).
- Has an IUD in place.
- Presence of intramural fibroids that impact the endometrial stripe, submucosal fibroids (any size), or endometrial polyps. Subserosal and intramural fibroids with no impact on the endometrial stripe are acceptable.
- Presence of endometrioma(s)
- Present history or condition that causes non-endometriosis related dyspareunia (e.g. vulvar vestibulitis).
- Past or present history of thrombophlebitis or thromboembolic disorders.

- Known or suspected carcinoma of the breast or reproductive organs.
- Known history of abnormal ECG that, in the opinion of the investigator, is clinically significant and will prevent the subject from completing the study, including a QTc of greater than 450 ms.
- Cervical dysplasia classified as Atypical Squamous Cells of Undetermined Significance (ASCUS) associated with high-risk human papilloma virus (HPV) or Low/High Grade Squamous Intraepithelial Lesion (LGSIL or HGSIL).
- History of abnormal endometrial biopsy including the presence of EIN.
- Recent history (within past 6 months) of alcoholism or drug abuse.
- Known active infection with HIV, Hepatitis A, B or C.
- Previous history of auto-immune disease and/or positive antinuclear antigen (ANA).
- Endometrial stripe ≥18 mm in thickness at Visit 1.
- Subject is currently taking cimetidine or spironolactone.
- Previous use of telapristone acetate or participation in a Repros clinical study
- Clinically significant abnormal findings on screening examination and laboratory assessments or any condition which in the opinion of the investigator would interfere with the participant's ability to comply with the study instructions or endanger the participant if she took part in the study.

[redacted]



[redacted]



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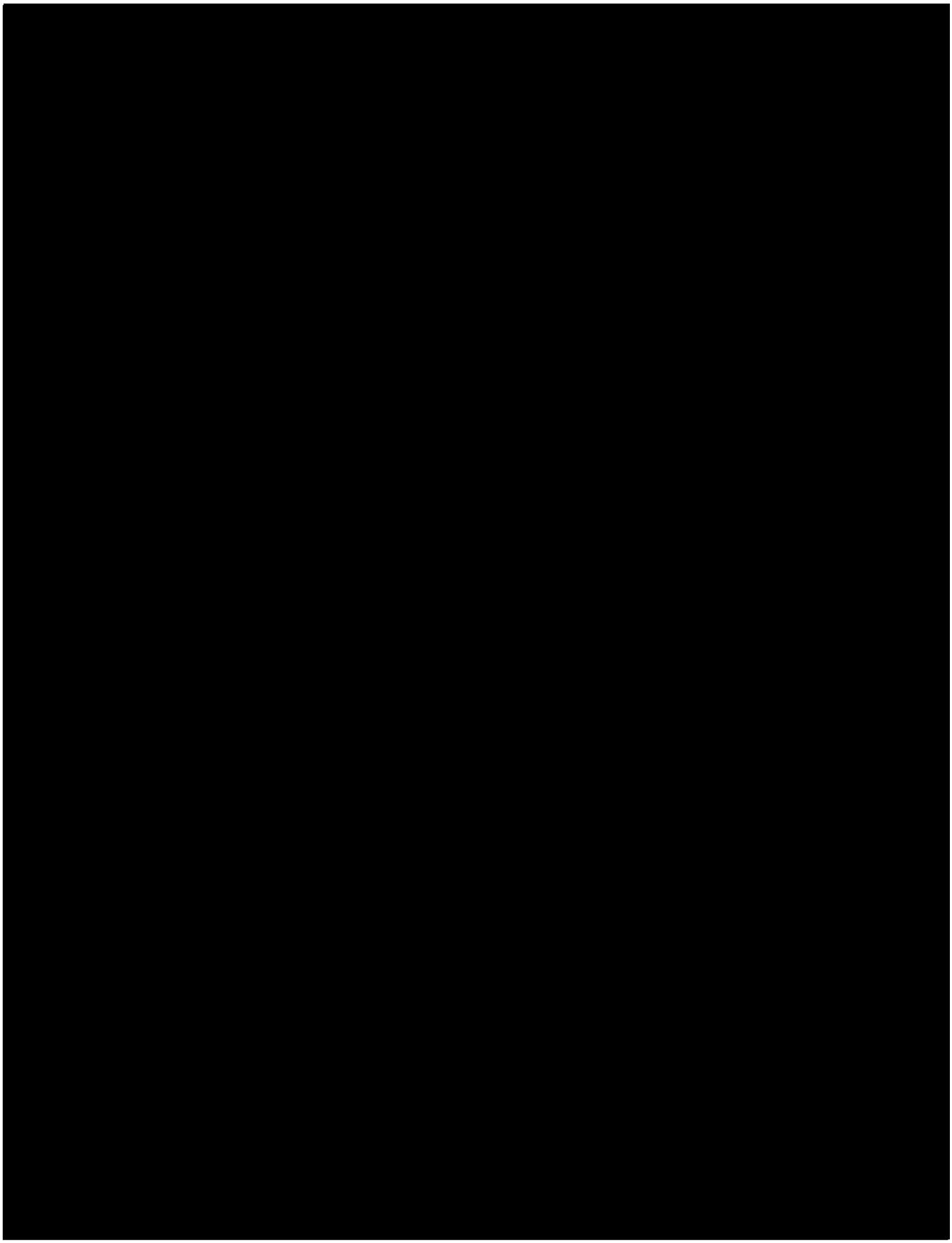
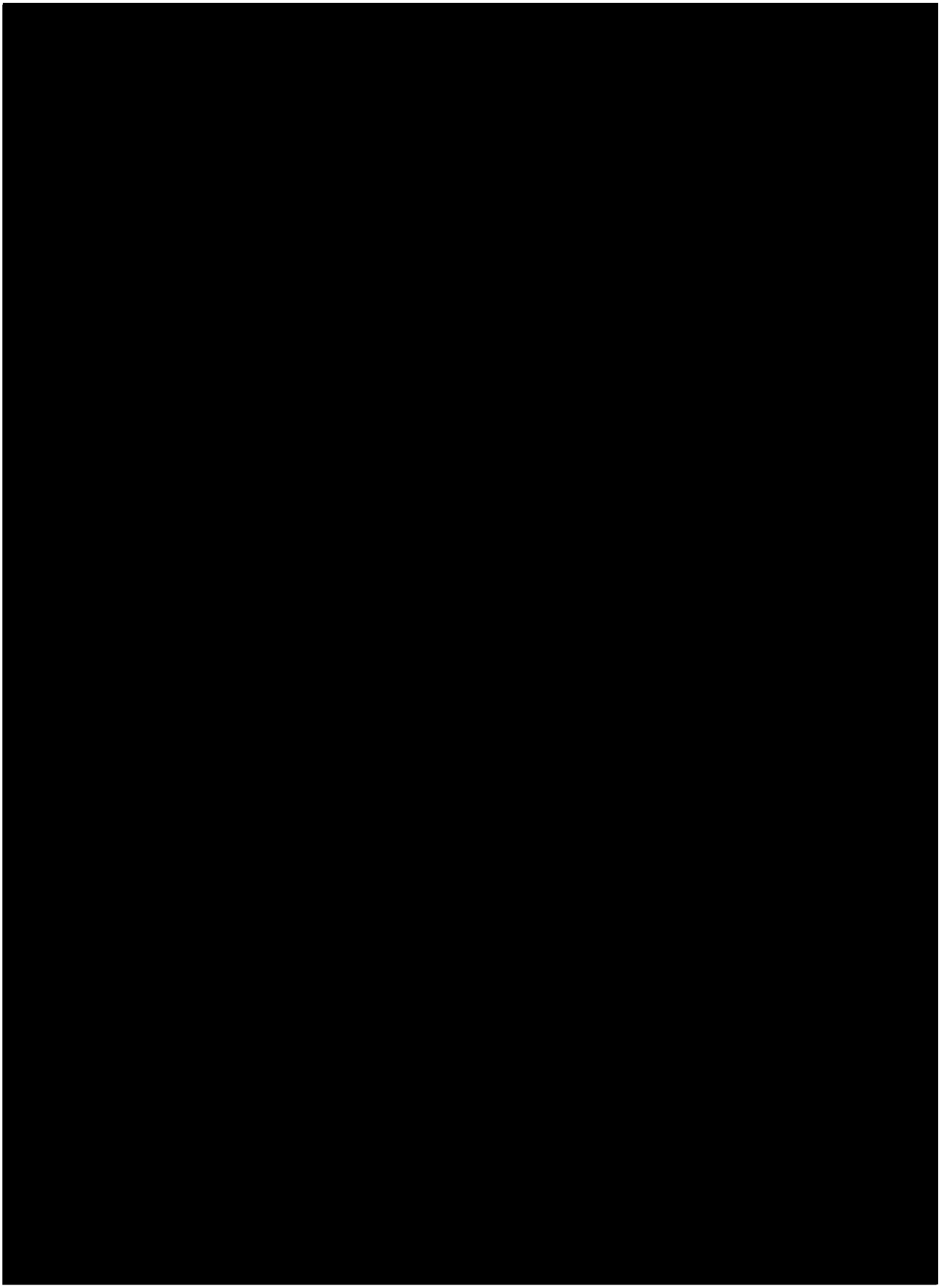
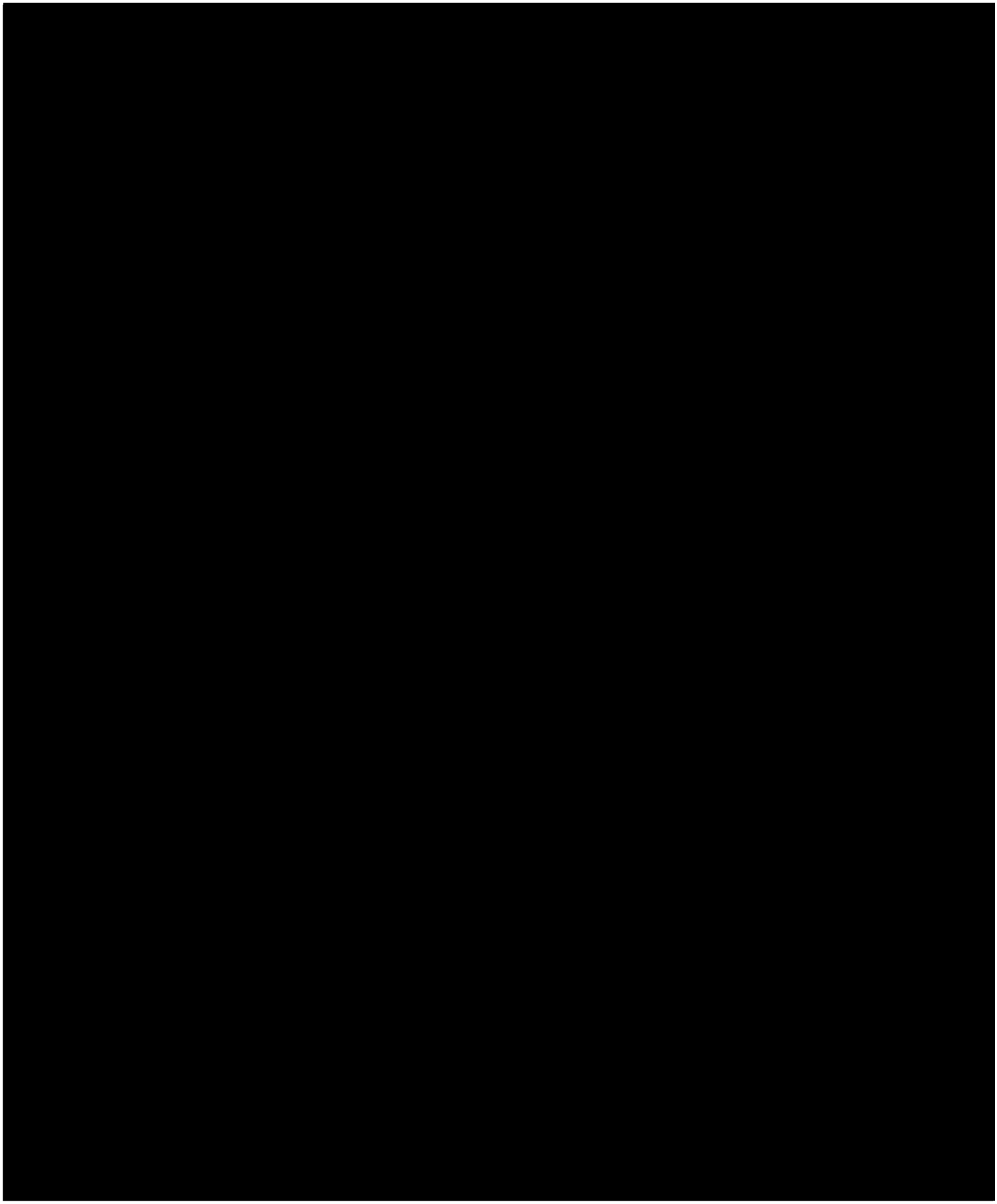






10. ASSESSMENT OF EFFICACY

10.1 Study Endpoints

Primary Endpoint

- Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle.

Secondary Endpoints

- Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment.
- Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change in daily average use and percent change of overall analgesic use, prescription and over the counter, from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change and percent change in BBSS score incorporating the two physician-reported scores by study visit and treatment cycle.
- Change from baseline in pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle.
- Change from baseline in daily average dysmenorrhea and non-menstrual pelvic pain using an 11-point numerical rating scale (NRS) by study visit and treatment cycle.

[redacted]

11.1 Adverse Events

11.1.1 Reporting Adverse Experiences

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this investigational drug, whether or not considered related to the investigational product, shall be documented on the CRF. All AEs reported by the subject or observed by the Principal Investigator will be individually listed. The signs and symptoms, time of onset (24-hour clock), duration, action taken and follow-up procedures will be reported.

11.1.2 Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) – An adverse drug experience that results in any of the following outcomes: death, a life-threatening experience, requires or prolongs subject hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

Cases of liver transaminases that increase above 3 times the upper limit of normal must be reported as SAEs regardless of whether the above defined SAE criteria are met.

Unexpected Adverse Event: Any adverse event that is not identified in nature, severity, or frequency in the current Investigator's Brochure.

Additionally, the Principal Investigator will evaluate all AEs as follows:

Action taken: whether or not the AE caused the subject/patient to discontinue the study medication.

Intensity, to be graded as:

DEGREE	DESCRIPTION
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent daily activity
Severe	Unable to carry out usual activity

Relationship to study medication, to be graded as:

DEGREE	DESCRIPTION
Definitely	There is evidence of exposure to the study drug, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the medication is reasonable; the AE is most likely to be explained by the treatment than by another cause; the AE shows a pattern consistent with previous knowledge of the treatment.
Probably	There is evidence of exposure to the study drug; the temporal sequence of the AE onset relative to medication administration is reasonable; the AE is more likely explained by the treatment than by another cause.
Possibly	There is evidence of exposure to the study drug; the temporal sequence of the AE relative to the medication administration is reasonable; the AE could have been due to another equally likely cause.
Probably not	There is evidence of exposure to the study drug; there is another more likely cause of the AE.
Definitely not	The subject/patient did not receive the study drug; or temporal sequence of the AE onset relative to administration of the study drug is not reasonable; or there is another obvious cause of the AE.

11.1.3 Serious Adverse Events (SAEs)

The Principal Investigator shall document all SAEs in a subject receiving study drug [redacted] and must be reported to the Repros Therapeutics Inc. Safety Monitor within 24 hours by Fax or telephone, even if the SAE does not appear to be drug-related. This report should include all available information at the time of notification. This notification should be followed with submitting a SAE Report Form provided by Repros Therapeutics Inc. All additional follow-up reports must be reported to the Repros Therapeutic Inc. monitor as soon as available.

Cases of liver transaminases that increase above 3 times the upper limit of normal must be reported as SAEs regardless of whether the above defined SAE criteria are met.

12. CONCOMITANT MEDICATIONS

12.1 Prescription Analgesics Permitted During the Study

12.1.1 Treatment of Endometriosis-Related Pain

Subjects should not take any analgesics during the study unless necessary for pain. In the event that a subject needs to use prescription analgesics for endometriosis-related pain, one of the following regimens should be prescribed:

- Hydrocodone/Acetominophen: 5-10 mg/325 -750 mg, 1-2 tabs every 4-6 hours prn
- Acetaminophen with Codeine: 1 tab 300/30 mg to 300/60 mg every 4 hours prn
- Oxycodone: 5-15 mg every 4-6 hours prn OR 10 mg (continuous release) every 12 hours prn
- Tramadol: 50-100 mg every 4-6 hours prn up to 400 mg/day
- Ponstel (mefenamic acid) (500 mg initial dose, then 250 mg every 6 hours)
- Hydrocodone/Ibuprofen: 7.5/200 mg, 1-2 tabs every 6-8 hrs prn

Any deviation from this list requires pre-approval by Repros. Note: Over-the-counter medications (e.g. ibuprofen, naproxen) do not qualify as prescription medications for entrance into the study, even if a prescription has been written for the specific medication.

12.1.2 Treatment of Non-Endometriosis–Related Pain

If the subject experiences pain (not related to endometriosis), she should be treated as medically appropriate. The choice of drug will depend on the medical condition. Dosage forms and route of administration should be as per product specifications.

All narcotic, non-narcotic and over–the-counter medication for endometriosis-related pain will be captured in the subjects' daily diary.

All narcotic, non-narcotic and over–the-counter medications for non-endometriosis-related pain will be recorded in the appropriate section of the CRF.

Analgesic medications will not be provided by Repros Therapeutics Inc.

12.2 Prohibited Medications

The following medications are prohibited during the study:

- Testosterone
- Progestin
- Androgen
- Estrogen
- Anabolic steroids
- DHEA
- Other hormonal products
- CYP3A4 inhibitors, e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin.
- St. John's Wort
- Spironolactone
- Cimetidine

12.3 Other Medications Taken During the Study

Any other prescription or over-the-counter medication taken during the study will be recorded in the appropriate section of the CRF. Subject must be on a stable dosage of approved concomitant medications at least 48 hours prior to drug administration.

13. STATISTICAL METHODS

13.1 Determination of Sample Size

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. [redacted] a sample of 18 subjects per group would provide 80% power to detect a statistically significant difference between the treatment groups.

13.2 Statistical and Analytical Plan

A statistical analysis will be conducted once all subjects have completed the placebo-controlled portion of the study, Stage 2. A Statistical Analysis Plan will be developed that outlines in detail all planned analyses. This document will be completed prior to unblinding study data for the placebo-controlled portion of the study.

A separate analysis and reporting will occur once all subjects have completed all study treatment. A separate Statistical Analysis Plan will describe these analyses. This summary will focus on the results noted in Stage 3 of the study.

13.2.1 Demographics and Subject Characteristics

For all subjects included in this study, subject accountability, baseline demographic and medical history data will be summarized for each treatment group. Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. No statistical testing will be performed to compare these factors between treatment groups.

13.2.2 Efficacy Analyses

An analysis will be conducted once Stage 2, the first cycle of treatment, has been completed. A later analysis will focus on the data collected from the active treatment stage of the study, Stage 3.

Efficacy analyses of the first cycle of treatment will be conducted in the Intent-to-Treat population, which will consist of all subjects who are randomized and who receive study drug. Subjects with missing post-baseline data will have a value of "no change" imputed for analysis.

