NCT02811159

Study ID: ZPU-203EXT

Title: An Open-Label Extension Study of 12 mg Proellex® (Telapristone Acetate) Administered Orally in the Treatment of Premenopausal Women with Confirmed Symptomatic Uterine Fibroids

Protocol Amendment 1 Date: 13 July 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.

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An Open-Label Extension Study of 12 mg Proellex® (Telapristone Acetate) Administered Orally in the Treatment of Premenopausal Women with Confirmed Symptomatic Uterine Fibroids

Original Protocol: June 22, 2016
Amendment 1: July 13, 2016

SPONSOR:

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

[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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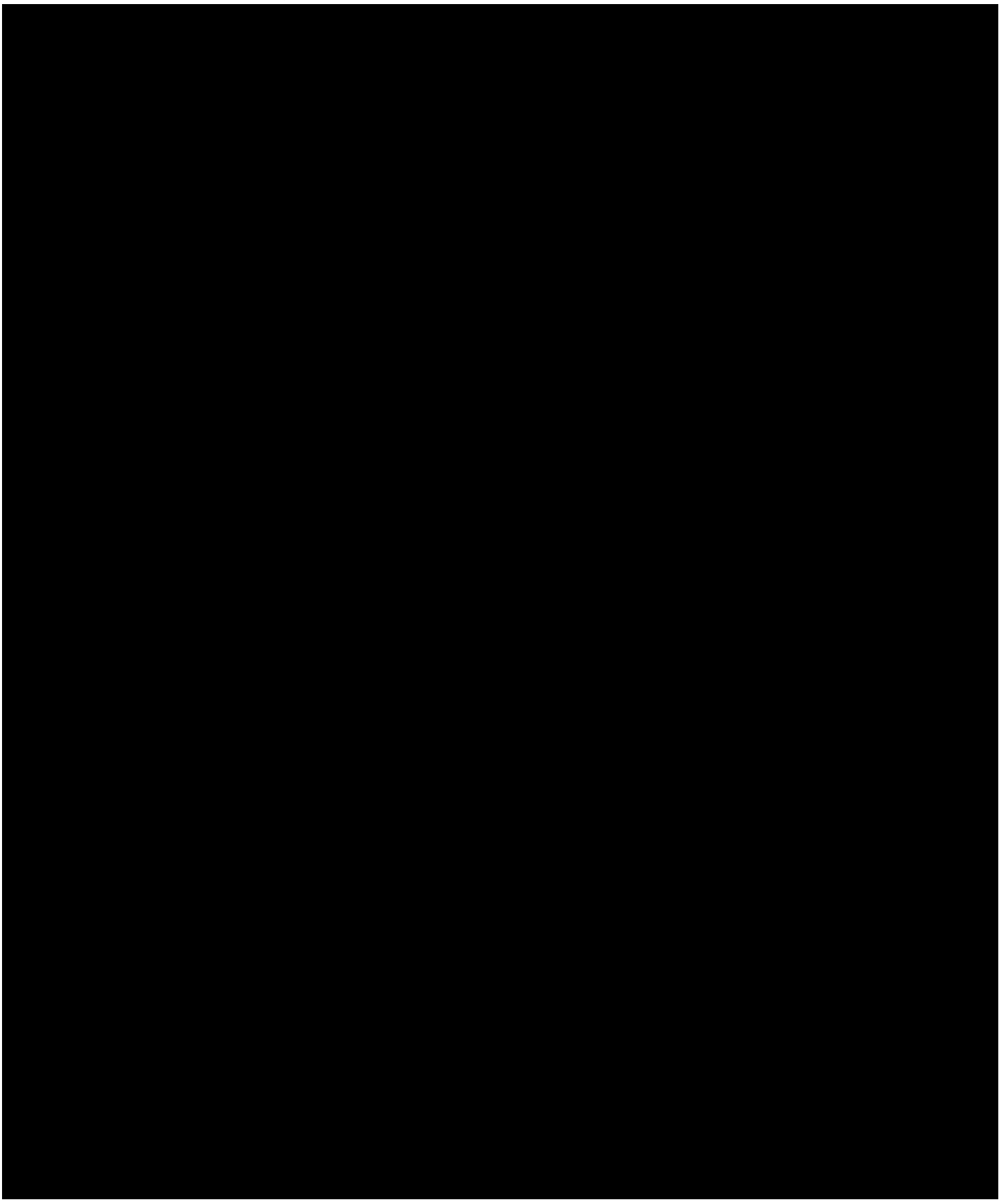
3. PROTOCOL SYNOPSIS