13.2.2.1 Prescription Analgesic Usage

The change and percent change in daily average use of prescription analgesics comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing in Cycle 1 (Week 18) will be summarized for each treatment group. For each subject, the total number of pills or tablets of prescription analgesics during each 28 day menstrual cycle will be calculated, and the daily average use of prescription analgesics will be determined by dividing the total number of pills/tablets of prescription analgesics taken during the 28 day nominal period by 28. The percent change from baseline in the prescription analgesic usage will be determined by subtracting the baseline prescription analgesic usage from the prescription analgesic usage during the last nominal 28 day menstrual cycle, dividing by the baseline prescription analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline prescription analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

Changes in prescription analgesic use during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.2 Over the Counter Analgesic Usage

The change in daily average use of over the counter analgesics comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing in Cycle 1 (Week 18) will be summarized for each treatment group. For each subject, the total number of doses of over the counter analgesics during each menstrual cycle will be calculated, and the daily average use of over the counter analgesics will be determined by dividing the total number of doses of over the counter analgesics by the number of days in the menstrual cycle

(number of doses per day). The percent change from baseline in the over the counter analgesic usage will be determined by subtracting the baseline over the counter analgesic usage from the over the counter analgesic usage during each menstrual cycle, dividing by the baseline over the counter analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline over the counter analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

Changes in over the counter analgesic use during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.3 Overall Analgesic Use

The change and percent change in daily average use of all analgesics (prescription and over the counter) comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing in Cycle 1 (Week 18) will be summarized for each treatment group. For each subject, the total number of pills or tablets of analgesics taken during each 28 day menstrual cycle will be calculated, and the daily average use of prescription analgesics will be determined by dividing the total number of pills/tablets of analgesics taken during the 28 day nominal period by 28. The percent change from baseline in the analgesic usage will be determined by subtracting the baseline analgesic usage from the analgesic usage during the last nominal 28 day menstrual cycle, dividing by the baseline analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

Changes in analgesic use during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.4 BBSS Physician Reported Scores

The BBSS score incorporating the two physician-reported scores will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing in Cycle 1 (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including baseline BBSS score and treatment in the model. Pairwise comparisons of the treatment groups will be made using a t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. [redacted]

The BBSS patient and physician scores during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.5 BBSS Patient Reported Scores

The percent change from baseline in each of the daily average combined BBSS patient-reported scores (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing in Cycle 1 (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including baseline BBSS score and treatment in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. [redacted]

The BBSS patient scores during the active treatment stage of the study (stage 3) will also be summarized

13.2.2.6 Menstrual or Non-menstrual Vaginal Bleeding

The number of days and intensity of menstrual and non-menstrual vaginal bleeding will be summarized from the diary data. The total number of days and average intensity will be summarized from the days preceding each visit. An overall comparison among the 3 treatment groups will be performed on both the total number of days and average intensity using a one-way Analysis of Covariance, including the baseline score (number of days or average intensity) and treatment in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment

will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits and visit post-recovery menses. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

The number of days and intensity of menstrual and non-menstrual vaginal bleeding will also be summarized from active treatment (Stage 3) diary data collected.

13.2.2.7 VAS Assessment of Pain

The percentage change from baseline VAS pain score will be analyzed within treatment group and between treatment groups. An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. Pairwise comparisons of the treatment groups will be made using t-test or non-parametric test as appropriate. While the primary assessment will be based on scores at Visit 12 (after 18 weeks of treatment), summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

The VAS pain scores collected during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.8 Assessment of Pain Using the NRS

The average daily assessment will be calculated separately for dysmenorrhea and pelvic pain within each key 28-day baseline and treatment period. The percentage change from baseline NRS pain score will be analyzed within treatment group and between treatment groups. An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. Pairwise comparisons of the treatment groups will be made using t-test or non-parametric test as appropriate. While the primary assessment will be based on scores during the 28-day period prior to Visit 12 (after 18 weeks of treatment), summaries will also be prepared for each of the other visits.

The average daily assessment of dysmenorrhea and pelvic pain scores collected during the active treatment stage of the study (Stage 3) will also be summarized.

[redacted]

[redacted]

13.3 General Statistical Issues

A Statistical Analysis Plan (SAP) will be developed prior to the analyses of the first cycle of treatment. Two analyses will be conducted. The first analysis will occur when all subjects have completed the first cycle of treatment (Week 18) and the second with be conducted once all subjects have completed the active treatment stage of the study (Stage 3).

[redacted] Statistical significance will be declared if the two-sided p-value is ≤ 0.05. Since the study was not powered for efficacy assessments based on statistical hypotheses, the p-values reported at the conclusion of the study are being reported to quantify the difference in the treatment effect between treatment groups. [redacted]

14. ETHICS

14.1 Subject Information and Consent

A properly executed, written informed consent in compliance with Food and Drug Administration (FDA) regulations and Good Clinical Practice (GCP) guidelines will be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure that involve a risk to the subject. The Principal Investigator will submit a copy of the informed consent document to the Institutional Review Board for review and approval before research subjects are enrolled. The Principal Investigator will provide a copy of the signed informed consent to the subject and the original will be maintained in the subject's medical record.

14.2 Institutional Review Board

The Principal Investigator will provide the Institutional Review Board with all requisite material, including a copy of the informed consent. The study will not be initiated until the IRB provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Principal Investigator and copies received by the Sponsor. Appropriate reports on the progress of this study by the Principal Investigator will be made to the Institutional Review Board and the Sponsor in accordance with the applicable government regulations and in agreement with the policy established by the Sponsor.

14.3 Monitoring Case Report Forms

Repros Therapeutics Inc. or their designee will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable federal regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

14.4 Study Record Retention

In accordance with FDA regulations and GCP guidelines, all study-related documentation shall be retained by the Principal Investigator for a minimum of 2 years after FDA approval of telapristone acetate or clinical development has been terminated. At that time, the Principal Investigator will contact Repros Therapeutics Inc. regarding further disposition of the study records and comply with instructions.

14.5 Data Quality Assurance

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing. The Principal Investigator will be responsible for the following:

1. Monitoring study conduct to ensure that the rights of subjects are protected;
2. Monitoring study conduct to ensure trial compliance with GCP guidelines; and
3. Monitoring accuracy, completion and verification from source documents of study data.

14.6 Confidentiality

All information provided to the Principal Investigator by Repros Therapeutics Inc. or their designees including non-clinical data, protocols, CRFs and verbal and written information will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be released in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Repros Therapeutics Inc. or their designees or in confidence to the IRB, except if required by law.

14.7 Publications

Following completion of the study, the data from the entire study or from subsets of the study may be considered for reporting at a scientific meeting or for publication in a scientific journal, in which case Repros Therapeutics Inc. will be responsible for these activities and will work with the Principal Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues.

15. INVESTIGATOR'S STATEMENT

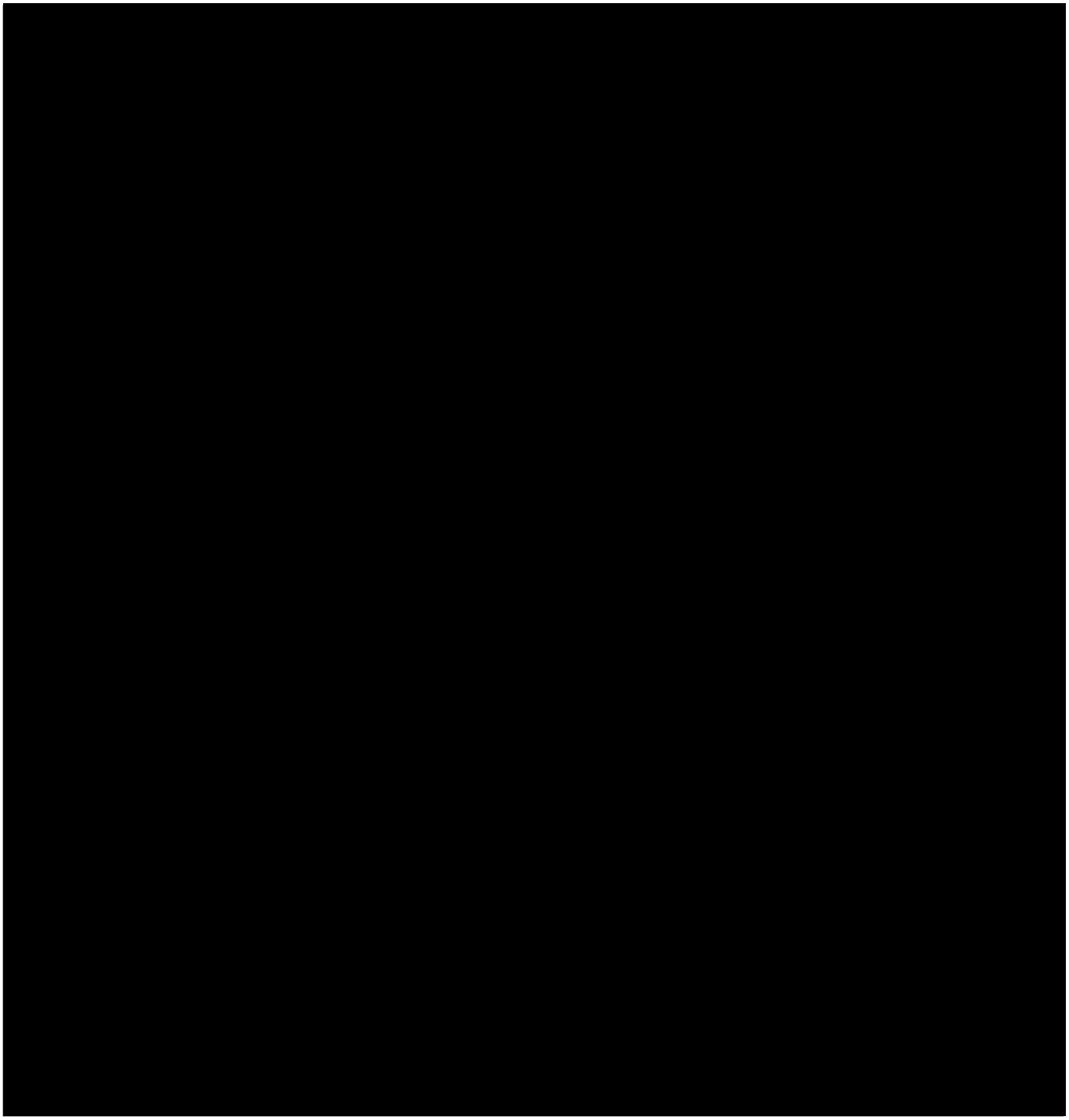
I have reviewed the ZPE-202 protocol and Investigator Brochure and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

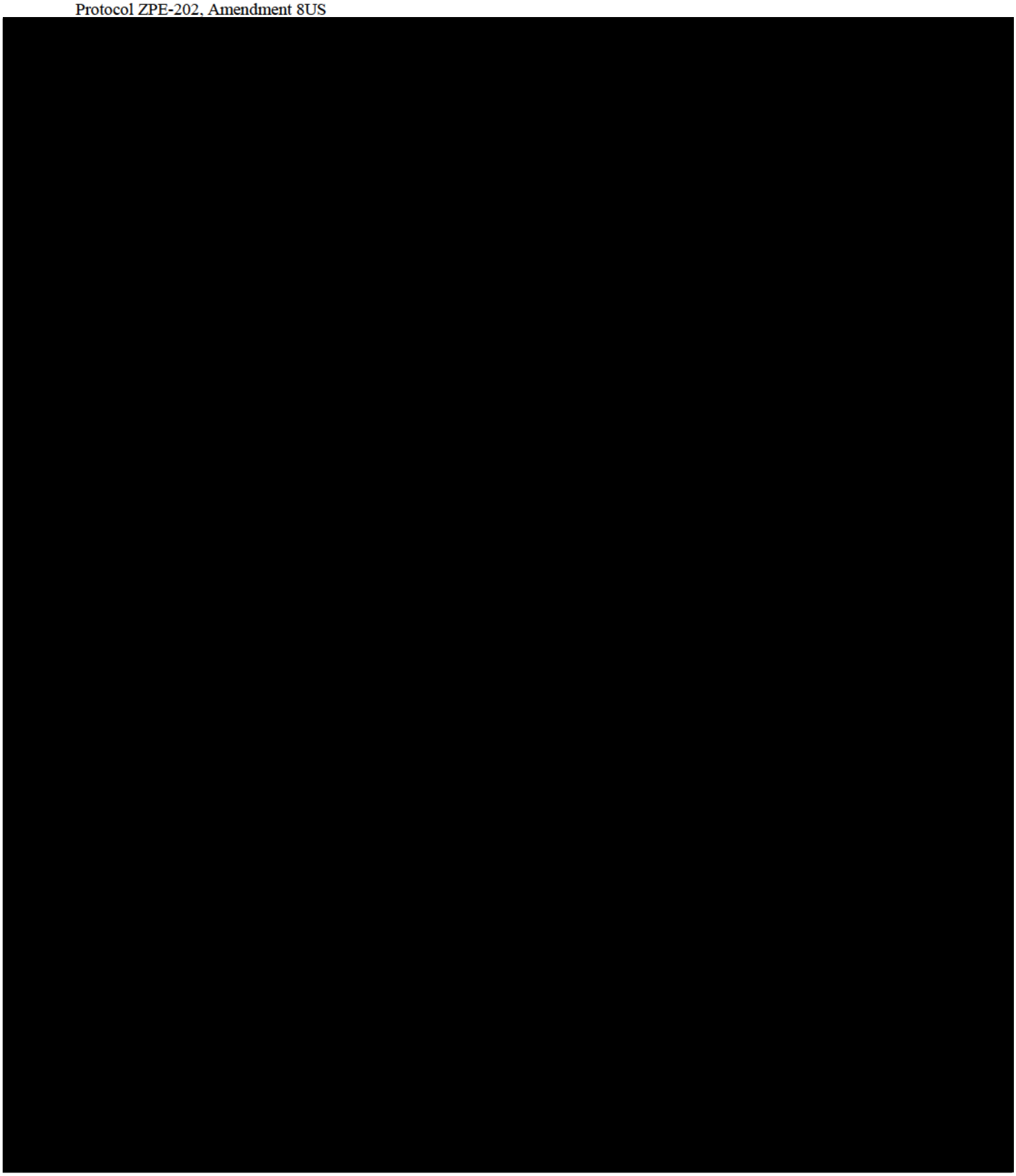
_____ _____

Investigator Date

_____

Printed name





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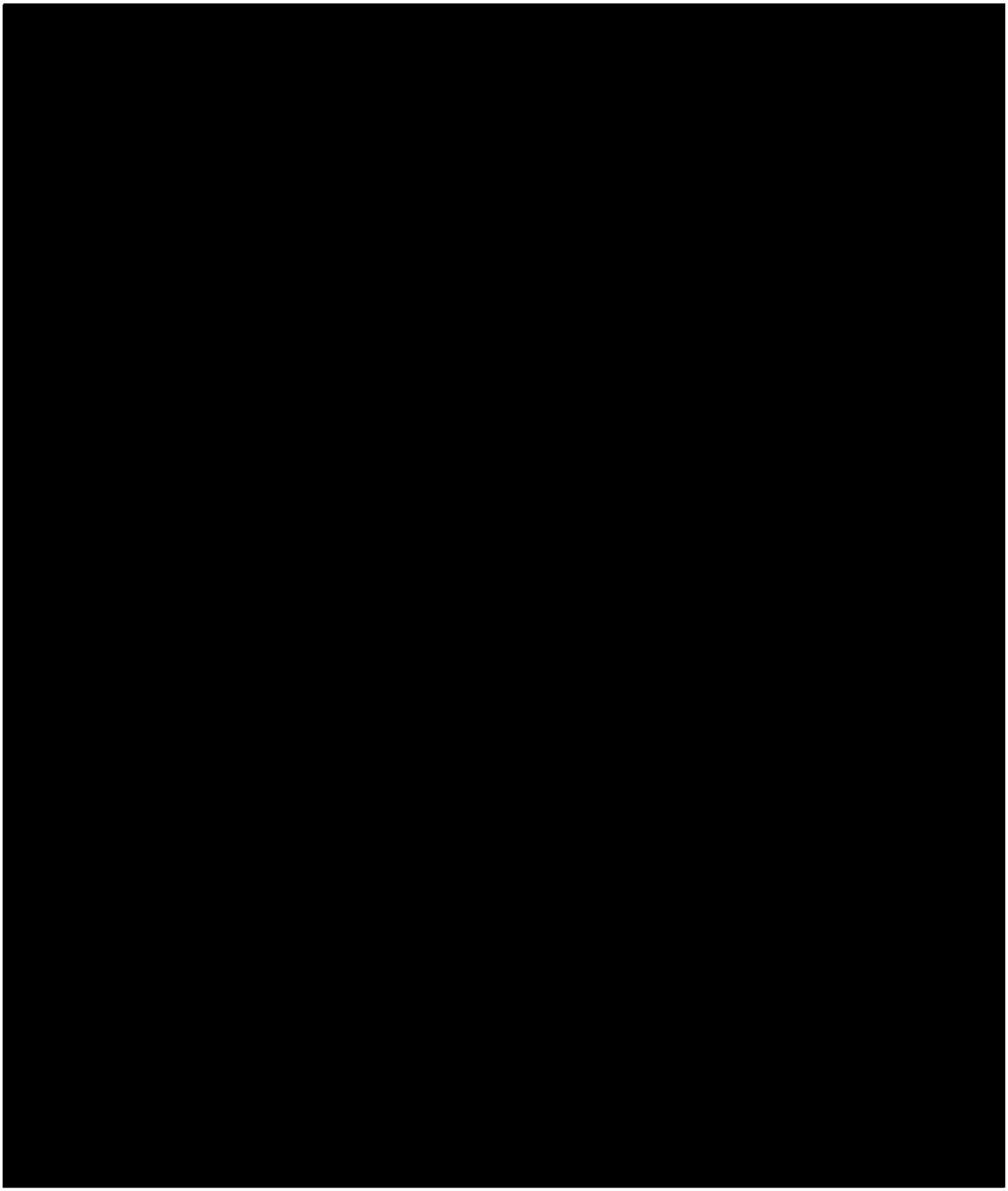

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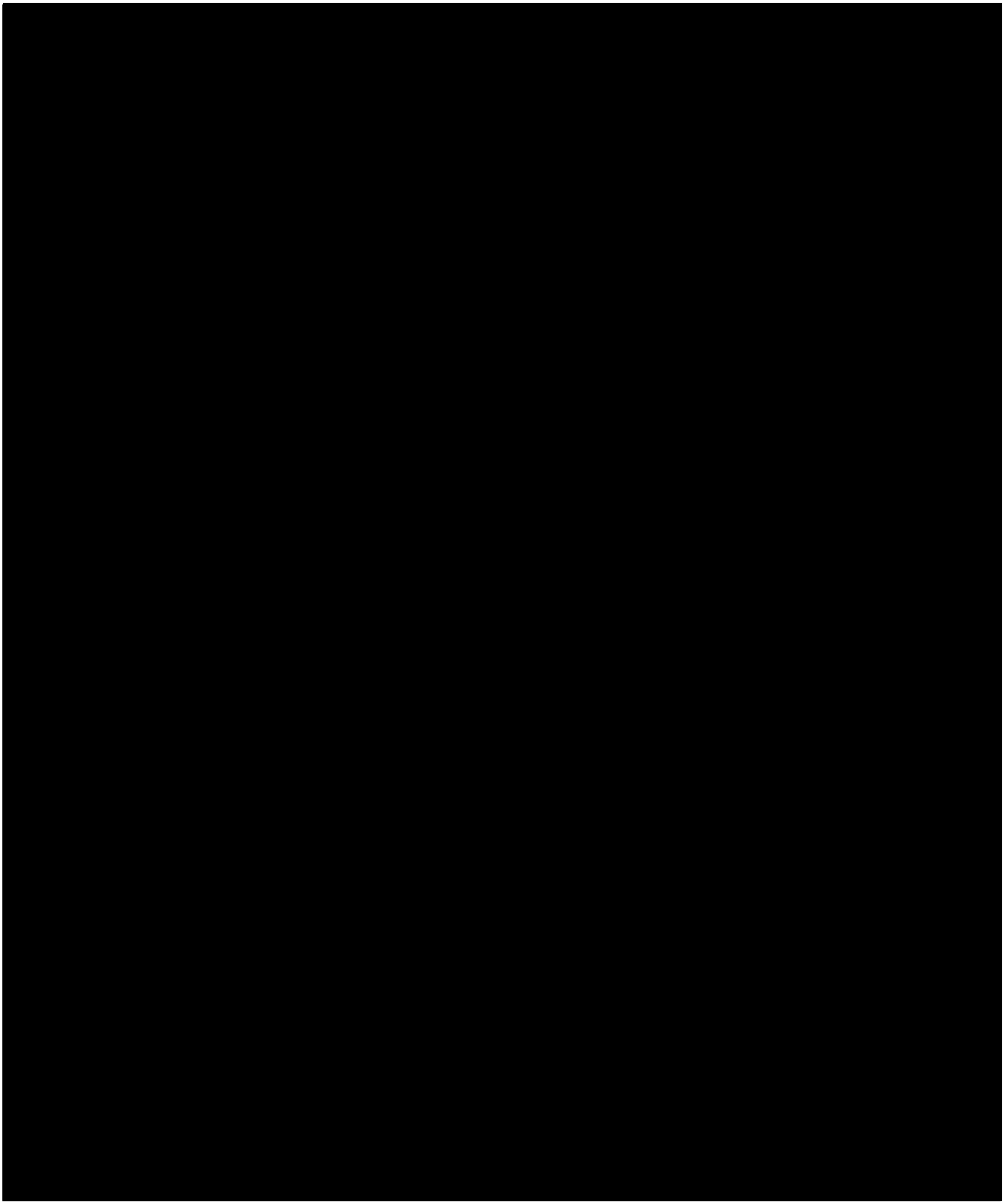