Test Drugs:	Proellex® (Telapristone Acetate): 12 mg gelatin capsules
Protocol Number:	ZPU-203EXT
Study Purpose:	To determine the safety of extended treatment with Proellex in women who have successfully completed either study ZPV-201 or ZPU-203 and meet eligibility criteria.
Study Design and Duration Of Treatment:	This study is an open-label, multi-center extension study to evaluate the safety of continued treatment with Proellex in subjects who successfully completed either study ZPV-201 or ZPU-203. The study requires 16 visits and is approximately 13 months in duration (up to 15 months for selected sites). Subjects will be treated orally with 12 mg Proellex/day for three 18-week courses, each separated by an ODI. Throughout the study women will record study information in the diary, PBAC, and questionnaires as outlined in the study procedures. The start of the first 18-week course of treatment (Course 1) should commence no later than 4 days after the end of bleeding, i.e. at visit 24 (or Visit 19, see Study Procedures below) of the previous study. Once dosing for Course 1 is stopped, subjects will be followed until menses returns. The start of the second and third 18 week courses of treatment (Courses 2 and 3) will commence no later than 4 days after the end of bleeding in the subject's menses following withdrawal of drug after the previous course has been completed. At *selected sites* subjects will commence dosing on the first day of bleeding in their next menstrual cycle after Visit 19 or Visit 24 (about 3 weeks after V19 or 24). The start of the second and third courses of treatment will start on the first day of bleeding in the subject's second menses following withdrawal of study drug. During the ODI, subjects will continue to record study information in the daily paper diary and PBAC charts. Any subject who has any 28-day period during treatment (not including the ODIs) without a bleeding score >1 will be deemed to have achieved amenorrhea. Subjects who do not achieve amenorrhea after 8 weeks of treatment will exit the study. After completion of 3 courses of treatment, subjects will be followed through the subsequent menstrual event (recovery menses). A DSMB will review any liver safety events (LFTs ≥3 x ULN or bilirubin ≥2 x ULN).
Subject Population:	The study will enroll women who have successfully completed either study ZPV-201 or ZPU-203 and meet eligibility criteria.
Number of Subjects:	Up to about 60 subjects
Number of Sites	Approximately 10 sites
Study Duration:	Total participation in the study is approximately 13 months.

[redacted]:	[redacted]
Study Endpoints	Endpoints will be: • Percentage of subjects who become amenorrheic • Change in UFS-QOL Symptom Severity score comparing to the previous study baseline and study baseline • Change in the individual UFS-QOL sub scores • Change in PBAC scores • Percentage change from parent study baseline and study baseline in total uterine fibroid volume measured by MRI • Incidence of significant adverse events • Changes in physical examination results • Changes in clinical laboratory results • Changes in liver function to values • Unexpected or excessive vaginal bleeding • Endometrial thickness assessed using vaginal ultrasounds • Change in number and intensity of bleeding days over the course of the treatment and ODI periods [redacted] • Pathology of the endometrium assessed by biopsies.

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. Continuous efficacy endpoints, such as the change from baseline in uterine tumor volumes will assess treatment effect using a within-group t-test or appropriate non-parametric technique. The percentage of subjects becoming amenorrheic will be determined. [redacted]

[redacted]



5. LIST OF ABBREVIATIONS

AE	Adverse event
CRF	Case report form
DHEA	Dehydroepiandrosterone
dL	Deciliter
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GnRH	Gonadotrophin releasing hormone
g	Grams
ICH	International Conference on Harmonization
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
MBL	Menstrual Blood Loss
mg	Milligram(s)
mL	Milliliter
ng	Nanograms
OC	Oral Contraceptive
ODI	Off-Drug Interval
PBAC	Pictorial Blood Loss Assessment Chart
PCOS	Polycystic Ovarian Syndrome
PK	Pharmacokinetic
RBC	Red blood cell
SAE	Serious adverse event
UFSQOL	Uterine Fibroid Symptom Quality of Life Survey
UFS-QOL	Uterine Fibroid Symptom Quality of Life Survey
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. [redacted]

Based on findings from the recently completed ZP-204 low dose study of oral Proellex, doses from 1 mg up to 12 mg daily were administered for 10 consecutive weeks with no observed elevations of liver enzymes or even trends towards increasing liver enzymes with increasing dose. At the same time induction of amenorrhea was seen in a consistent fashion starting at a 3 mg daily dose as long as trough levels of the drug were observed. The

sponsor believes there is a direct correlation of symptomatic relief for uterine fibroids and endometriosis with induction of amenorrhea.

[redacted] Typically women are dosed for 4 months (120 days) after which time the drug is withdrawn to allow for menses to return. Once menses has occurred women may resume treatment for another dosing period. In this fashion the drug can be used to control the symptoms of endometriosis and fibroids until the onset of menopause.

6.2 Non-Clinical Data

[redacted]

[redacted]