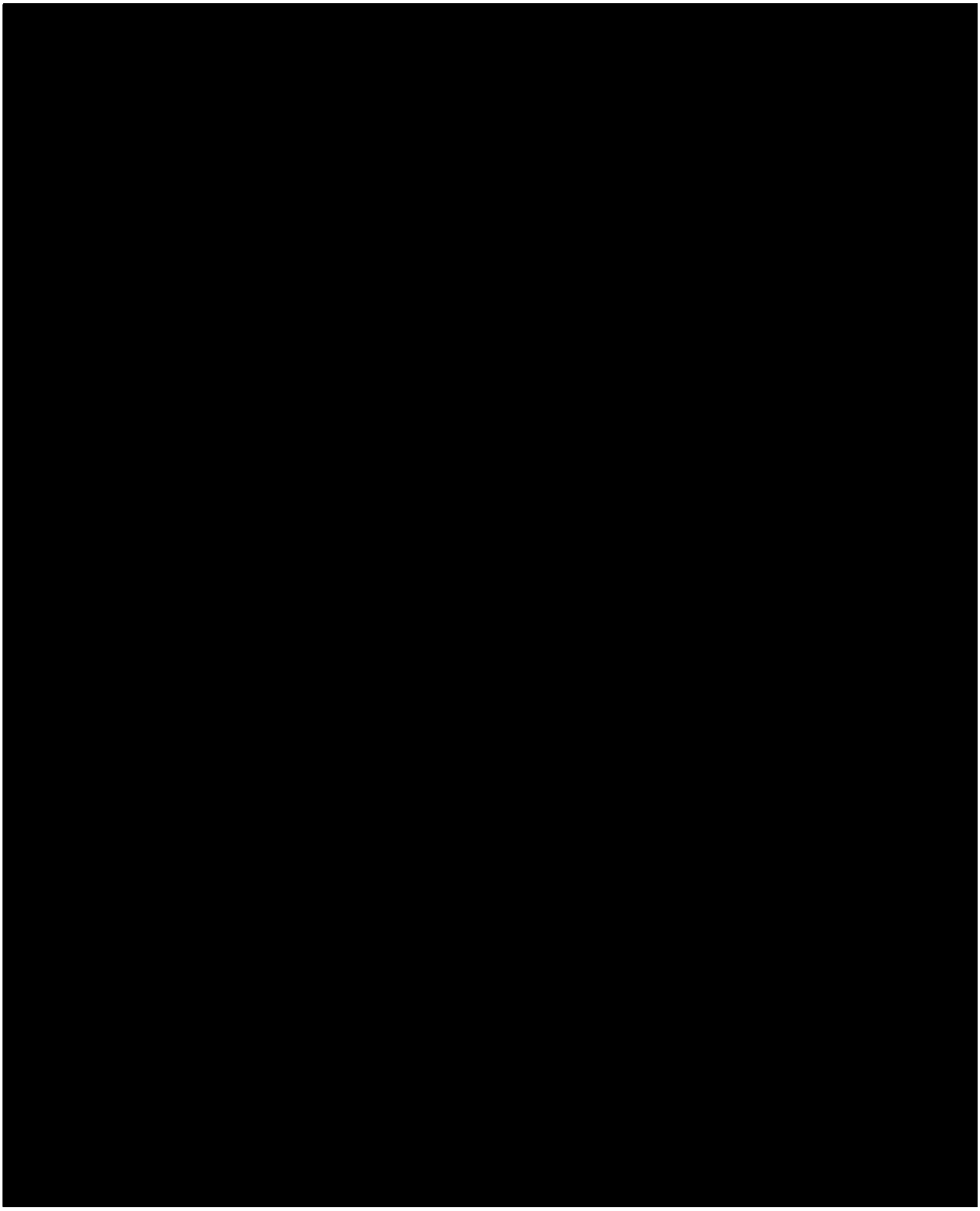

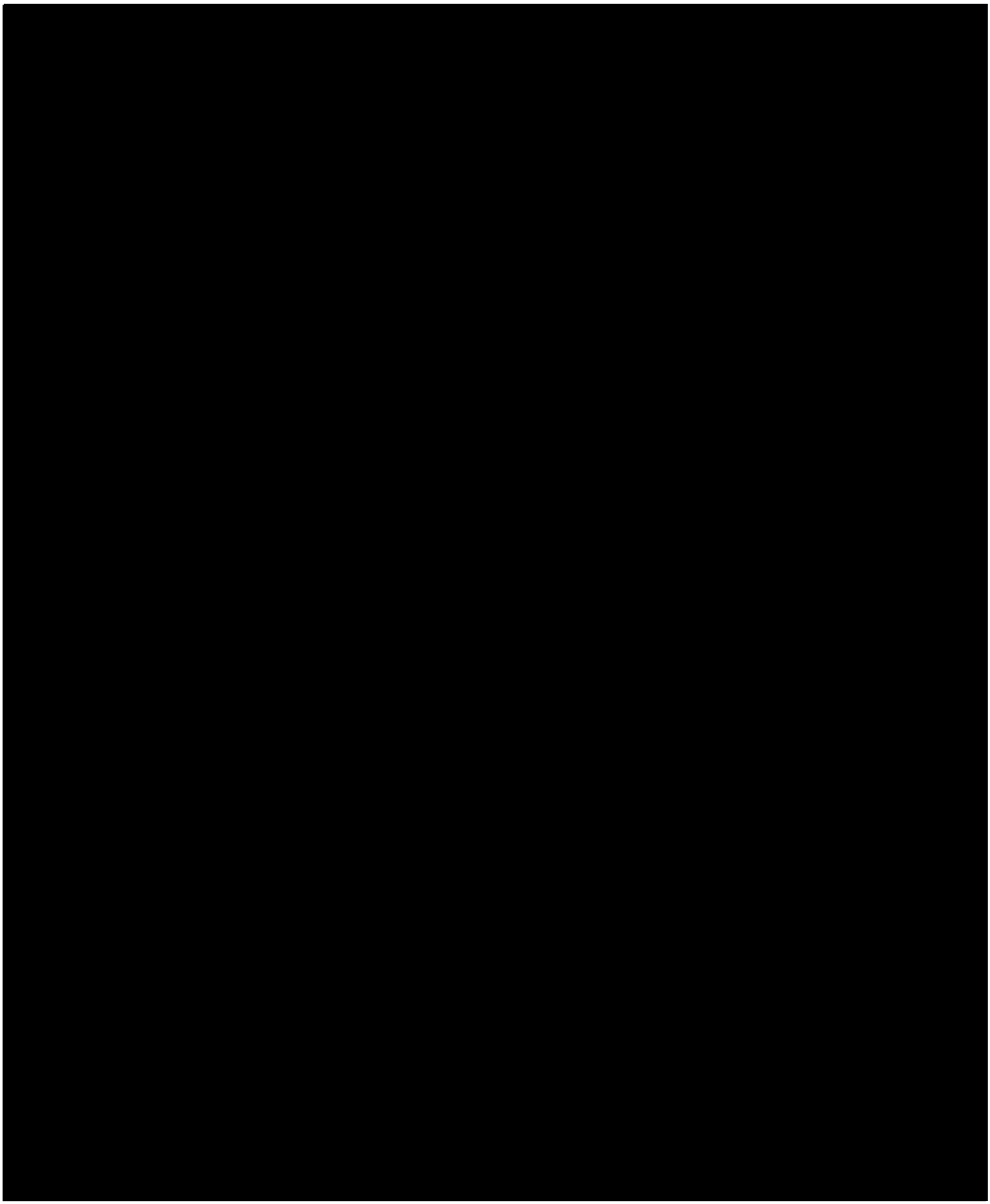

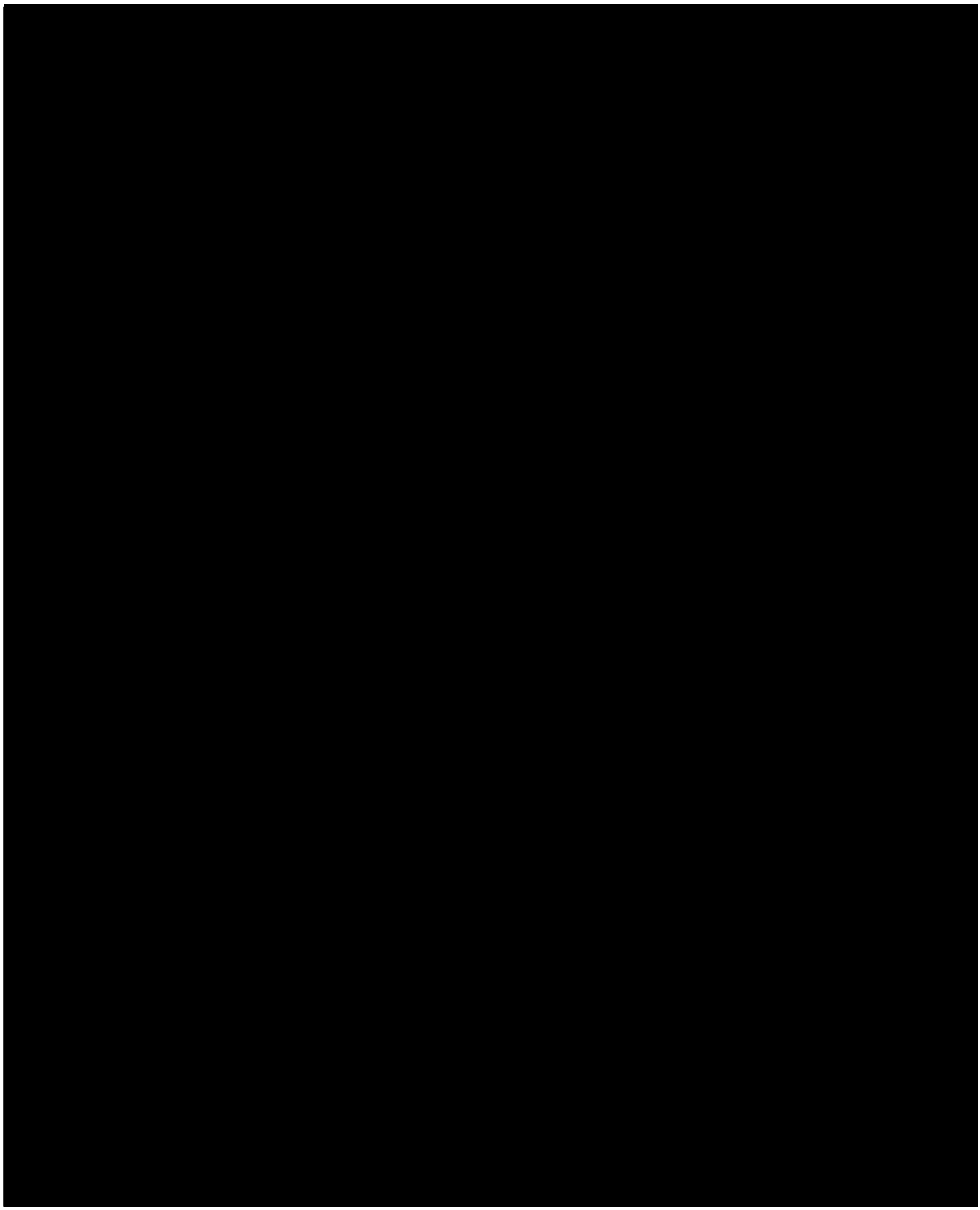

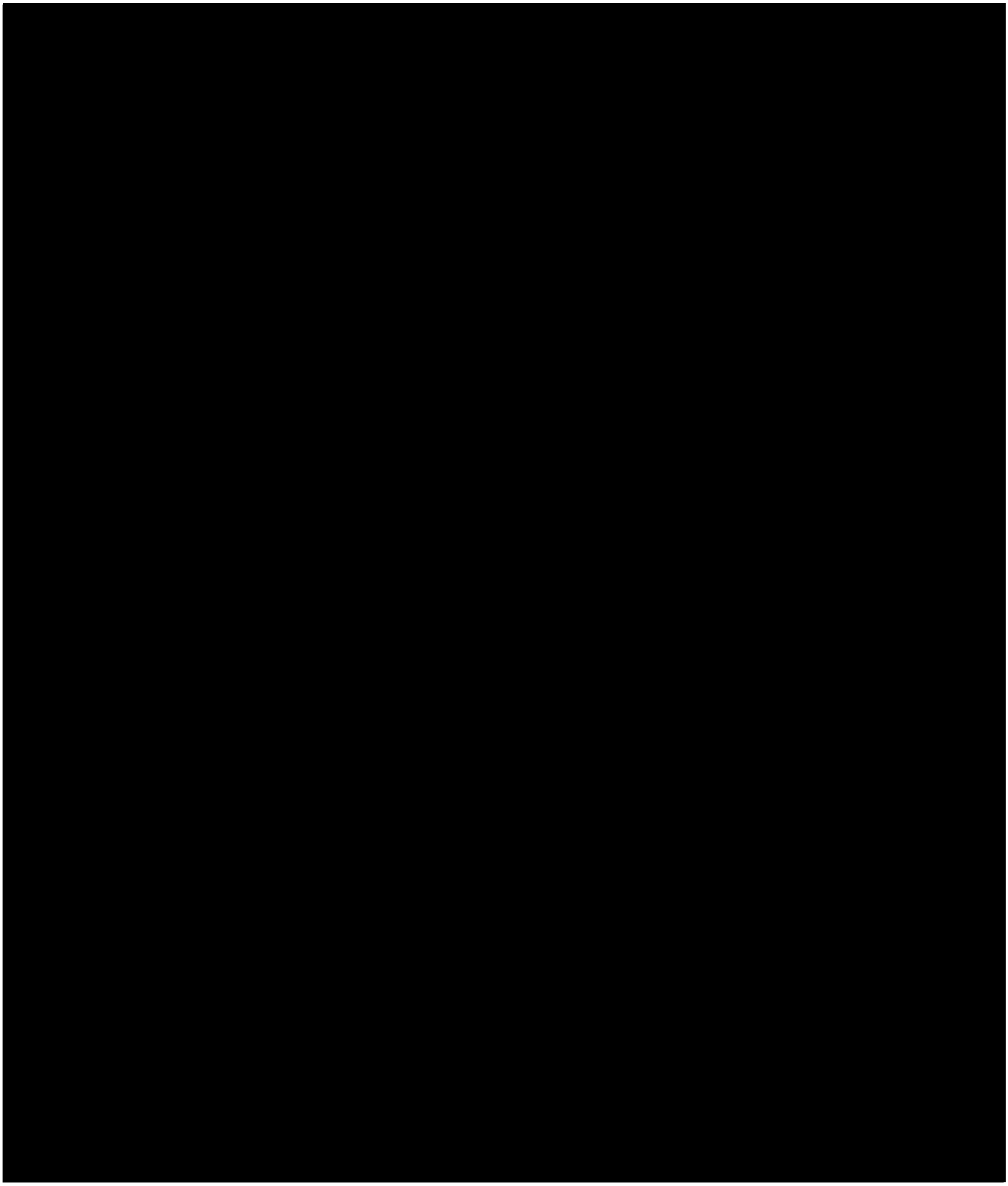

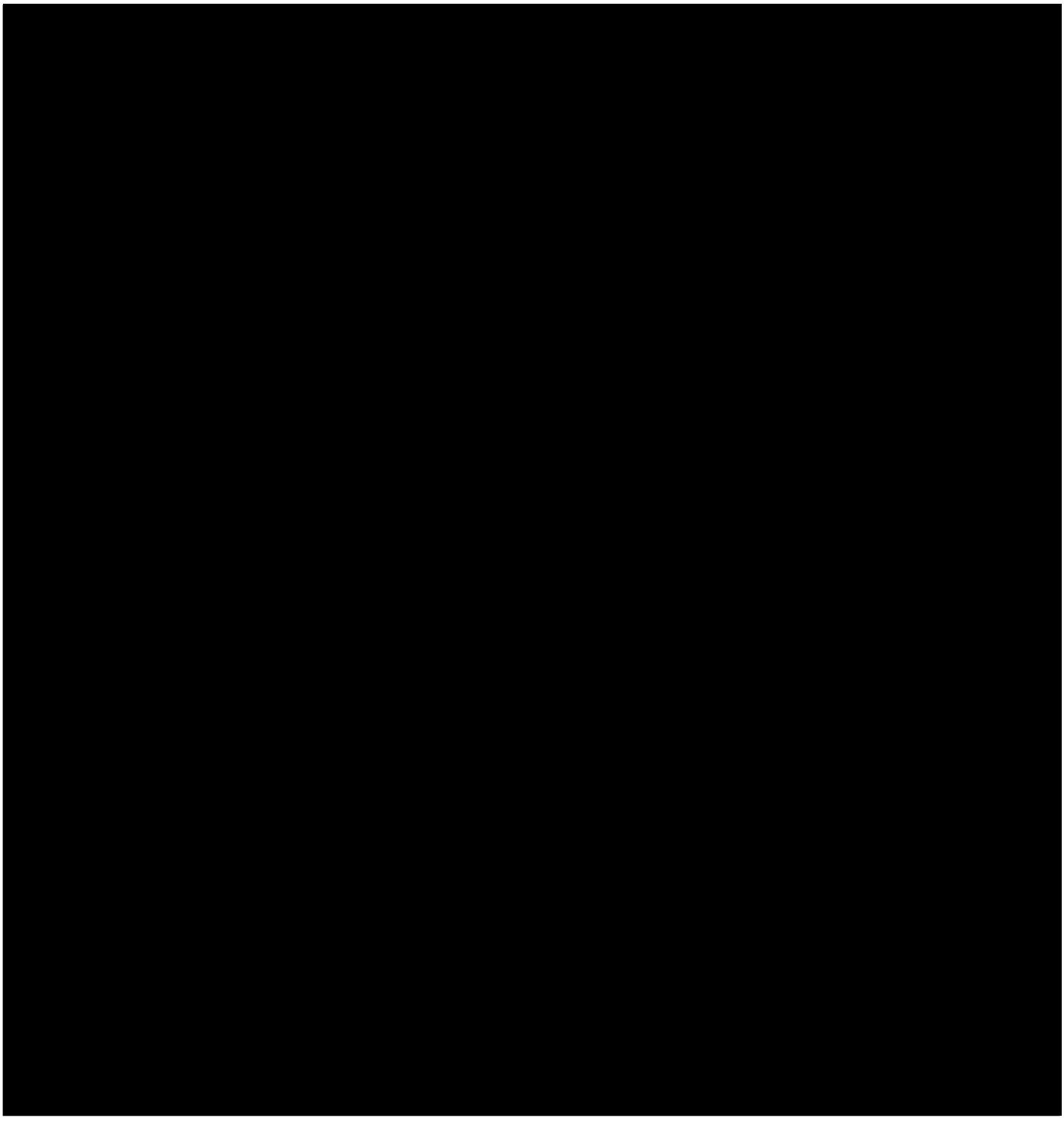

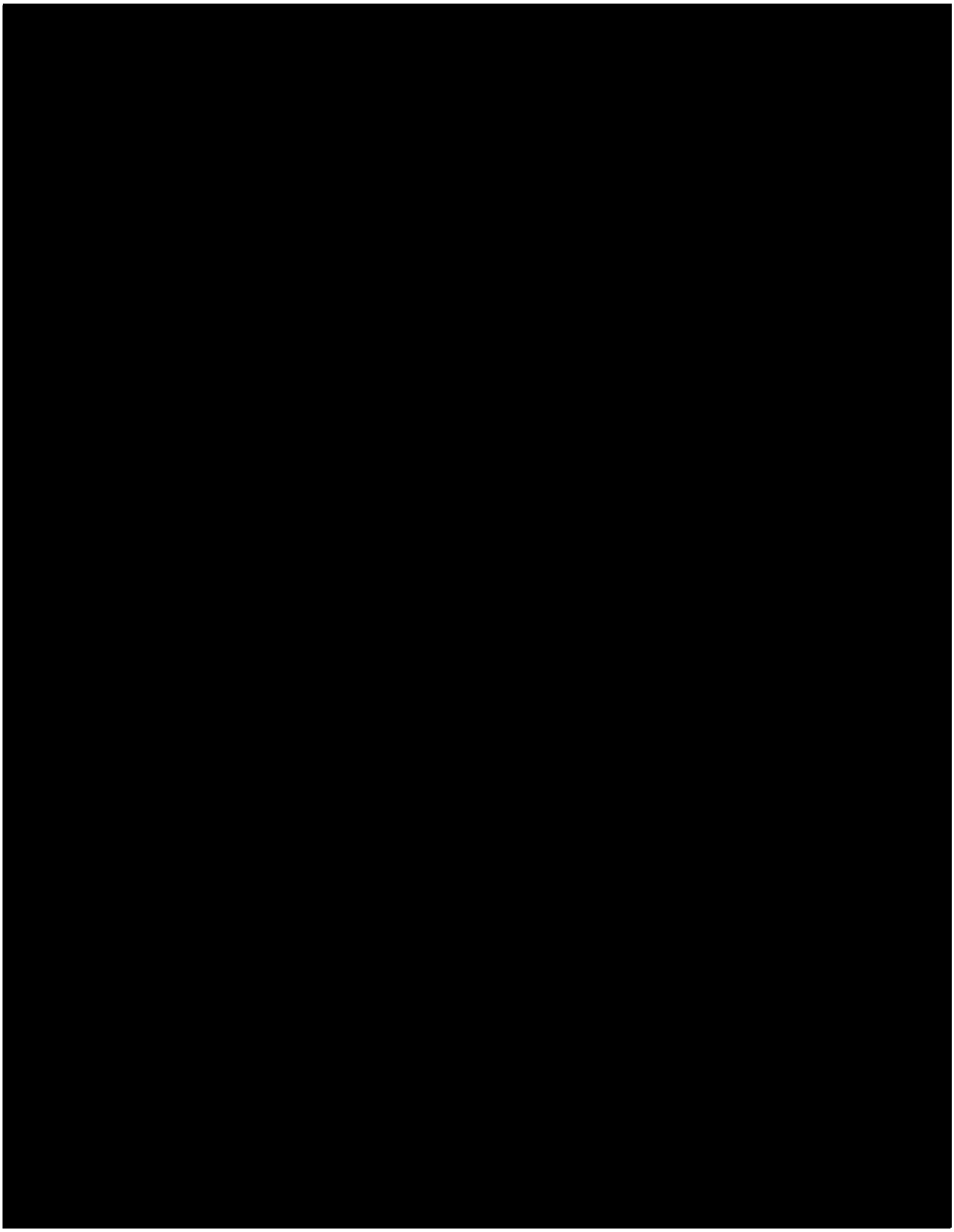

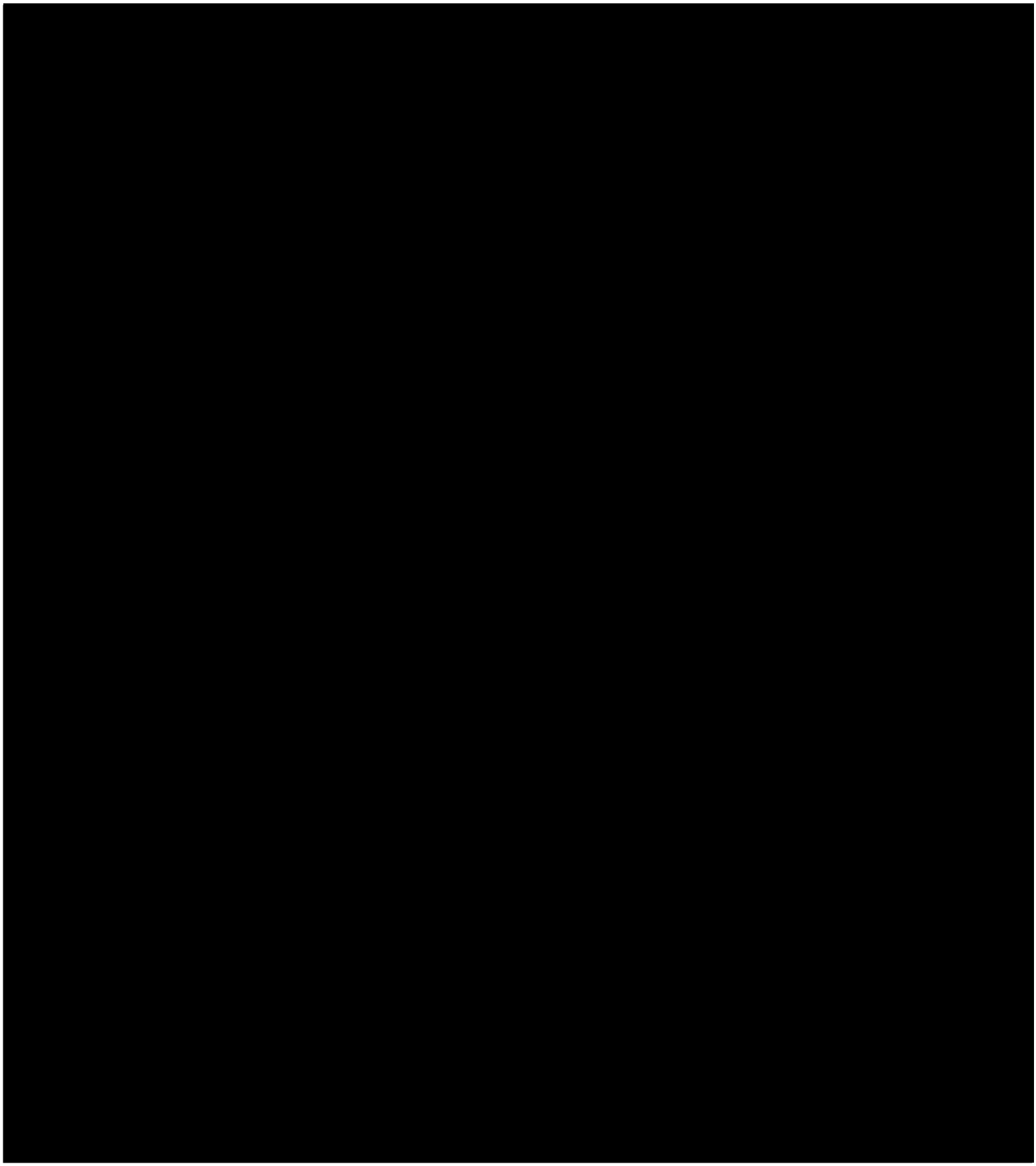

Repros
THERAPEUTICS INC

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

Original Protocol: July 18, 2012
Amendment 1: August 31, 2012
Amendment 2: October 24, 2012
Amendment 3: April 23, 2013
Amendment 4: June 12, 2013
Amendment 5: January 06, 2014
Amendment 6: January 7, 2014
Amendment 7: March 12, 2014
Amendment 8US: March 31, 2015
Amendment 9US: March 2, 2016

SPONSOR:

Repros Therapeutics Inc.®
2408 Timberloch Place, B-7
The Woodlands, TX 77380

IND 76,631

[redacted]

Confidentiality Statement
The confidential information in this document is provided to you as a Principal Investigator or consultant for review by you, your staff and the applicable Institutional Review Board / Independent Ethics Committee. Your acceptance of this document constitutes agreement that you will not disclose the information contained herein to others without written authorization from the Sponsor, Repros Therapeutics Inc.®

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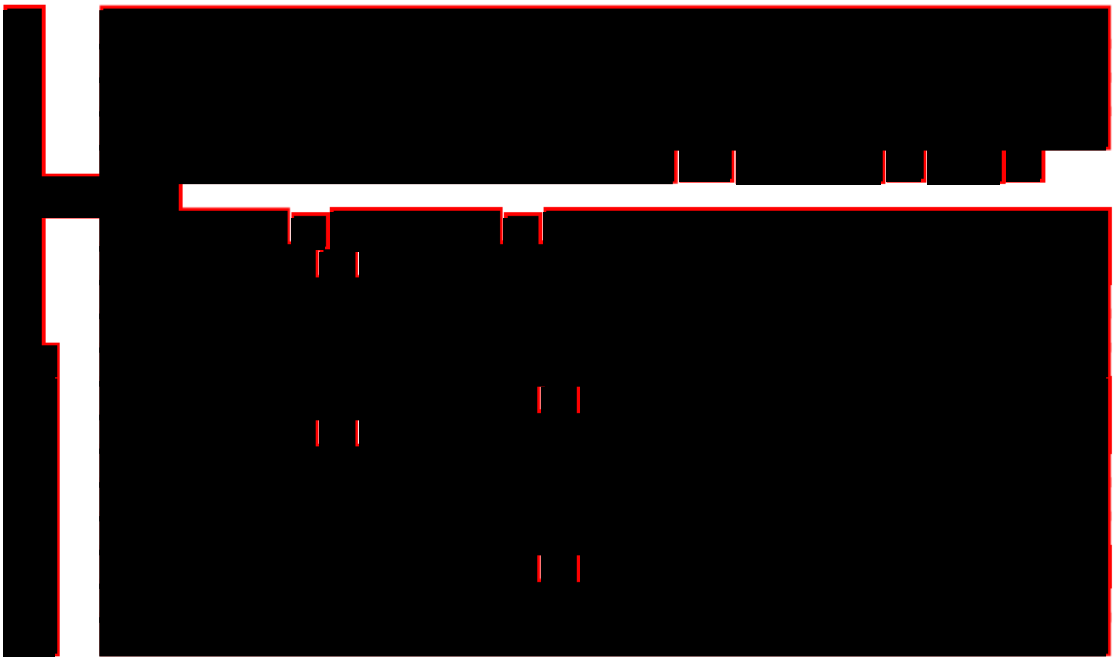
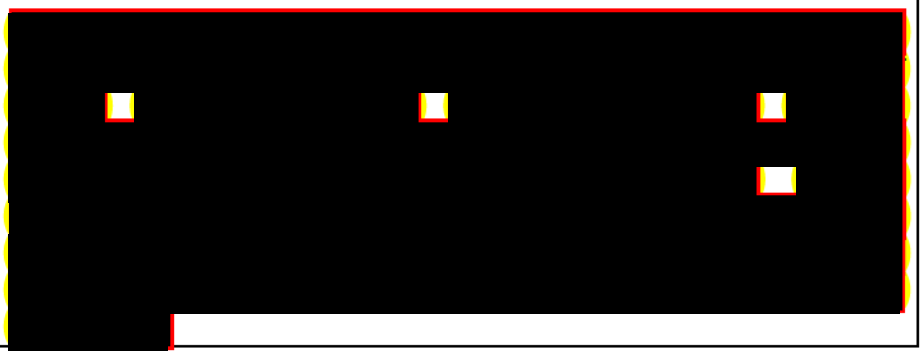


3. PROTOCOL SYNOPSIS

Test Drugs:	Proellex® (Telapristone Acetate): 6 and 12 mg gelatin capsules and matching placebo
Protocol Number:	ZPE-202
Study Purpose:	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 medications for symptomatic pain.
Study Design and Duration Of Treatment:	This study 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 no treatment until their second ovulation event. Endometriosis pain, dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS) as well as use of pain medications, vaginal bleeding intensity and alcohol use will be recorded using a daily diary. Daily subject ratings of dysmenorrhea and non-menstrual pelvic pain will be captured using an 11-point numerical rating scale (NRS) and Visual Analog Scale (VAS) pain assessment will be utilized. In the second stage, following the baseline assessment period, subjects will be randomized into one of 3 arms 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 this stage of the study, subjects may discontinue the study and still be eligible to qualify for up to 2 additional treatment cycles. In the third stage, 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 end of their first course of treatment (off-drug interval). Subjects will receive 2 courses of additional treatment separated by an off-drug interval (ODI), after which they will be followed until menses has returned. During the follow-up period subjects will continue to record study information in the daily diary. The final follow-up visit will be scheduled after blood flow has stopped. [redacted]