6.3 Clinical Data/Human Experience

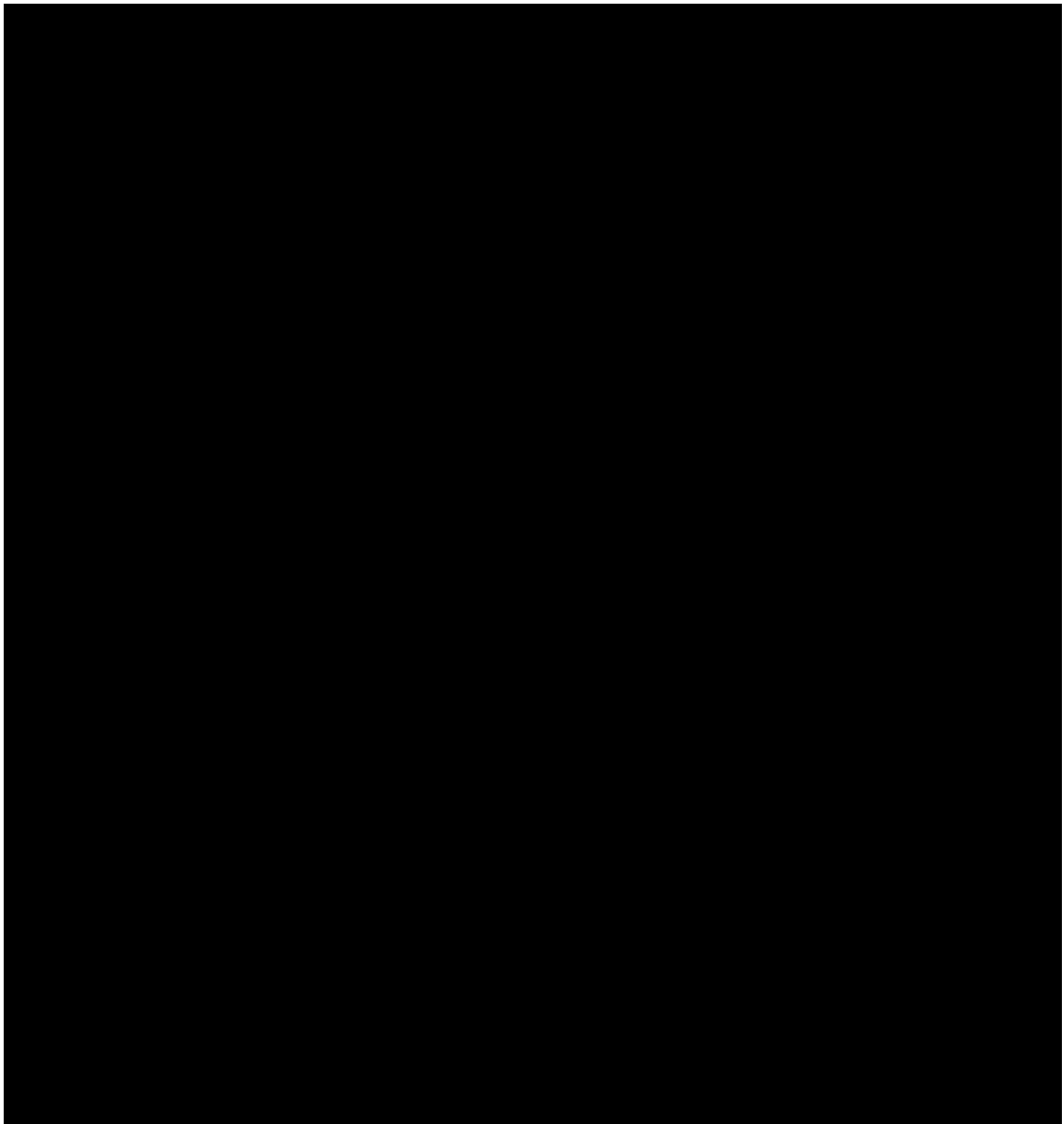
In addition to the preclinical studies, a Phase I/II study of orally administered Proellex in pre-menopausal women with symptomatic leiomyomata had been completed. The objectives of this study were to test the safety, efficacy, and pharmacokinetics of three doses of Proellex (12.5 mg, 25 mg, and 50 mg) administered as a once daily dose for 90 days, with study visits at one-month intervals. The safety and effectiveness of Proellex was compared to placebo and the active control leuprolide acetate for depot suspension (Lupron Depot). At the conclusion of this study, exploratory analyses showed statistically significant efficacy differences between treatment groups (overall and pair-wise).

[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. IntegReview, 3815 S. Capital of Texas Highway, Suite 320, Austin, TX 78704, will serve as an Institutional Review Board (IRB) for clinical sites who will accept their review.

6.6 Drug Safety Monitoring Board (DSMB)

A DSMB will review the data from any subject who has elevation of LFTs ≥3 x ULN and/or a bilirubin level ≥2 x ULN.

7. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this study is to determine the safety of orally administered Proellex administered at 12 mg/day for up to 3 courses of treatment (18 weeks each), each separated by an Off-Drug Interval (ODI), to women who have completed either ZPV-201 or ZPU-203.

To further investigate the effect of the timing of start of dosing upon the onset of amenorrhea, at selected sites the start of dosing in each cycle will be on the first day of bleeding rather than 0-4 days after stopping bleeding.

8. TRIAL DESIGN

8.1 Study Endpoints

- Percentage of subjects who become amenorrheic over the course of the study
- Change in UFS-QOL Symptom Severity Score comparing to the previous study baseline and study baseline
- Change in the individual UFS-QOL subscores over the course of the study
- Change in PBAC scores over the course of the study
- Percentage change from parent study baseline and study baseline in total uterine fibroid volume measured by MRI

8.2 Study Design

8.2.1 Overview of Study Design

This study is an open-label, multi-center extension study to evaluate the safety of continued treatment with Proellex in subjects who successfully completed either study ZPV-201 or ZPU-203. The study requires 16 visits and is approximately 13 months in duration. Subjects will be treated orally with 12 mg Proellex/day for three 18-week courses, each separated by an ODI. Subjects will use only sanitary supplies provided by the sponsor. Throughout the study women will record study information in the diaries and questionnaires as outlined in the study procedures.

Any subject who has **any** 28-day period during treatment (not including the ODIs) without a bleeding score >1 will be deemed to have achieved amenorrhea (in both the current or the previous study). Visit 1 of this study will also be Visit 24 of the previous study unless

the subject failed to achieve amenorrhea in the previous study. Such subjects may enroll at Visit 19 (after first recovery menses) in the previous study. Subjects who do not achieve amenorrhea after 8 weeks of treatment in this study will exit the study.

The start of the first 18-week course of treatment (Course 1) should commence no later than 4 days after the end of bleeding in the last menses, which should coincide with Visit 19 or 24 of the previous study. Once dosing for Course 1 is stopped, subjects will be followed until menses returns. The start of the second and third 18 week courses of treatment (Courses 2 and 3) will commence no later than 4 days after the end of bleeding following withdrawal of drug after the previous course has been completed.

At *selected sites* subjects will commence dosing on the first day of bleeding in their next menstrual cycle after Visit 19 or Visit 24 (about 3 weeks after V19 or 24). The start of the second and third courses of treatment will start on the first day of bleeding in the subject's *second* menses following withdrawal of drug.

During the ODI, subjects will continue to record study information in the daily paper diary.

After completion of 3 courses of treatment, subjects will be followed through the subsequent menstrual event (recovery menses).

A DSMB will review any liver safety events (LFTs ≥3 x ULN or bilirubin ≥2 x ULN) .

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, 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

As the study is open-label there will be no randomization or blinding.

8.2.4 Study Medication

All study drugs will be supplied by Repros Therapeutics Inc. Test drug, Proellex will be supplied in 40 count bottles and will be packaged by a clinical supplies contract vendor designated by Repros Therapeutics Inc. [redacted]

[redacted] and instructions to take 1 capsule daily in the morning with 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]

[redacted]

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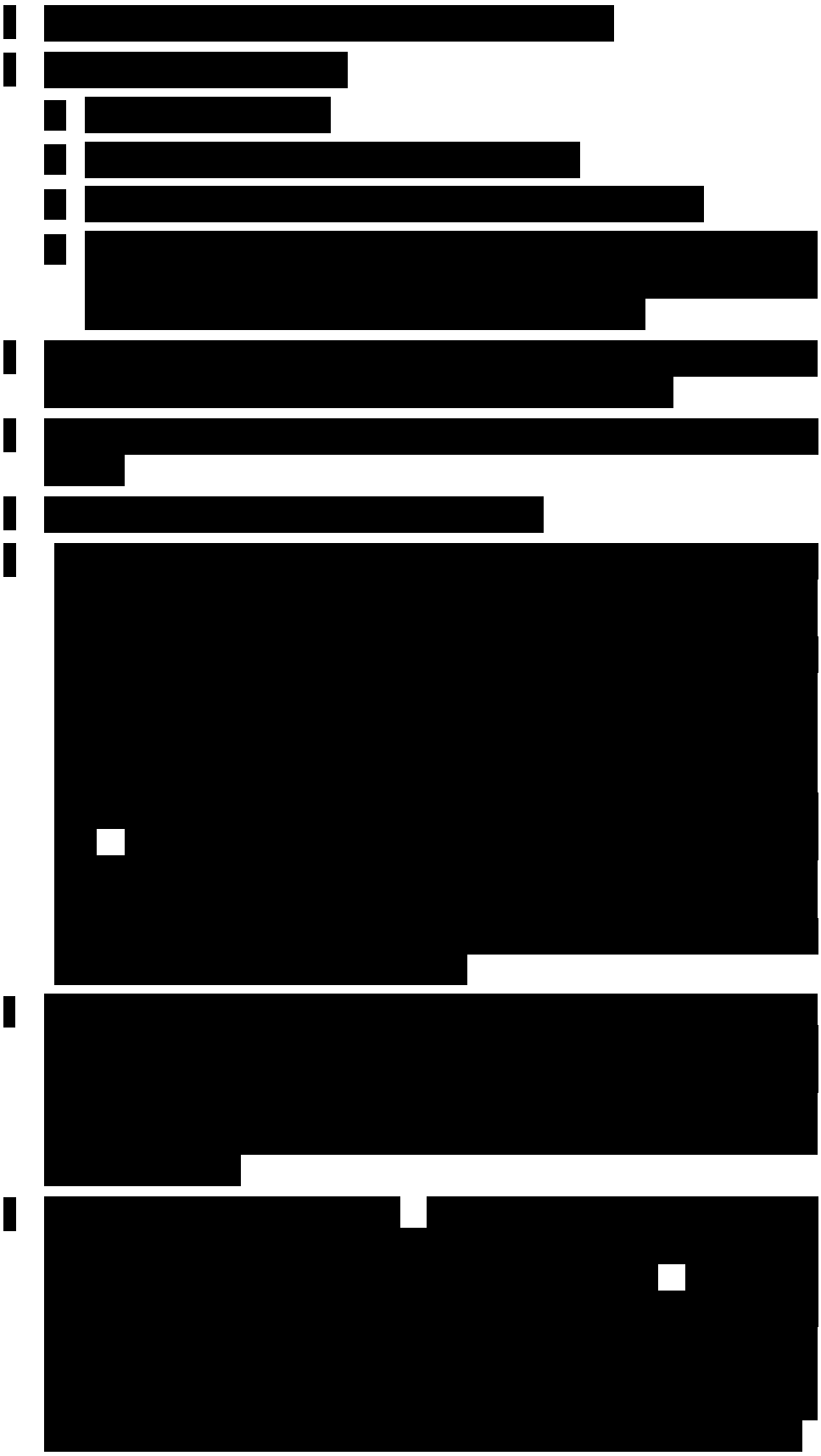


8.3.1 Inclusion Criteria

Subjects must meet the following criteria:

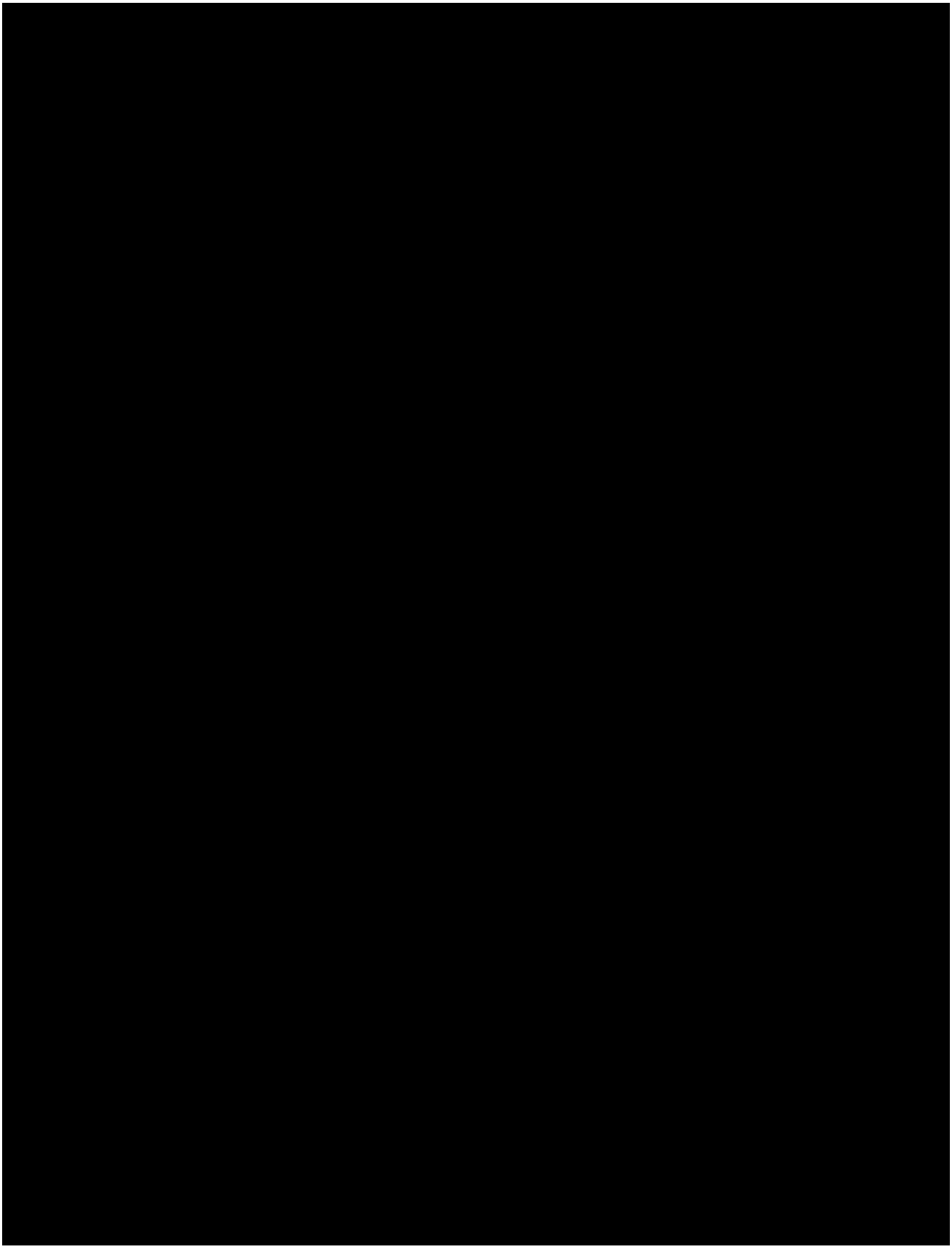
- Completed either study ZPV-201 or ZPU-203
- Agreement not to attempt to become pregnant during the trial
- Agreement to use alcohol in moderation and record the daily consumption (note: elevated liver enzymes may result in discontinuation from the study)
- Ability to complete a daily subject diary and study procedures in compliance with the protocol
- Agreement to use **only** sanitary supplies provided by the sponsor throughout the study
- Women of child-bearing potential must be willing to use double-barrier contraception during the study and off-drug intervals. 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 Visit 1
- Subject is available for all treatment and follow-up visits