	[redacted]
Subject Population:	The study will enroll healthy adult, non-obese pre-menopausal women with surgically confirmed endometriosis prescribed and/or using prescription medication for their endometriosis pain.
Number of Subjects:	Up to 60 female subjects, 20 per dose arm (US and Argentina)
Number of Sites	Approximately 10-20 sites
Study Duration:	Total participation in the study is approximately 18 months.
[redacted]	[redacted]

Study Endpoints	The study endpoints will be: *Primary Endpoint* • Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle. *Secondary Endpoints* • Change in daily average use and percent change of prescription medications from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment. • Change in daily average use and percent change of over the counter medications from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values. • Change in daily average use and percent change of overall medication use, prescription and over the counter, from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values. • Change and percent change in BBSS score incorporating the two physician reported scores by study visit and treatment cycle. • Change from baseline in pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle. • Change from baseline in daily average dysmenorrhea and non-menstrual pelvic pain using an 11-point numerical rating scale (NRS) by study visit and treatment cycle. 
Statistical Methods:	A Statistical Analysis Plan (SAP) will be developed prior to unblinding of the data that will outline all planned analyses and

	analysis populations. The first efficacy analysis will be conducted when all subjects complete the first cycle of treatment. A second analysis will summarize the subject's additional treatment cycles which will be conducted after all subjects complete study treatment and follow-up. Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. All summaries will be prepared for each treatment group. Summaries will be prepared for each treatment group of subject accountability, baseline demographic, and medical history data. Continuous efficacy endpoints, such as the percentage change from baseline in the use of prescription medications, will assess treatment effect using an Analysis of Covariance, including the baseline prescription medication usage and treatment in the model. Pairwise comparisons between treatment groups will be made using a two-sample t-test. Other continuous efficacy variables will be treated similarly. 

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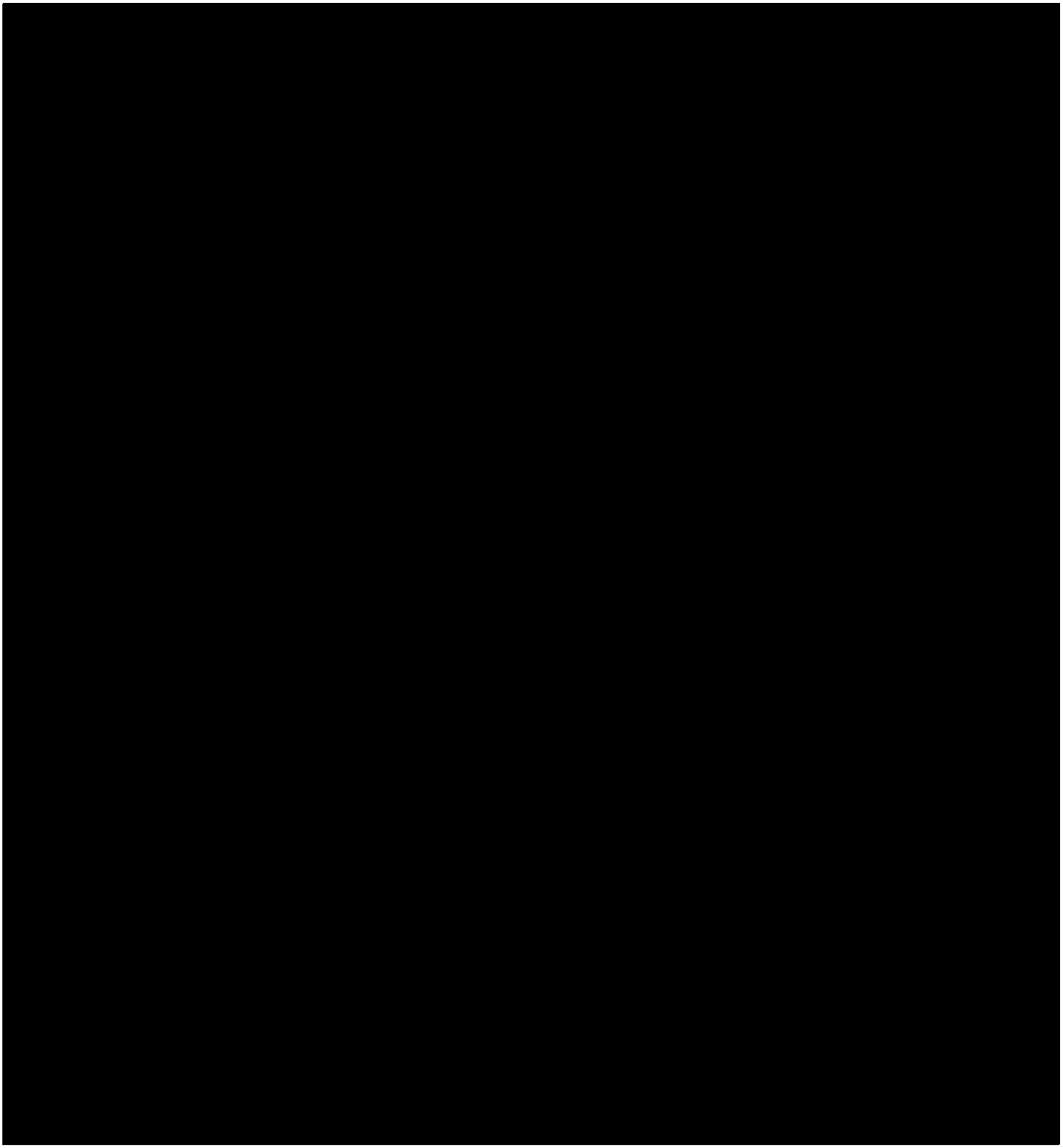
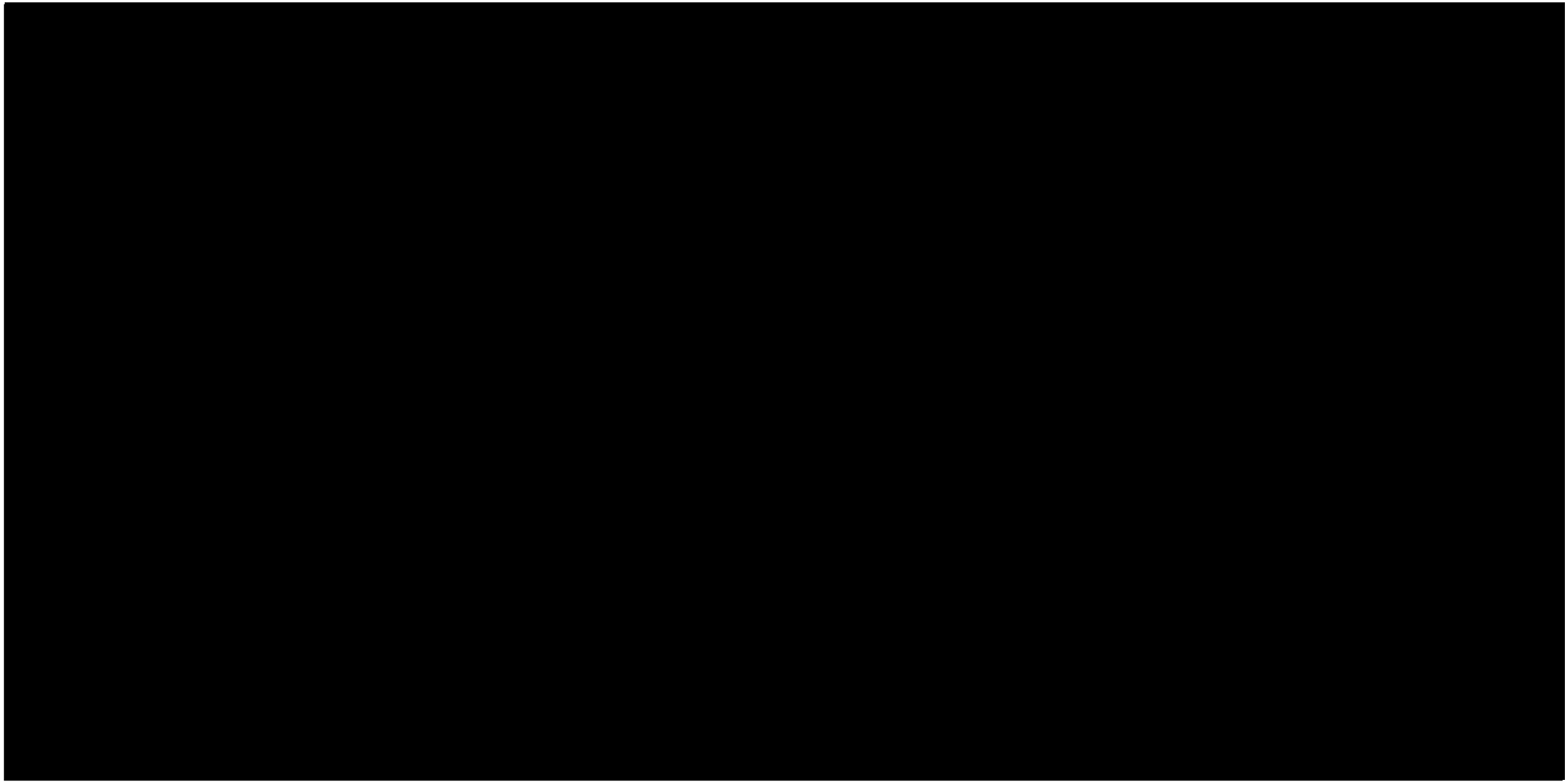




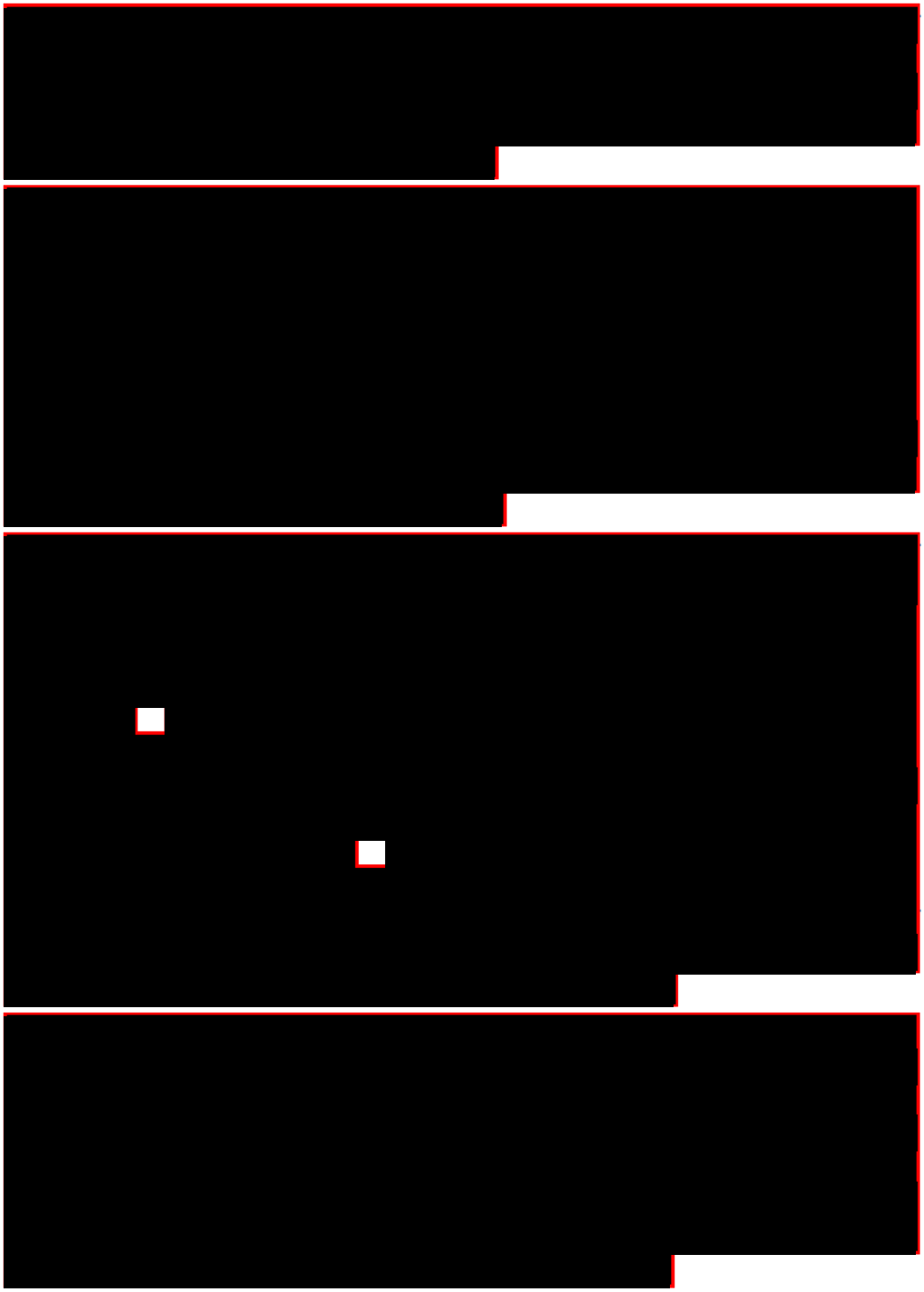
5. LIST OF ABBREVIATIONS

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
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

6. BACKGROUND INFORMATION

6.1 Rationale for Current Study

Repros believes telapristone offers the potential to provide significant symptomatic relief to women that suffer from a variety of reproductive disorders in which progesterone may be implicated. Most notably the sponsor has seen significant clinically relevant impact on the symptoms of both uterine fibroids and endometriosis.



[redacted]

FDA Guidance For Liver Enzyme Elevation Characterization as SAE

- 1. LFTs ≥ 8 x ULN
- 2. LFTs ≥ 5 x ULN for 2 consecutive weeks
- 3. LFTs ≥ 3 x ULN + Bilirubin 2 x ULN
- 4. LFTs ≥ 3 x ULN + clinical signs or symptoms (nausea; jaundice; etc.)

[redacted]

[redacted]

6.5 Ethical Conduct of the Study

This trial will be conducted in strict compliance with the protocol and all applicable FDA regulations and GCP guidelines to insure Good Clinical Practice standards. The Institutional Review Board (IRB) for this study is IntegReview, 3001 S. Lamar Blvd., Suite 210, Austin, Texas 78704.

[redacted]

7. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this study is to determine the safety and efficacy of two oral doses of Proellex administered to premenopausal women with pelvic pain associated with endometriosis confirmed within the last seven years and using prescription medications for endometriosis pain. Proellex will be administered for up to 3 cycles (18 or 16 weeks in duration), each separated by an Off-Drug Interval (ODI).

8. TRIAL DESIGN

8.1 Study Endpoints

Primary Endpoint

- Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle

Secondary Endpoints

- Change in daily average use and percent change of prescription analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment.
- Change in daily average use and percent change of over the counter analgesics from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change in daily average use and percent change of overall medication use, prescription and over the counter, from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change and percent change in BBSS score incorporating the two physician-reported scores by study visit and treatment cycle.
- Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle.
- Change from baseline in pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle.
- Change from baseline in daily average dysmenorrhea and non-menstrual pelvic pain using an 11-point numerical rating scale (NRS) by study visit and treatment cycle.

[redacted]

8.2 Study Design

8.2.1 Overview of Study Design

This study is a phase 2, 3-arm-study with an 18 week active dosing period and an option for subjects to receive 2 additional 16-week cycles of active treatment at their randomized dose (6 mg or 12 mg/day). Placebo subjects who elect additional treatment will receive treatment at 12 mg/day. The treatment dose will remain double-blind. The study will be conducted in 3 stages. In the first stage, women will undergo a baseline assessment period with no treatment. This stage will last as long as it takes to record at least one full menstrual cycle (ovulation until ovulation).

Subjects will be provided with a daily diary with which to record patient reported scores for the three elements of endometriosis pain: dysmenorrhea, non-menstrual pelvic pain and dyspareunia (BBSS).

[redacted]

For stage 2, following the baseline assessment period, at Visit 3, 60 subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of dosing should commence as soon as possible after ovulation following the end of the previous menstrual event.

Once the 18 week active dosing period is completed, subjects will be followed until menses has returned (usually within 21 days or less). Subjects may elect to receive up to 2 additional cycles of treatment at their randomized dose (6 mg or 12 mg/day), placebo-treated subjects will receive treatment at 12 mg/day. In stage 3 all subjects will receive active treatment but the treatment dose will remain double-blind. For subjects who do not choose additional treatment cycles, this will be their final follow-up visit. During the follow-up period subjects will continue to record study information in the daily diary.

For stage 3, subjects who are eligible to receive additional cycles of treatment and who elect to continue treatment will be scheduled at 21 ± 2 days after start of bleeding in their first menses after Visit 12 (recovery menses). Subjects will receive 2 cycles of treatment separated by an off-drug interval (ODI), after which they will be

followed until menses has returned. During the follow-up period subjects will continue to record study information in the daily diary. The final follow-up visit will be scheduled after blood flow has stopped.

Subjects who complete at least 28 days after Visit 3 and wish to discontinue treatment due to lack of efficacy will be eligible to start active treatment (stage 3). Subjects who discontinue the study prior to this date will not be eligible for additional treatment.

8.2.2 Study Drug Accountability

The designee assigned by the Principal Investigator at each site will maintain accurate records of receipt of all study drugs, including dates of receipt. Reasons for deviation from the expected dispensing regimen must also be recorded. A Drug Dispensing Form will be provided for this purpose. To satisfy regulatory requirements regarding drug accountability and destruction, the Principal Investigator at each site will return all used, unused, or empty and partially used study medication with dispensing records to the Sponsor for final accountability and disposal, after accountability has been verified by the study monitor.

8.2.3 Randomization and Blinding

All subjects will receive no treatment from Visit 1 until Visit 3. At Visit 3, subjects will be randomized to treatment in Arms 1, 2, or 3. Subjects will be treated with one capsule daily of 6 mg or 12 mg of Proellex, or placebo, which will be administered for 18 weeks. Subjects who elect to receive additional treatment cycles will be treated at their previously randomized dose level. Subjects randomized to placebo treatment will receive treatment at 12 mg/day. In stage 3 all subjects will receive active treatment but the treatment dose will remain double-blind. Each treatment cycle will be separated by an ODI. Blinded treatments kits will be randomized and distributed by the packaging company.

For the statistical analysis at Week 18, only statistical staff will be unblinded once the acute portion of the study database is locked. All clinical operations staff and staff at investigative sites will remain blinded until completion of the study.

8.2.4 Study Medication

All study drugs will be supplied by Repros Therapeutics Inc. Test drug, Proellex, will be [redacted] and will be packaged by a clinical supplies contract vendor designated by Repros Therapeutics Inc. The placebo will also be [redacted] and will be packaged by the same clinical supplies contract vendor. Active and matching placebo capsules will be bottled in identical packaging. Each bottle will have a label containing bottle number, number of capsules, expiration date, a statement "Caution: New Drug – Limited by Federal Law (US) to Investigational use" and instructions to take 1 capsule daily in the morning before breakfast. Subjects will take one capsule with approximately 8 ounces of water and study medication should be taken roughly at the same time every day. Subjects will record study medication date and time on subject drug diary cards. [redacted]

Subjects will not be provided with medication medications by Repros Therapeutics Inc.

8.2.5 [redacted]

8.3 Selection and Withdrawal of Subjects

Subjects for the study will be selected during screening based on the inclusion and exclusion criteria and clinical assessments listed below. Subjects will be discontinued from the study prematurely if:

- Unacceptable adverse events occur considered by the investigator to be associated with use of the study drug
- The subject requests to be withdrawn from the study
- Any of the following occur:
  - ALT or AST >8xULN

- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

- A need arises for concomitant medication prohibited by the protocol
- The Principal Investigator decides that it is in the subject's best interest
- The subject is noncompliant with the protocol
- Any subject who develops an endometrial thickness ≥ 18 mm will undergo endometrial biopsy. The endometrial biopsy will be forwarded to a member of the Expert Panel for expedited review. If the biopsy shows EIN or hyperplasia (per Expert Panel review), subject will be discontinued from the study. If EIN or hyperplasia is diagnosed the sponsor will be notified and subject discontinued from the study. Appropriate follow up treatment will be provided as deemed necessary by the investigator.
- Any subject who experiences heavy bleeding (bleeding intensity of 4 or more per the Daily Diary Card in Appendix 3) for 7 consecutive days or more will be discontinued from the study. This does not apply if heavy bleeding occurs in the first recovery menses after withdrawal of drug at the end of treatment, or is no heavier than bleeding was prior to treatment.
- Any subject who develops an endometrial thickness ≥ 18 mm and excessive bleeding that requires dilatation and curettage or hysterectomy will be discontinued from the study and undergo endometrial biopsy. Women with such findings will not be eligible for extension of treatment. Appropriate follow up treatment will be provided as deemed necessary by the investigator.
- Subjects with a biopsy that shows clear evidence of neoplasia, as determined by the expert panel, will be discontinued and be ineligible for extension of treatment.
- The decision to withdraw from the study because of an adverse event, including pain from endometriosis or from another condition, is decided by the subject and the investigator or her personal physician. The event, and any treatment should be recorded in the study records.

8.3.1 Inclusion Criteria

Subjects must meet the following criteria:

- Healthy adult females between 18 and 47 years of age (inclusive) prescribed prescription medication or taking a prescription strength dose of over-the-counter medication for endometriosis pain, and with a BBSS score ≥7 at screening (assessed over the previous 28

days, [redacted]

- Endometriosis diagnosis must have been surgically confirmed within 7 years. A laparoscopic diagnosis is acceptable.
- Subjects must have a history of at least 3 regular menstrual cycles in which symptoms of endometriosis occurred immediately prior to screening
- Normal or abnormal but non-clinically significant transvaginal ultrasound
- History of menstrual events occurring in regular cycles
- Agreement not to attempt to become pregnant during the trial
- Agreement to use alcohol in moderation and to avoid alcohol consumption within 48 hours before each visit
- Ability to complete a daily subject diary and study procedures in compliance with the protocol
- Women of child-bearing potential must be willing to use double-barrier contraception during the study and for 30 days after discontinuation of study medication. Acceptable double-barrier methods are: male condom with spermicide; male condom with diaphragm; diaphragm containing spermicide plus additional intra-vaginal spermicide
- Has a negative pregnancy test at the Screening and Baseline visits, and subsequent study visits
- A Body Mass Index (BMI) between 18 and 39 inclusive
- Is available for all treatment and follow-up visits

8.3.2 Exclusion Criteria

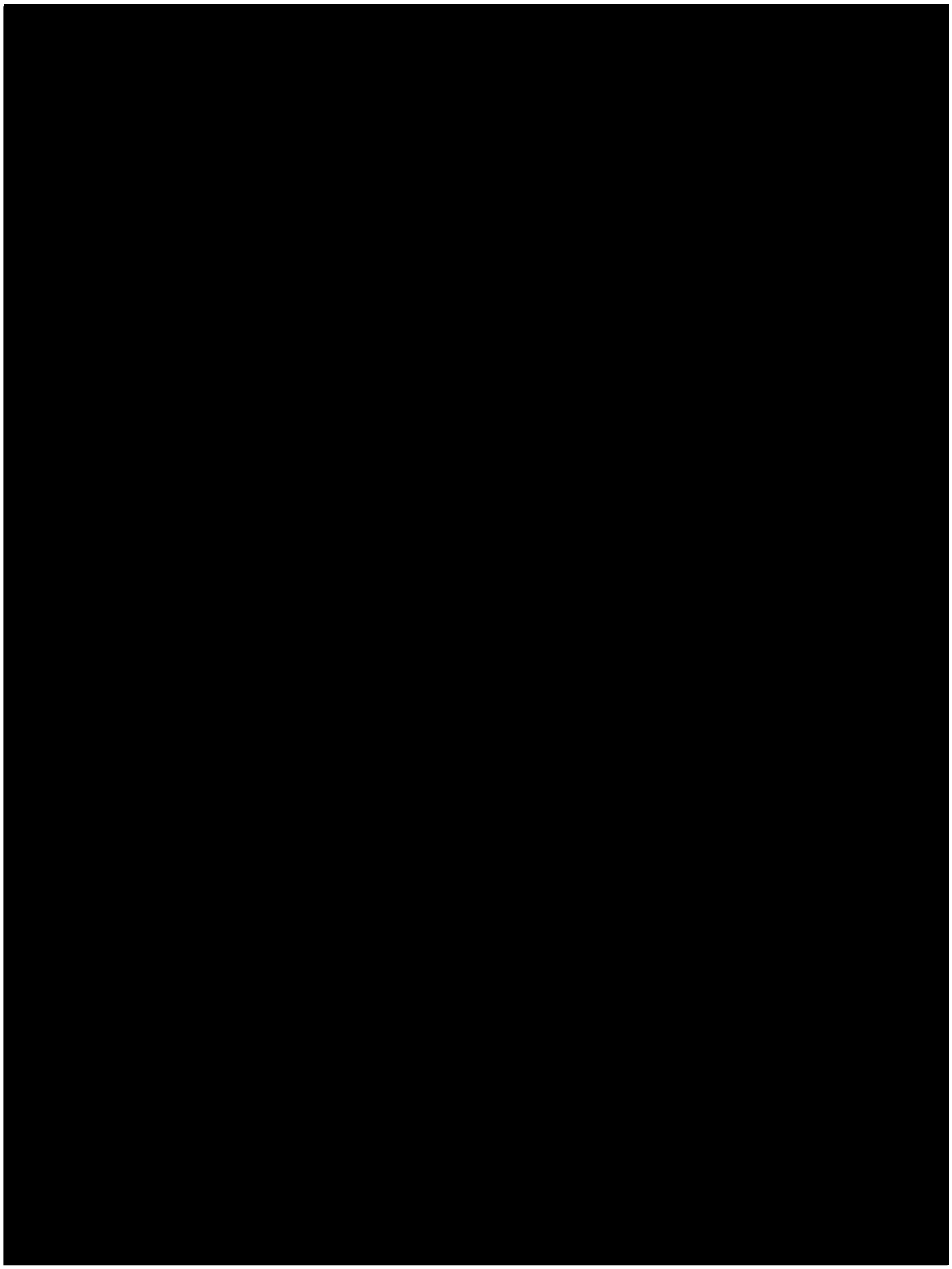
Subjects meeting any of the following criteria will be excluded from the study:

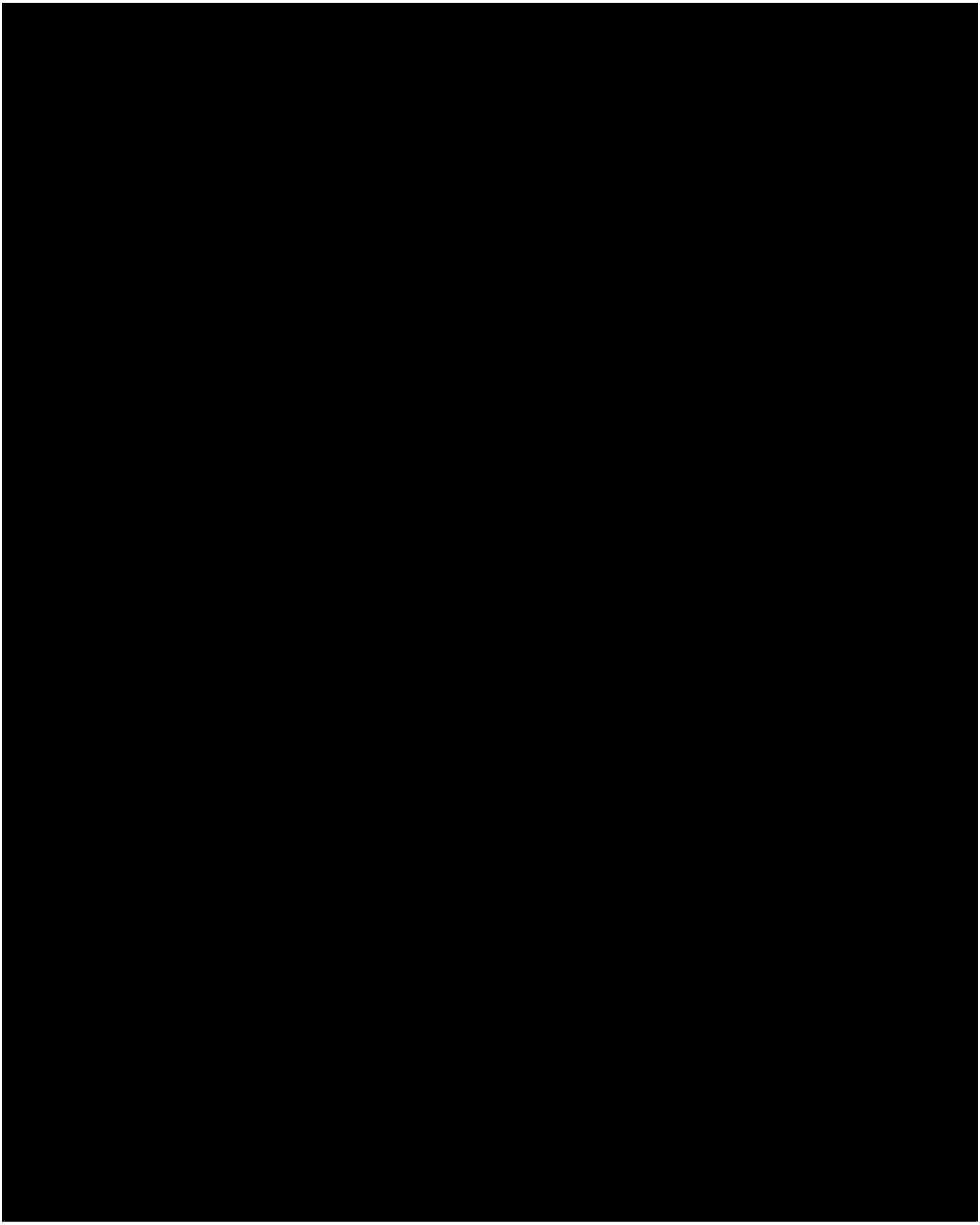
- Subject is a post-menopausal woman, defined as either; six (6) months or more (immediately prior to screening visit) without a menstrual period, or prior hysterectomy and/or oophorectomy.
- Subject is pregnant or lactating or is attempting or expecting to become pregnant during participation in the study
- Subjects with abnormally high liver enzymes or liver disease. (ALT or AST exceeding 2 x ULN AND total bilirubin exceeding

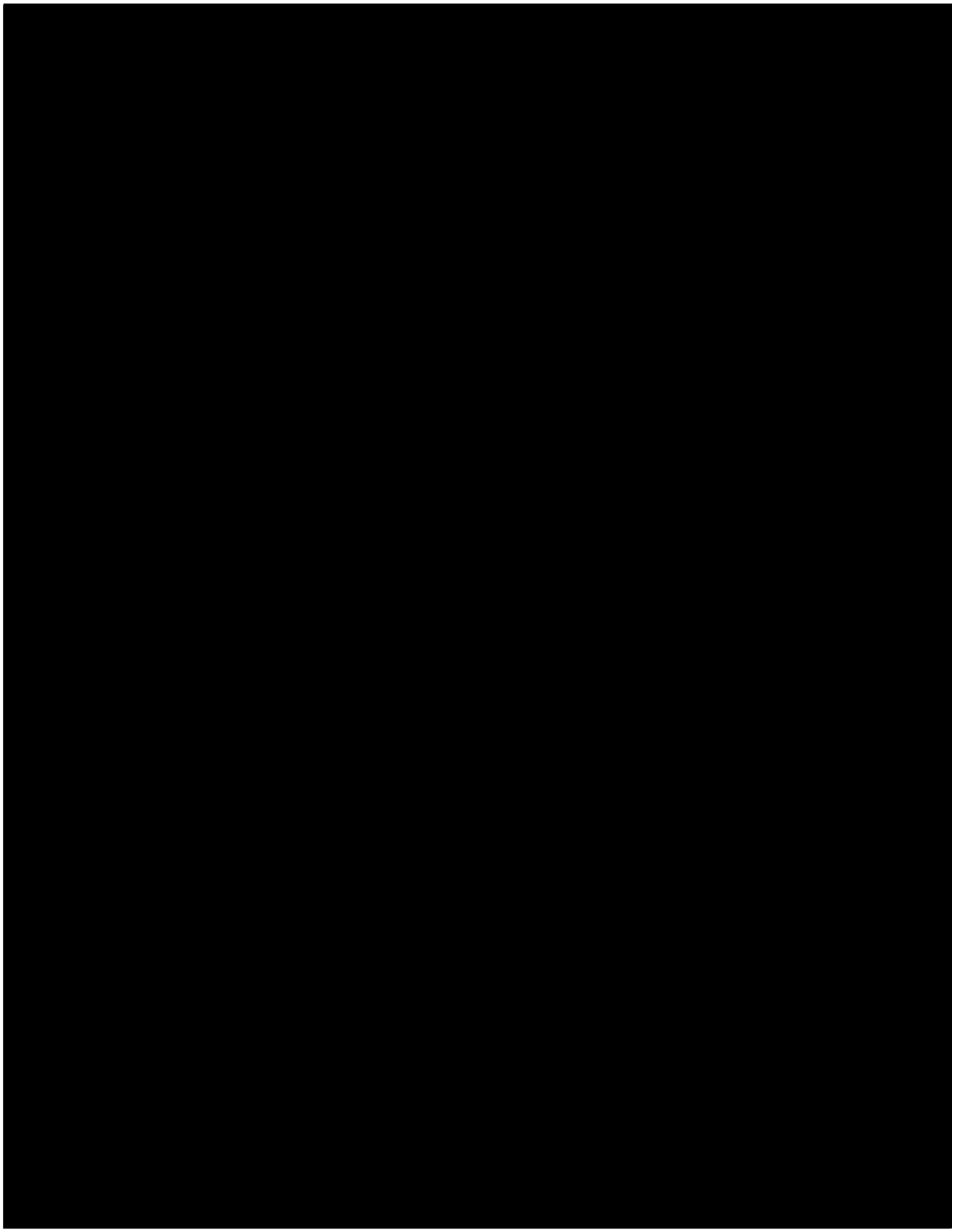
1.5xULN at screening and confirmed on repeat).

- Received an investigational drug in the 30 days prior to the screening for this study
- Subject has a history of PCOS
- Concurrent use of any testosterone, progestin, androgen, estrogen, anabolic steroids, DHEA or hormonal products for at least 2 weeks prior to screening and during the study.
- Use of oral contraceptives in the preceding 30 days. Use of Depo-Provera® in the preceding 10 months.
- Use of GnRHas (e.g. Lupron Depot) within 3 months of the first dose of study drug (Lupron Depot must have a wash-out period of 3 months after the period of duration of the Lupron dose).
- Has an IUD in place.
- Presence of intramural fibroids that impact the endometrial stripe, submucosal fibroids (any size), or endometrial polyps. Subserosal and intramural fibroids with no impact on the endometrial stripe are acceptable.
- Presence of endometrioma(s)
- Present history or condition that causes non-endometriosis related dyspareunia (e.g. vulvar vestibulitis).
- Past or present history of thrombophlebitis or thromboembolic disorders.
- Known or suspected carcinoma of the breast or reproductive organs.
- Known history of abnormal ECG that, in the opinion of the investigator, is clinically significant and will prevent the subject from completing the study, including a QTc of greater than 450 ms.
- Cervical dysplasia classified as Atypical Squamous Cells of Undetermined Significance (ASCUS) associated with high-risk human papilloma virus (HPV) or Low/High Grade Squamous Intraepithelial Lesion (LGSIL or HGSIL).
- History of abnormal endometrial biopsy including the presence of EIN.
- Recent history (within past 6 months) of alcoholism or drug abuse.
- Known active infection with HIV, Hepatitis A, B or C.
- Previous history of auto-immune disease and/or positive antinuclear antigen (ANA).

- Endometrial stripe ≥18 mm in thickness at Visit 1.
- Subject is currently taking cimetidine or spironolactone.
- Previous use of telapristone acetate or participation in a Repros clinical study
- Clinically significant abnormal findings on screening examination and laboratory assessments or any condition which in the opinion of the investigator would interfere with the participant's ability to comply with the study instructions or endanger the participant if she took part in the study.







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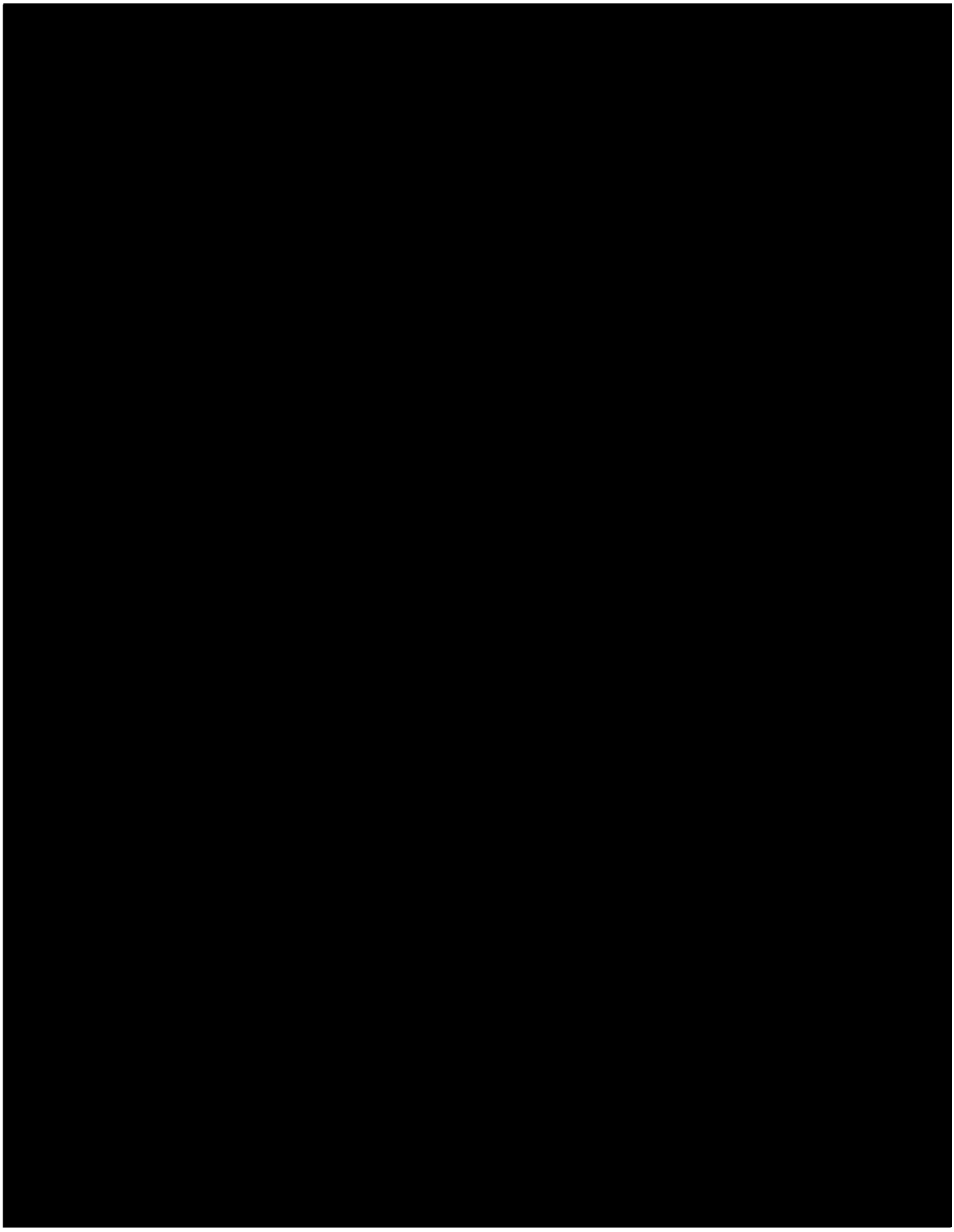
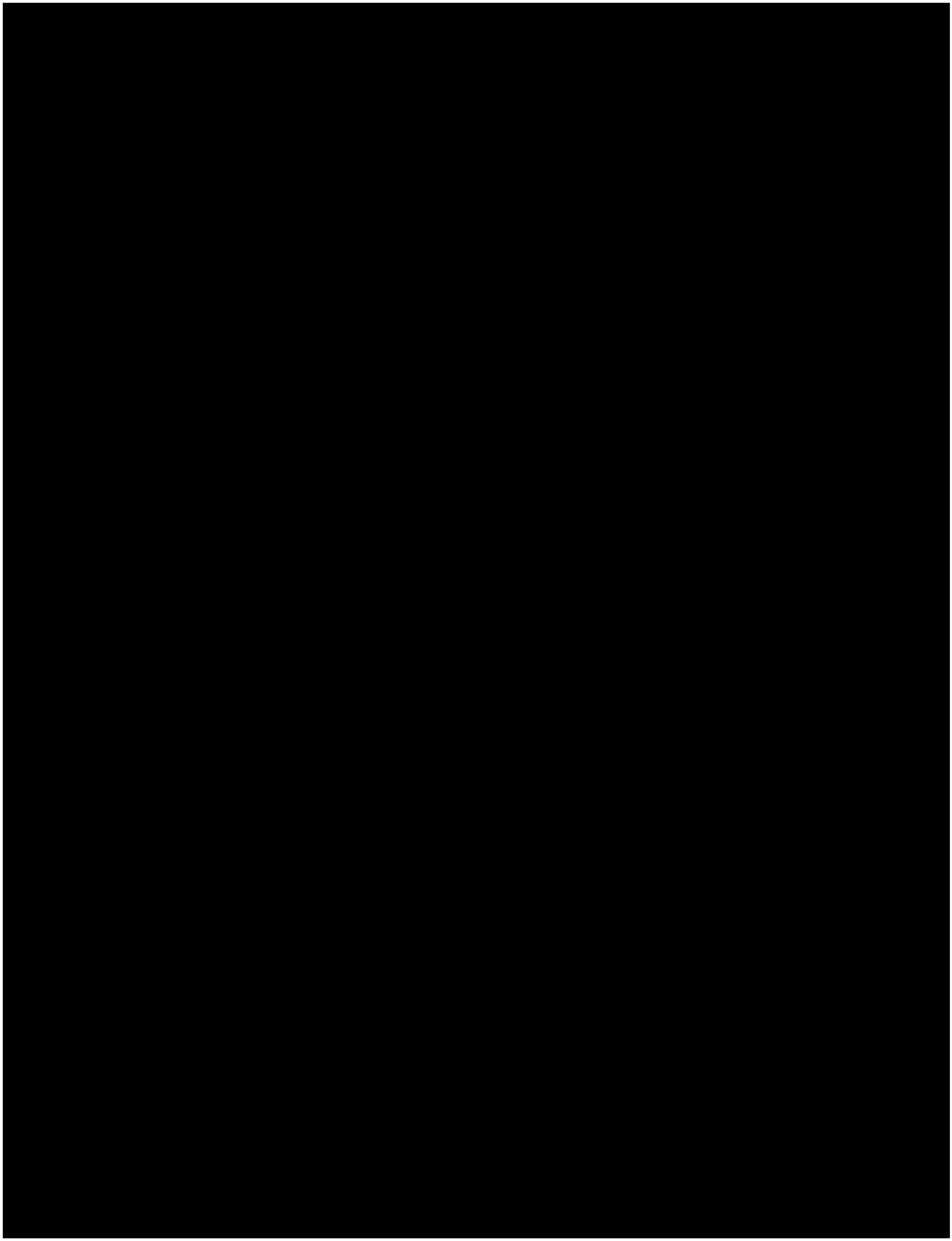
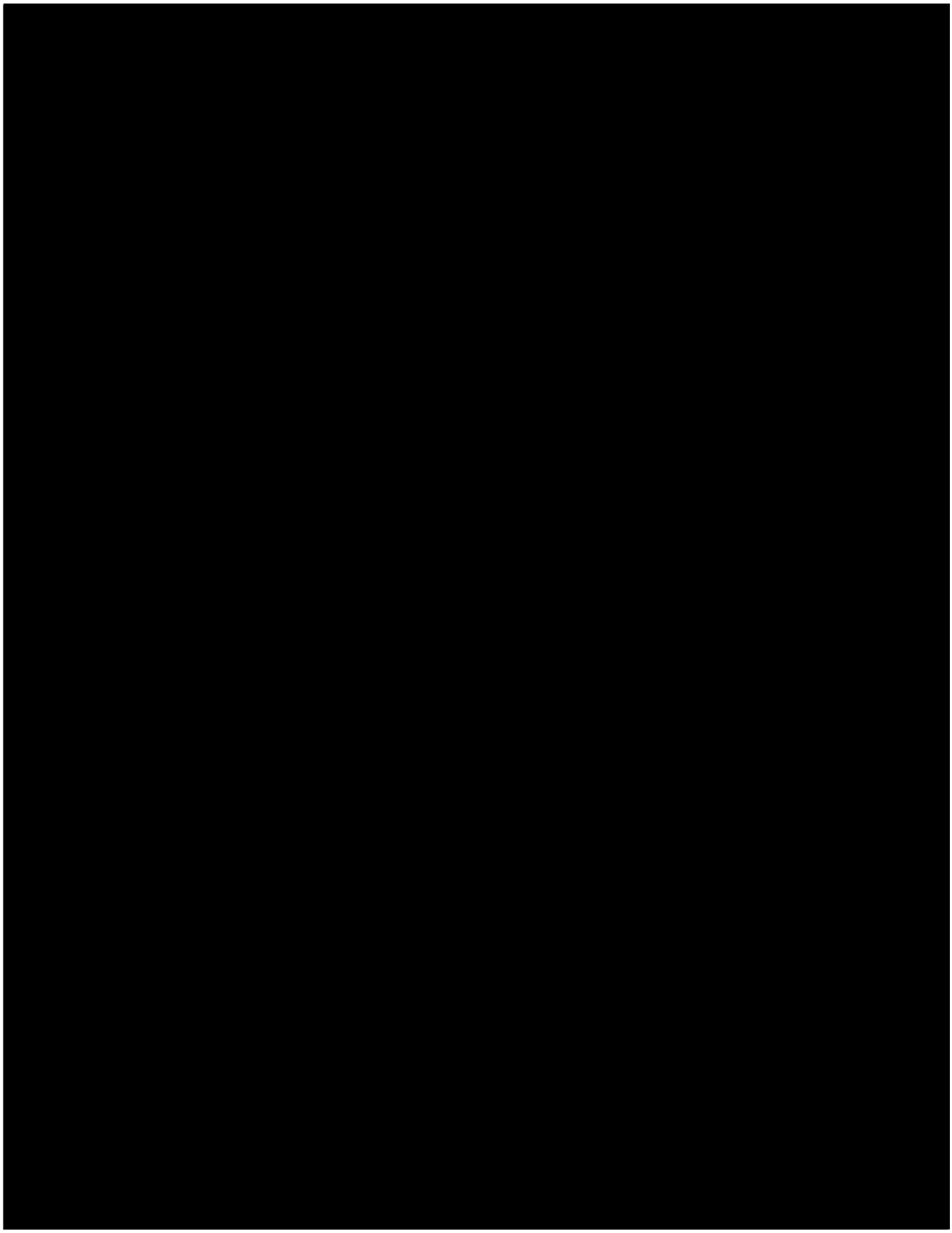






10. ASSESSMENT OF EFFICACY

10.1 Study Endpoints

Primary Endpoint

- Change and percent change in the individual BBSS scores of the three patient reported outcomes (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) by study visit and treatment cycle.