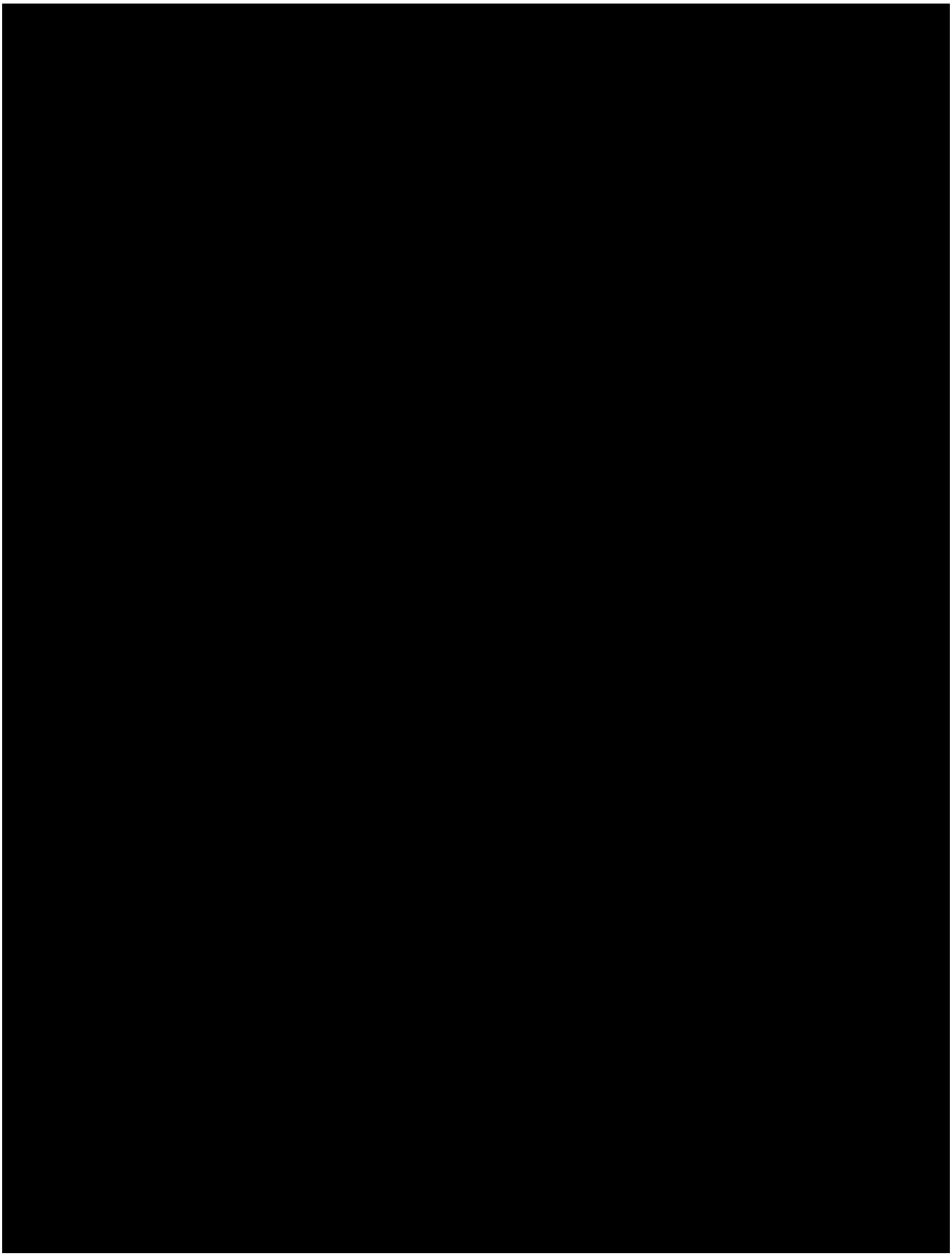
8.3.2 Exclusion Criteria

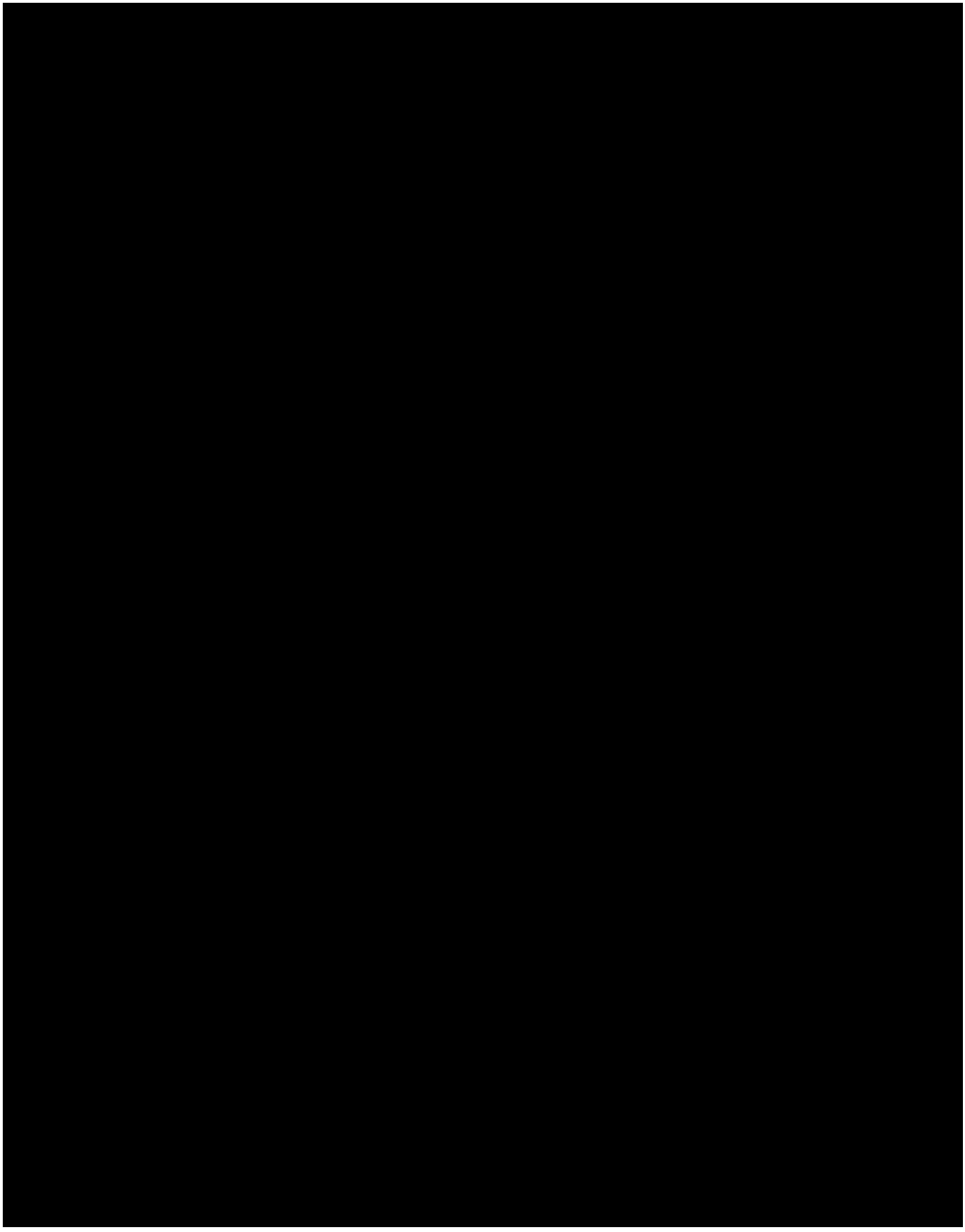
Subjects meeting any of the following criteria will be excluded from the study:

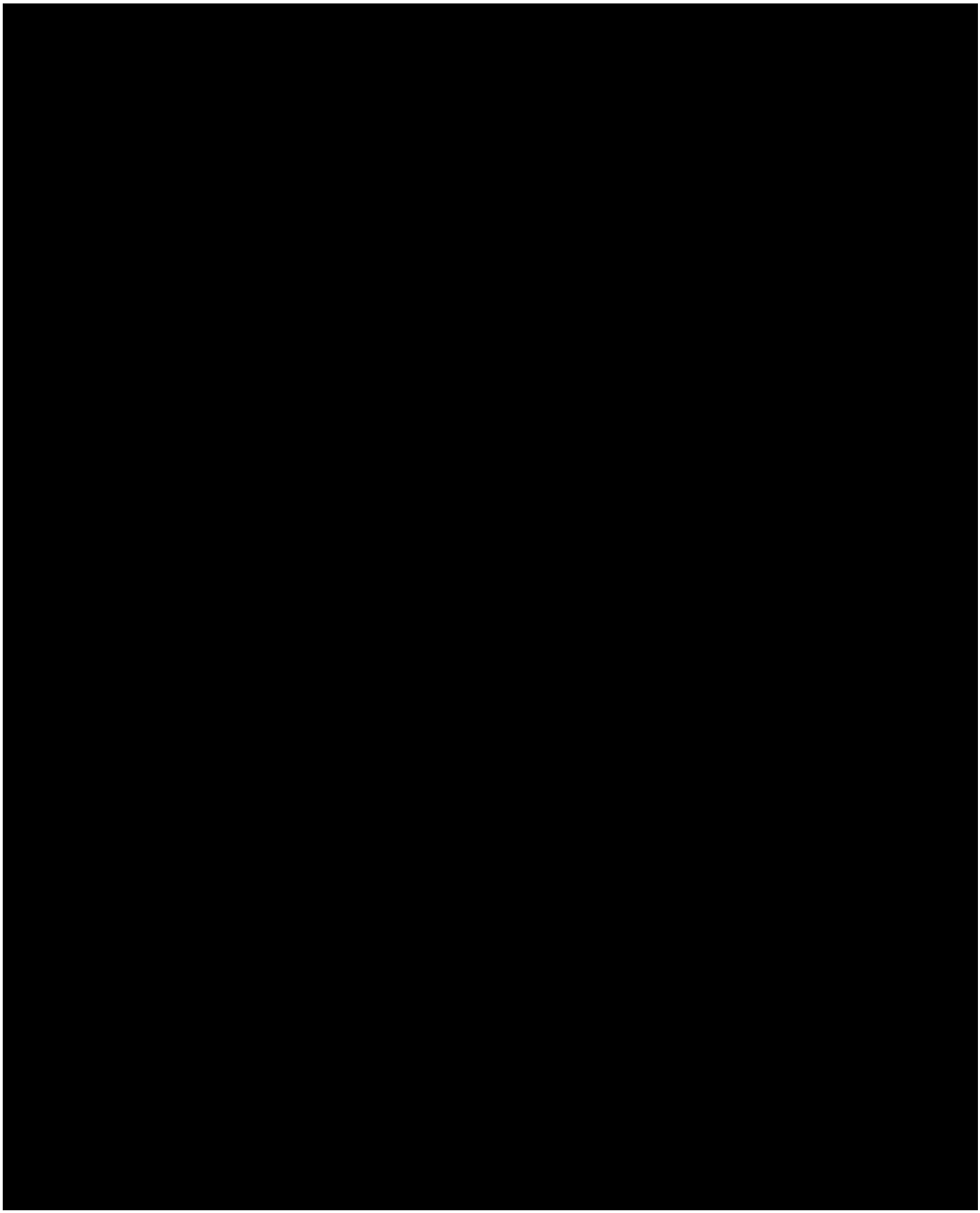
- Subject had a significant decrease in bone mineral density while participating in ZPV-201 or ZPU-203 (total hip or spine measurement decreased by more than 5%)
- Subject has undergone hysterectomy and/or bilateral oophorectomy since enrollment in ZPV-201 or ZPU-203.
- Subject is pregnant or lactating or is attempting or expecting to become pregnant during the entire study period
- Subjects with abnormally high liver enzymes or liver disease. (ALT or AST exceeding 2 x ULN AND total bilirubin exceeding 1.5 x ULN at Visit 1 and confirmed on repeat).
- Subject has a hemoglobin of <7.5 g/dL at Visit 1
- At sponsor discretion, subject had poor compliance in study ZPV-201 or ZPU-203
- Concurrent use of any testosterone, progestin, androgen, estrogen, anabolic steroids, DHEA or hormonal products for at least 2 weeks prior to Visit 1