Secondary Endpoints

- Change in daily average use and percent change of prescription medications from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment.
- Change in daily average use and percent change of over the counter medications from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change in daily average use and percent change of overall medication use, prescription and over the counter, from the baseline menstrual cycle to the matching period leading up to Week 18, the last day of dosing of the first cycle of treatment, calculated based on days with reported values.
- Change and percent change in BBSS score incorporating the two physician-reported scores by study visit and treatment cycle.
- Change from baseline in endometrial pain assessed using a Visual Analog Scale (VAS) by study visit and treatment cycle.
- Change from baseline in daily average dysmenorrhea and non-menstrual pelvic pain using an 11-point numerical rating scale (NRS) by study visit and treatment cycle.

[redacted]

11.1 Adverse Events

11.1.1 Reporting Adverse Experiences

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this investigational drug, whether or not considered related to the investigational product, shall be documented on the CRF. All AEs reported by the subject or observed by the Principal Investigator will be individually listed. The signs and symptoms, time of onset (24-hour clock), duration, action taken and follow-up procedures will be reported.

11.1.2 Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) – An adverse drug experience that results in any of the following outcomes: death, a life-threatening experience, requires or prolongs subject hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly or birth defect.

Cases of liver transaminases that increase above 3 times the upper limit of normal must be reported as SAEs regardless of whether the above defined SAE criteria are met.

Unexpected Adverse Event: Any adverse event that is not identified in nature, severity, or frequency in the current Investigator's Brochure.

Additionally, the Principal Investigator will evaluate all AEs as follows:

Action taken: whether or not the AE caused the subject/patient to discontinue the study medication.

Intensity, to be graded as:

DEGREE	DESCRIPTION
Mild	Awareness of signs and symptoms; easily tolerated
Moderate	Discomfort sufficient to interfere, but not prevent daily activity
Severe	Unable to carry out usual activity

Relationship to study medication, to be graded as:

DEGREE	DESCRIPTION
Definitely	There is evidence of exposure to the study drug, for example, reliable history or acceptable compliance assessment; the temporal sequence of the AE onset relative to the medication is reasonable; the AE is most likely to be explained by the treatment than by another cause; the AE shows a pattern consistent with previous knowledge of the treatment.
Probably	There is evidence of exposure to the study drug; the temporal sequence of the AE onset relative to medication administration is reasonable; the AE is more likely explained by the treatment than by another cause.
Possibly	There is evidence of exposure to the study drug; the temporal sequence of the AE relative to the medication administration is reasonable; the AE could have been due to another equally likely cause.
Probably not	There is evidence of exposure to the study drug; there is another more likely cause of the AE.
Definitely not	The subject/patient did not receive the study drug; or temporal sequence of the AE onset relative to administration of the study drug is not reasonable; or there is another obvious cause of the AE.

11.1.3 Serious Adverse Events (SAEs)

The Principal Investigator shall document all SAEs in all subjects after signing informed consent [redacted] and they must be reported to the Repros Therapeutics Inc. Safety Monitor within 24 hours by Fax or telephone, even if the SAE does not appear to be drug-related. This report should include all available information at the time of notification. This notification should be followed with submitting a SAE Report Form provided by Repros Therapeutics Inc. All additional follow-up reports must be reported to the Repros Therapeutic Inc. monitor as soon as available.

Cases of liver transaminases that increase above 3 times the upper limit of normal must be reported as SAEs regardless of whether the above defined SAE criteria are met.

12. CONCOMITANT MEDICATIONS

12.1 Prescription Analgesics Permitted During the Study

12.1.1 Treatment of Endometriosis-Related Pain

Subjects should not take any analgesics during the study unless necessary for pain. In the event that a subject needs to use prescription analgesics for endometriosis-related pain, one of the following regimens should be prescribed:

- Hydrocodone/Acetominophen: 5-10 mg/325 -750 mg, 1-2 tabs every 4-6 hours prn
- Ibuprofen 400 mg, 600 mg or 800 mg every 6 hours prn
- Acetaminophen with Codeine: 1 tab 300/30 mg to 300/60 mg every 4 hours prn
- Oxycodone: 5-15 mg every 4-6 hours prn OR 10 mg (continuous release) every 12 hours prn
- Tramadol: 50-100 mg every 4-6 hours prn up to 400 mg/day
- Ponstel (mefenamic acid) (500 mg initial dose, then 250 mg every 6 hours)
- Hydrocodone/Ibuprofen: 7.5/200 mg, 1-2 tabs every 6-8 hrs prn

Any deviation from this list requires pre-approval by Repros. Note: Over-the-counter medications (e.g. ibuprofen, naproxen) do not qualify as prescription medications for entrance into the study, even if a prescription has been written for the specific medication.

12.1.2 Treatment of Non-Endometriosis–Related Pain

If the subject experiences pain (not related to endometriosis), she should be treated as medically appropriate. The choice of drug will depend on the medical condition. Dosage forms and route of administration should be as per product specifications.

All narcotic, non-narcotic and over–the-counter medication for endometriosis-related pain will be captured in the subjects' daily diary.

All narcotic, non-narcotic and over–the-counter medications for non-endometriosis-related pain will be recorded in the appropriate section of the CRF.

Analgesic medications will not be provided by Repros Therapeutics Inc.

12.2 Prohibited Medications

The following medications are prohibited during the study:

- Testosterone
- Progestin
- Androgen
- Estrogen
- Anabolic steroids
- DHEA
- Other hormonal products
- CYP3A4 inhibitors, e.g. atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, omeprazole.
- St. John's Wort
- Spironolactone
- Cimetidine

12.3 Other Medications Taken During the Study

Any other prescription or over-the-counter medication taken during the study will be recorded in the appropriate section of the CRF. Subject must be on a stable dosage of approved concomitant medications at least 48 hours prior to drug administration.

13. STATISTICAL METHODS

13.1 Determination of Sample Size

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. [redacted] a sample of 18 subjects per group would provide 80% power to detect a statistically significant difference between the treatment groups.

13.2 Statistical and Analytical Plan

A statistical analysis will be conducted once all subjects have completed the placebo-controlled portion of the study, Stage 2. A Statistical Analysis Plan will be developed that outlines in detail all planned analyses. This document will be completed prior to unblinding study data for the placebo-controlled portion of the study.

A separate analysis and reporting will occur once all subjects have completed all study treatment. A separate Statistical Analysis Plan will describe these analyses. This summary will focus on the results noted in Stage 3 of the study.

13.2.1 Demographics and Subject Characteristics

For all subjects included in this study, subject accountability, baseline demographic and medical history data will be summarized for each treatment group. Summaries for quantitative variables include the sample size, mean, median, standard deviation, minimum, and maximum. Summaries for categorical variables include the number and percent of patients for each outcome. No statistical testing will be performed to compare these factors between treatment groups.

13.2.2 Efficacy Analyses

An analysis will be conducted once Stage 2, the first cycle of treatment, has been completed. A later analysis will focus on the data collected from the active treatment stage of the study, Stage 3.

Efficacy analyses of the first cycle of treatment will be conducted in the Intent-to-Treat population, which will consist of all subjects who are randomized and who receive study drug. Subjects with missing post-baseline data will have a value of "no change" imputed for analysis.

13.2.2.1 Prescription Analgesic Usage

The change and percent change in daily average use of prescription analgesics comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing in Cycle 1 (Week 18) will be summarized for each treatment group. For each subject, the total number of pills or tablets of prescription analgesics during each 28 day menstrual cycle will be calculated, and the daily average use of prescription analgesics will be determined by dividing the total number of pills/tablets of prescription analgesics taken during the 28 day nominal period by 28. The percent change from baseline in the prescription analgesic usage will be determined by subtracting the baseline prescription analgesic usage from the prescription analgesic usage during the last nominal 28 day menstrual cycle, dividing by the baseline prescription analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline prescription analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

Changes in prescription analgesic use during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.2 Over the Counter Analgesic Usage

The change in daily average use of over the counter analgesics comparing the baseline menstrual cycle to a similar period leading up to the last day of dosing in Cycle 1 (Week 18) will be summarized for each treatment group. For each subject, the total number of doses of over the counter analgesics during each menstrual cycle will be calculated, and the daily average use of over the counter analgesics will be determined by dividing the total number of doses of over the counter analgesics by the number of days in the menstrual cycle

(number of doses per day). The percent change from baseline in the over the counter analgesic usage will be determined by subtracting the baseline over the counter analgesic usage from the over the counter analgesic usage during each menstrual cycle, dividing by the baseline over the counter analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline over the counter analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

Changes in over the counter analgesic use during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.3 Overall Analgesic Use

The change and percent change in daily average use of all analgesics (prescription and over the counter) comparing the baseline menstrual cycle (28 days) to the 28 days leading up to the last day of dosing in Cycle 1 (Week 18) will be summarized for each treatment group. For each subject, the total number of pills or tablets of analgesics taken during each 28 day menstrual cycle will be calculated, and the daily average use of prescription analgesics will be determined by dividing the total number of pills/tablets of analgesics taken during the 28 day nominal period by 28. The percent change from baseline in the analgesic usage will be determined by subtracting the baseline analgesic usage from the analgesic usage during the last nominal 28 day menstrual cycle, dividing by the baseline analgesic usage, and multiplying by 100%.

An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including the baseline analgesic usage and treatment group in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

Changes in analgesic use during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.4 BBSS Physician Reported Scores

The BBSS score incorporating the two physician-reported scores will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing in Cycle 1 (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including baseline BBSS score and treatment in the model. Pairwise comparisons of the treatment groups will be made using a t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. [redacted]

The BBSS patient and physician scores during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.5 BBSS Patient Reported Scores

The percent change from baseline in each of the daily average combined BBSS patient-reported scores (dysmenorrhea, dyspareunia and non-menstrual pelvic pain) will be analyzed to compare the baseline menstrual cycle to a similar period leading up to the last day of dosing in Cycle 1 (Week 18). An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Covariance, including baseline BBSS score and treatment in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits. [redacted]

The BBSS patient scores during the active treatment stage of the study (stage 3) will also be summarized

13.2.2.6 Menstrual or Non-menstrual Vaginal Bleeding

The number of days and intensity of menstrual and non-menstrual vaginal bleeding will be summarized from the diary data. The total number of days and average intensity will be summarized from the days preceding each visit. An overall comparison among the 3 treatment groups will be performed on both the total number of days and average intensity using a one-way Analysis of Covariance, including the baseline score (number of days or average intensity) and treatment in the model. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. While the primary assessment

will be based on Visit 12 (after 18 weeks of treatment) summaries will also be prepared for each of the other visits and visit post-recovery menses. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

The number of days and intensity of menstrual and non-menstrual vaginal bleeding will also be summarized from active treatment (Stage 3) diary data collected.

13.2.2.7 VAS Assessment of Pain

The percentage change from baseline VAS pain score will be analyzed within treatment group and between treatment groups. An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. Pairwise comparisons of the treatment groups will be made using t-test or non-parametric test as appropriate. While the primary assessment will be based on scores at Visit 12 (after 18 weeks of treatment), summaries will also be prepared for each of the other visits. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

The VAS pain scores collected during the active treatment stage of the study (Stage 3) will also be summarized.

13.2.2.8 Assessment of Pain Using the NRS

The average daily assessment will be calculated separately for dysmenorrhea and pelvic pain within each key 28-day baseline and treatment period. The percentage change from baseline NRS pain score will be analyzed within treatment group and between treatment groups. An overall comparison among the 3 treatment groups will be performed using a one-way Analysis of Variance. Pairwise comparisons of the treatment groups will be made using t-test or non-parametric test as appropriate. While the primary assessment will be based on scores during the 28-day period prior to Visit 12 (after 18 weeks of treatment), summaries will also be prepared for each of the other visits.

The average daily assessment of dysmenorrhea and pelvic pain scores collected during the active treatment stage of the study (Stage 3) will also be summarized.

[redacted]

13.3 General Statistical Issues

A Statistical Analysis Plan (SAP) will be developed prior to the analyses of the first cycle of treatment. Two analyses will be conducted. The first analysis will occur when all subjects have completed the first cycle of treatment (Week 18) and the second with be conducted once all subjects have completed the active treatment stage of the study (Stage 3).

Statistical significance will be declared if the two-sided p-value is ≤ 0.05. Since the study was not powered for efficacy assessments based on statistical hypotheses, the p-values reported at the conclusion of the study are being reported to quantify the difference in the treatment effect between treatment groups.

14. ETHICS

14.1 Subject Information and Consent

A properly executed, written informed consent in compliance with Food and Drug Administration (FDA) regulations and Good Clinical Practice (GCP) guidelines will be obtained from each subject prior to entering the study or performing any unusual or non-routine procedure that involve a risk to the subject. The Principal Investigator will submit a copy of the informed consent document to the Institutional Review Board for review and approval before research subjects are enrolled. The Principal Investigator will provide a copy of the signed informed consent to the subject and the original will be maintained in the subject's medical record.

14.2 Institutional Review Board

The Principal Investigator will provide the Institutional Review Board with all requisite material, including a copy of the informed consent. The study will not be initiated until the IRB provides written approval of the protocol and the informed consent and until approved documents have been obtained by the Principal Investigator and copies received by the Sponsor. Appropriate reports on the progress of this study by the Principal Investigator will be made to the Institutional Review Board and the Sponsor in accordance with the applicable government regulations and in agreement with the policy established by the Sponsor.

14.3 Monitoring Case Report Forms

Repros Therapeutics Inc. or their designee will monitor all aspects of the study with respect to current GCP and standard operating procedures for compliance with applicable federal regulations. These individuals will have access to all records necessary to ensure integrity of the data and will periodically review progress of the study with the Principal Investigator.

14.4 Study Record Retention

In accordance with FDA regulations and GCP guidelines, all study-related documentation shall be retained by the Principal Investigator for a minimum of 2 years after FDA approval of telapristone acetate or clinical development has been terminated. At that time, the Principal Investigator will contact Repros Therapeutics Inc. regarding further disposition of the study records and comply with instructions.

14.5 Data Quality Assurance

All data recorded during the study will be available for audit against source data and for compliance with GCP and specific protocol requirements. Monitoring of the study progress and conduct will be ongoing. The Principal Investigator will be responsible for the following:

1. Monitoring study conduct to ensure that the rights of subjects are protected;
2. Monitoring study conduct to ensure trial compliance with GCP guidelines; and
3. Monitoring accuracy, completion and verification from source documents of study data.

14.6 Confidentiality

All information provided to the Principal Investigator by Repros Therapeutics Inc. or their designees including non-clinical data, protocols, CRFs and verbal and written information will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be released in confidence to the IRB. In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than to Repros Therapeutics Inc. or their designees or in confidence to the IRB, except if required by law.

14.7 Publications

Following completion of the study, the data from the entire study or from subsets of the study may be considered for reporting at a scientific meeting or for publication in a scientific journal, in which case Repros Therapeutics Inc. will be responsible for these activities and will work with the Principal Investigator to determine how the manuscript is written and edited, the number and order of authors, the publication to which it will be submitted and other related issues.

15. INVESTIGATOR'S STATEMENT

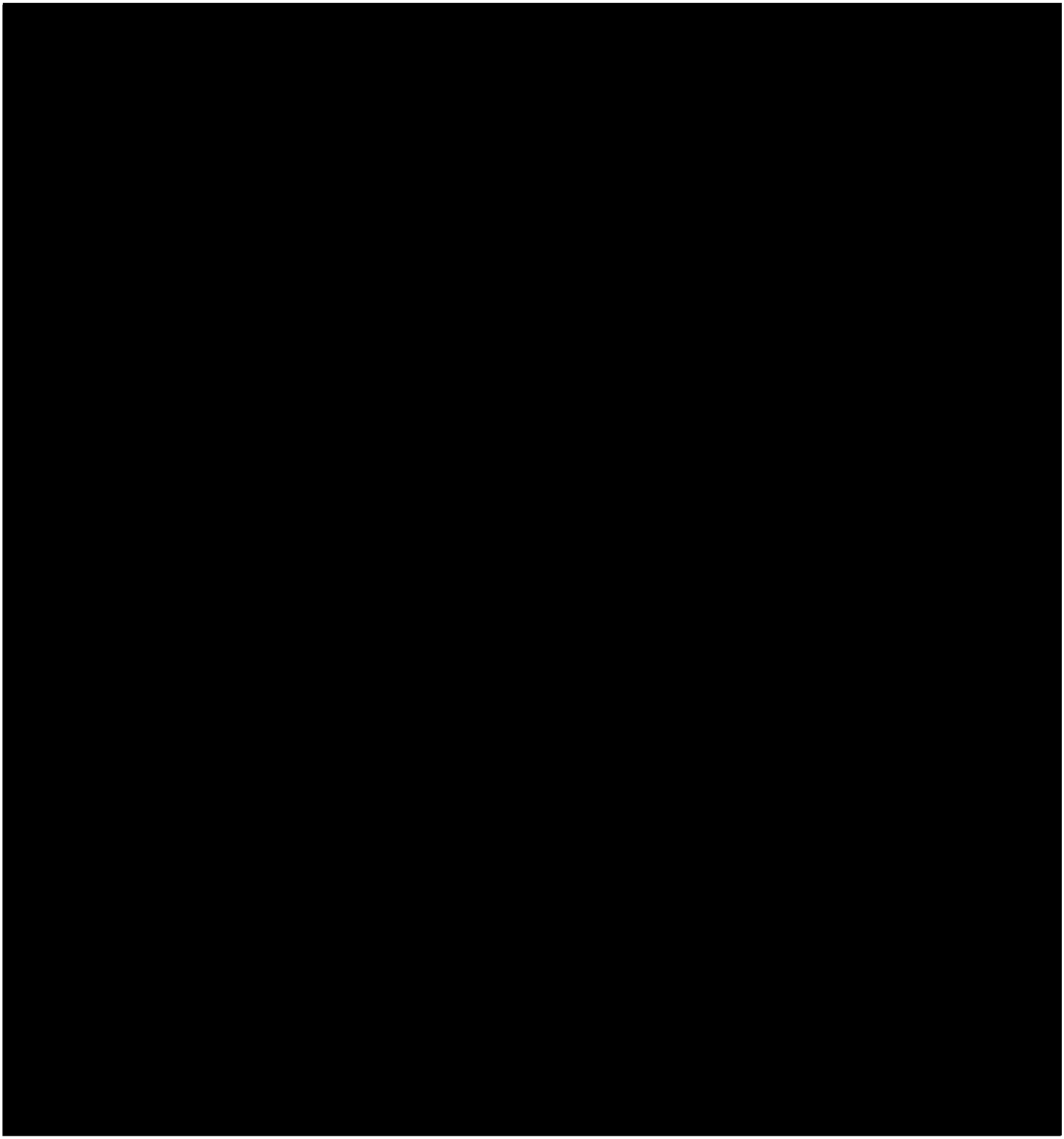
I have reviewed the ZPE-202 protocol and Investigator Brochure and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

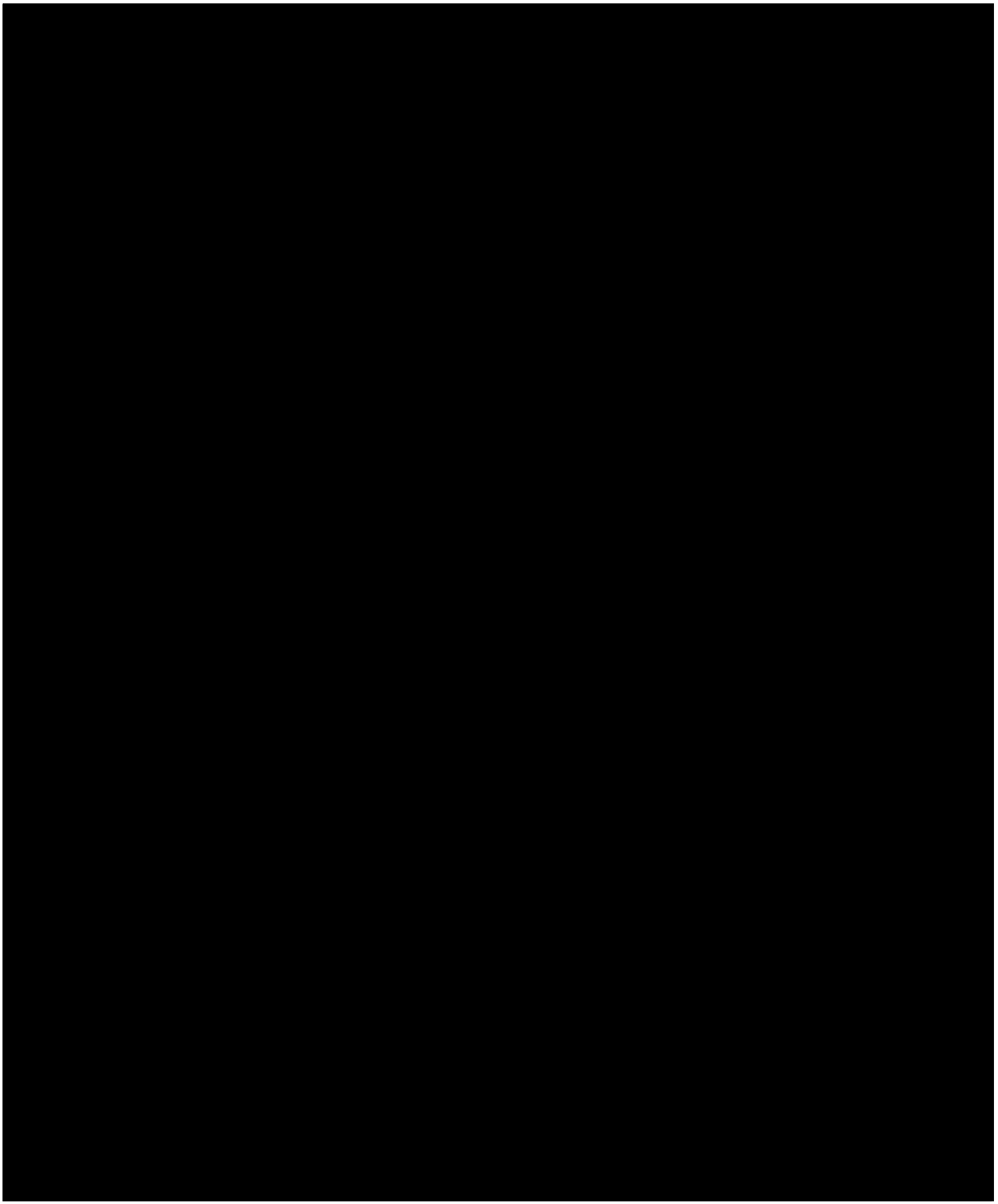
_____ _____

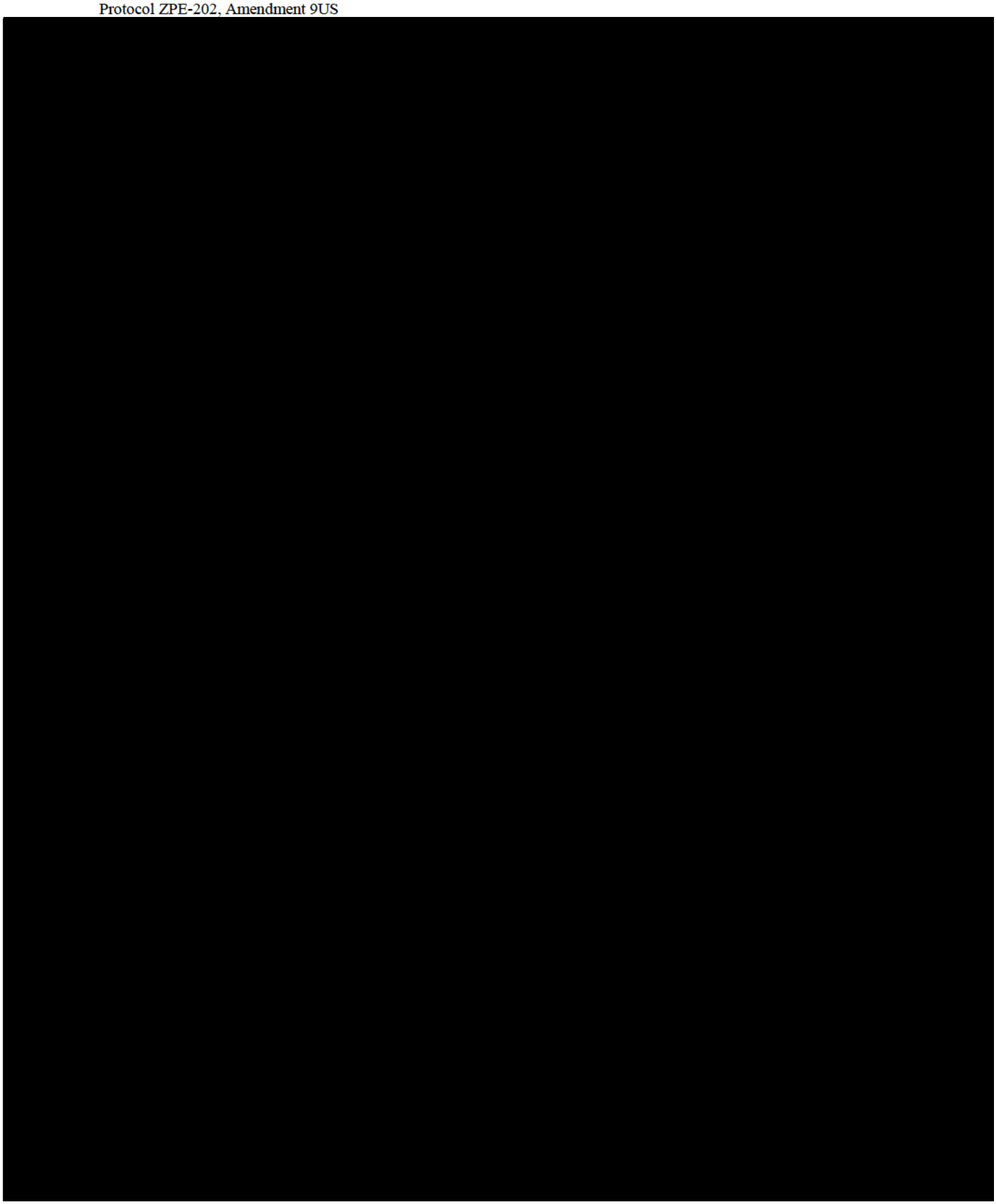
Investigator Date

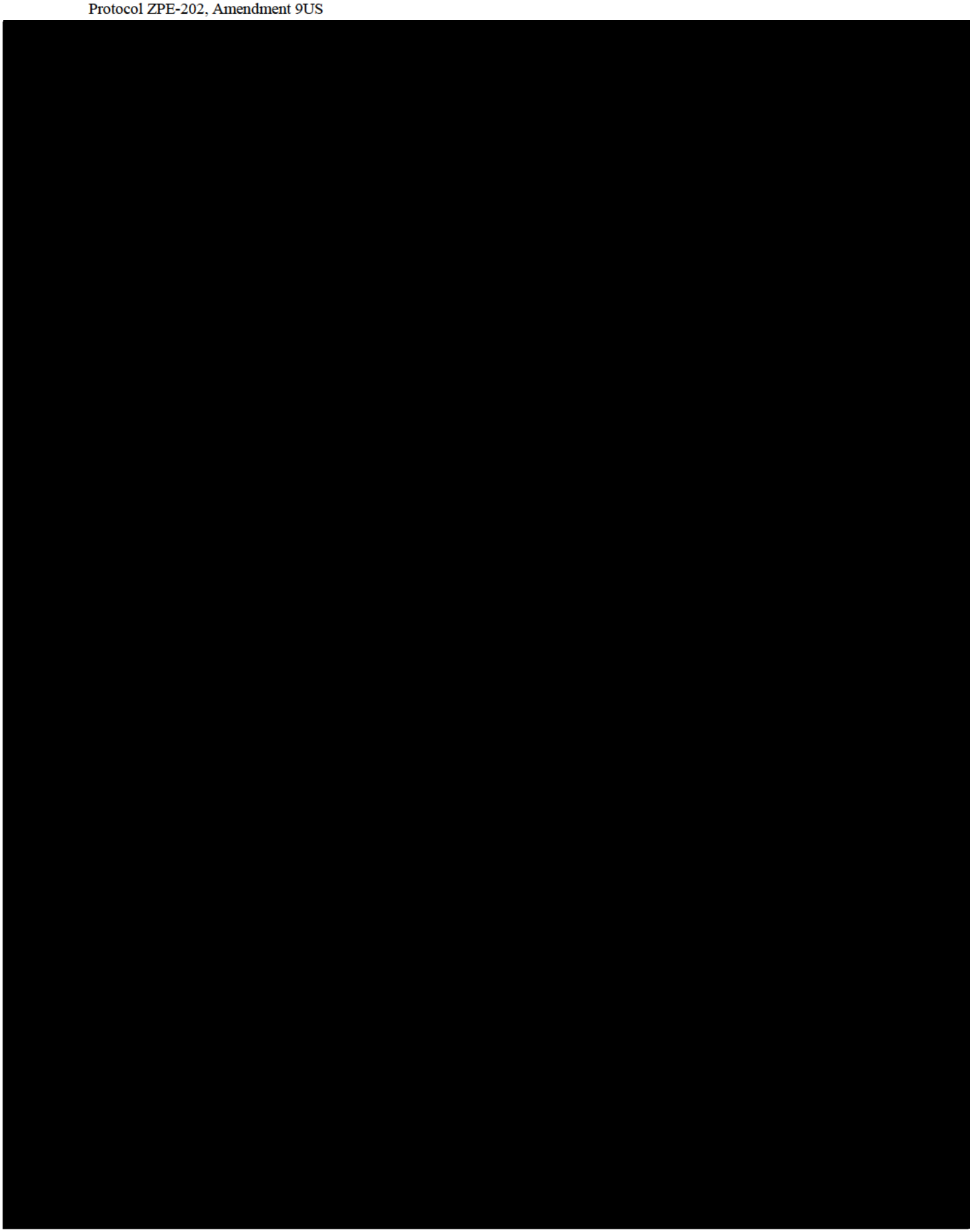
_____

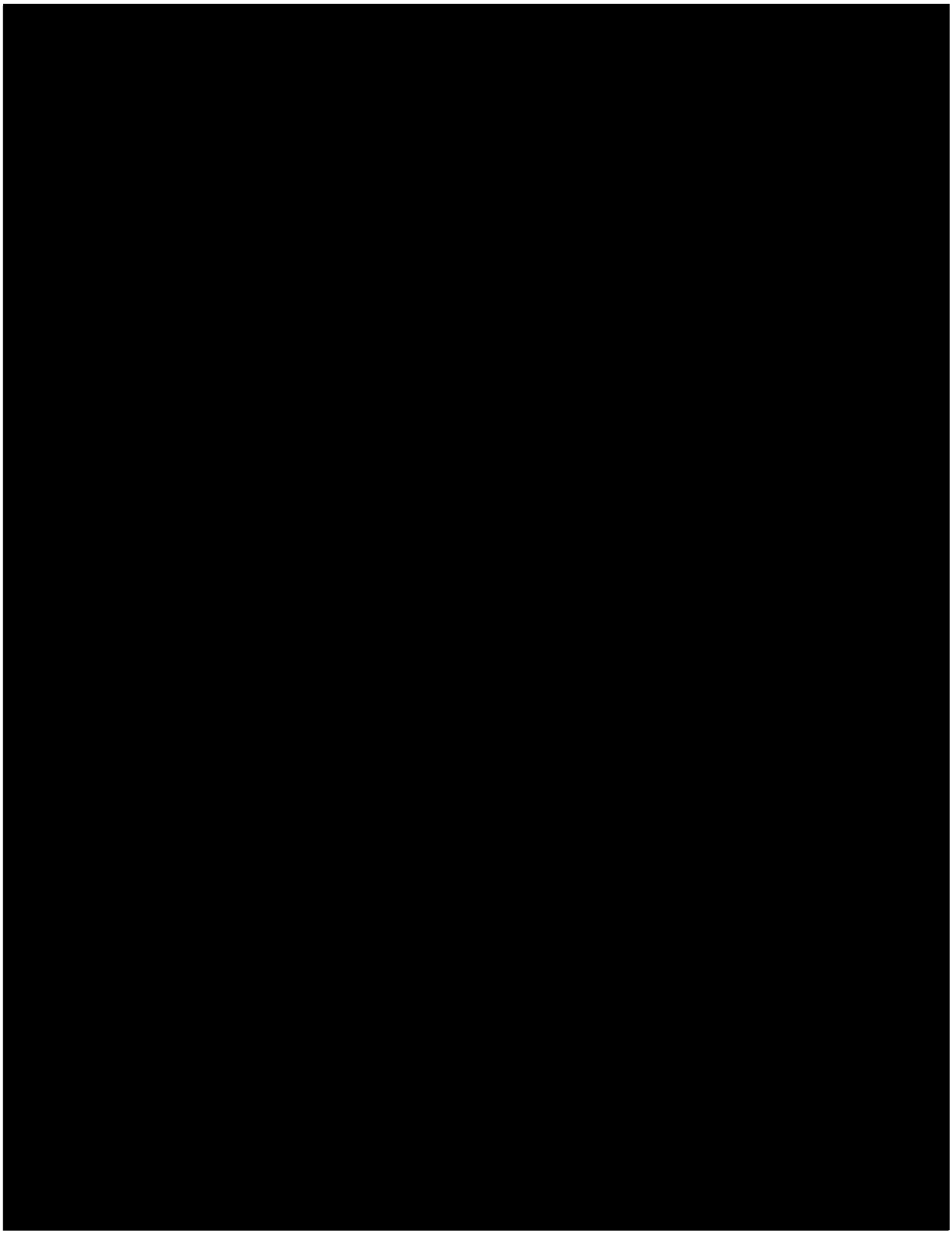
Printed name

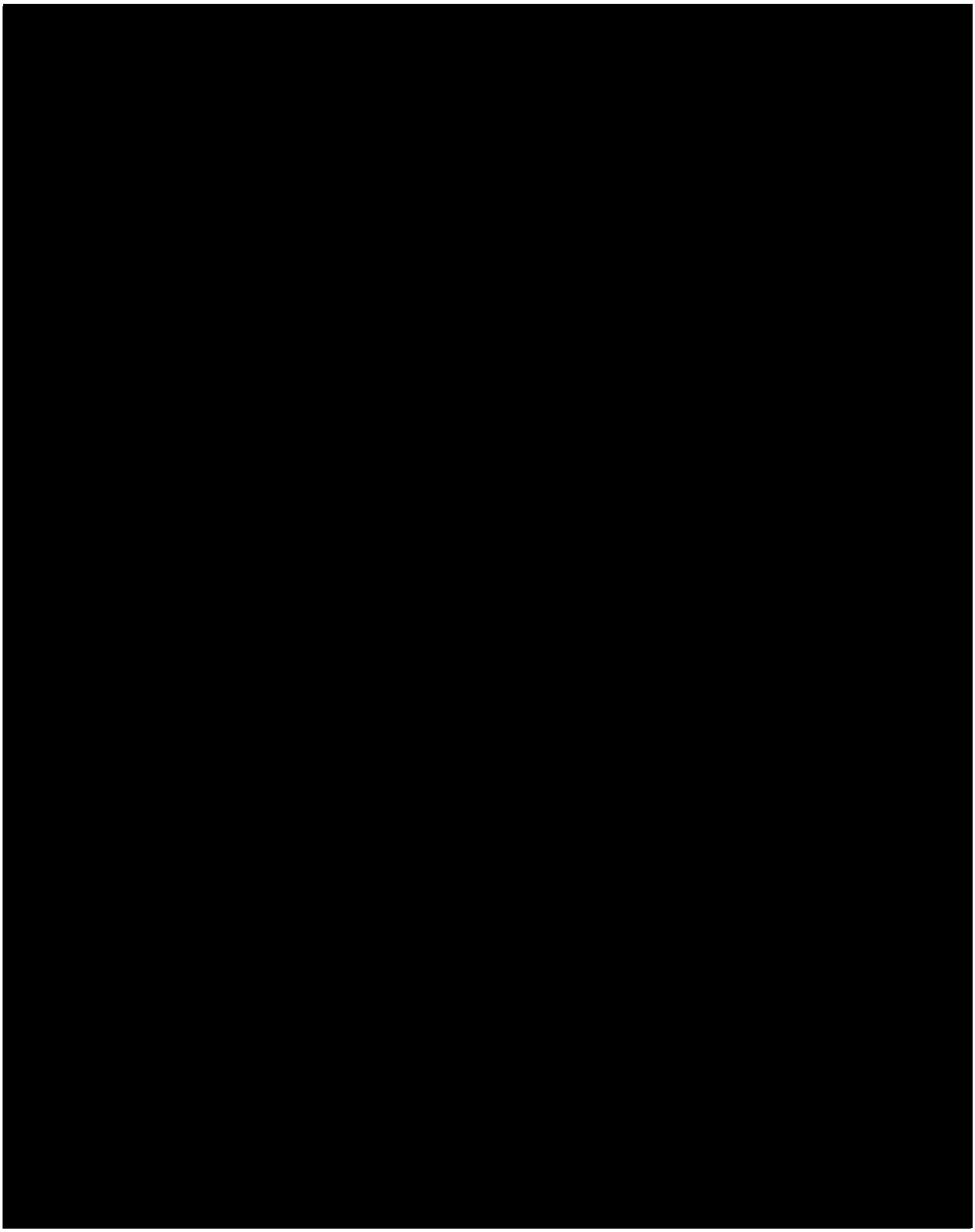












ZPE-202 DEXA phantom scan acquisition protocol v3.1