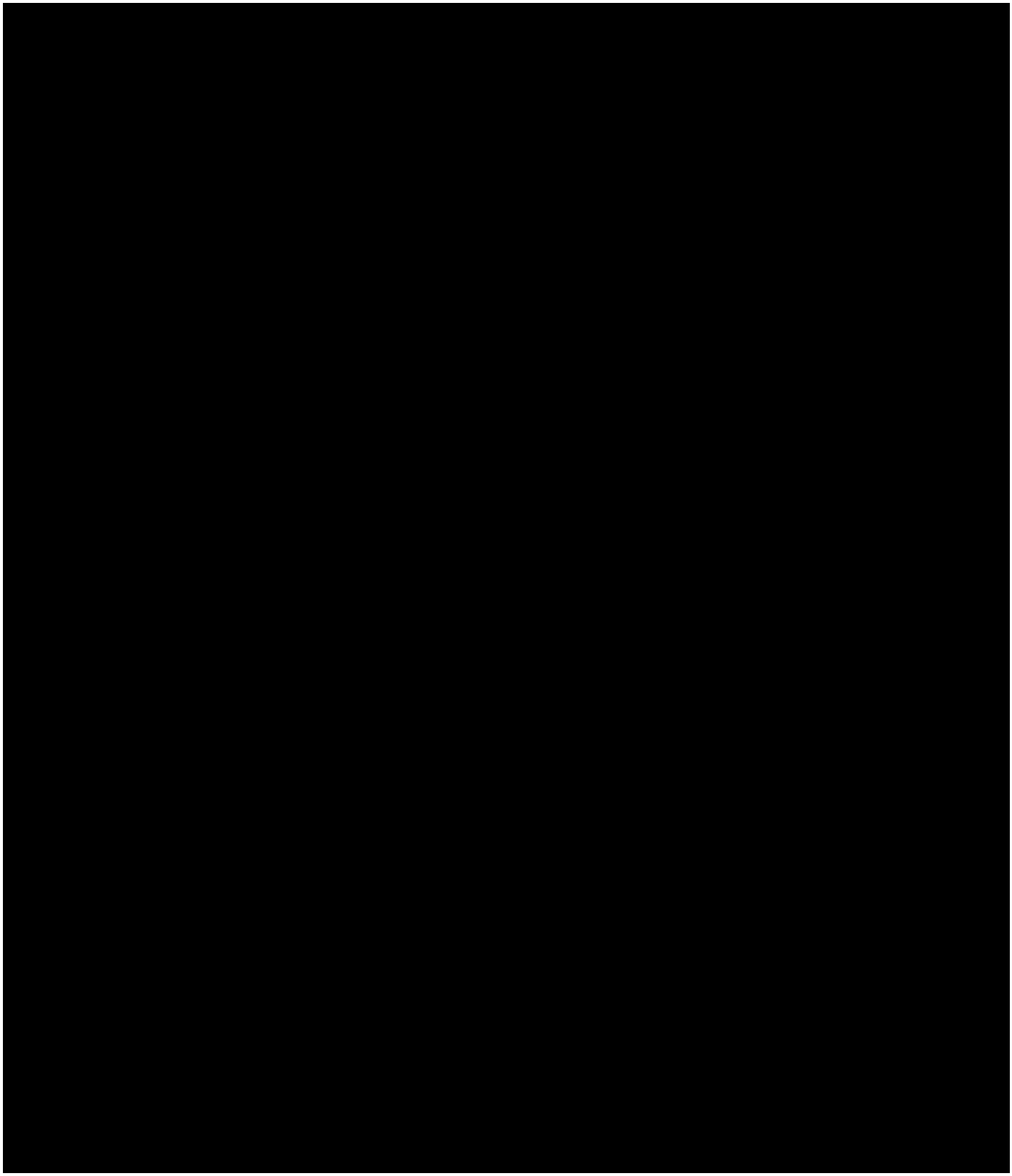
- Use of oral contraceptives in the 30 days preceding screening. Use of Depo-Provera® in the preceding 10 months.
- Use of GnRHas (e.g. Lupron Depot) within 3 months prior to screening (Lupron Depot must have a wash-out period of 3 months prior to screening)
- Has an IUD in place
- Current cervical dysplasia classified as Atypical Squamous Cells of Undetermined Significance (ASCUS) associated with high-risk human papilloma virus (HPV)
- Current diagnosis of Low/High Grade Squamous Intraepithelial Lesion (LGSIL or HGSIL), endometrial polyps or hyperplasia
- Observation or history of abnormal endometrial biopsy including the presence of EIN
- Recent history (within past 6 months) of alcoholism or drug abuse
- Endometrial stripe ≥18 mm in thickness at Visit 1 (subject may be enrolled with sponsor approval)
- Subject is currently taking cimetidine or spironolactone or has taken them in the last 30 days
- Clinically significant abnormal findings on Visit 1 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 SAFETY

[redacted]

10.1 Adverse Events

10.1.1 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 and eDC. All SAEs and AEs reported by the subject or observed by the Principal Investigator for up to 30 days after the last dose of study medication will be individually listed. The signs and symptoms, time of onset (24-hour clock), duration, action taken and follow-up procedures will be reported.

10.1.2 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.

10.1.3 Serious Adverse Events (SAEs)

The Principal Investigator shall document all SAEs in a subject receiving study drug until completion of the study 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, and notifying the IRB.

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.

11. CONCOMITANT MEDICATIONS

11.1 Prohibited Medications

The following medications are prohibited during the study:

- Testosterone
- Progestin
- Androgen
- Estrogen
- Anabolic steroids
- DHEA
- Other hormonal products
- Any other treatment for uterine fibroids

11.2 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.

12. STATISTICAL METHODS

12.1 Determination of Sample Size

This is a extension study and the number of subjects will be dependent on the number of subjects completing the parent studies. No more than 60 subjects are expected to enroll.

12.2 Statistical and Analytical Plan

Analyses in this study will focus on comparison to two baseline assessments. One baseline is associated with the original parent study baseline and the other is associated with the 28-day period prior to the start of this extension study. Reference to baseline in this section refers to each baseline definition.

12.2.1 Demographics and Subject Characteristics

For all subjects included in this study, subject disposition and demographic data will be summarized. 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.

12.2.2 Incidence of Amenorrhea

The percentage of subjects who become amenorrheic during the 28 days leading up to the last day of dosing in each course will be determined. The incidence of amenorrhea during the entire course and after the 11^{th} day of the course will also be investigated.

A subject is deemed amenorrheic if they have no bleeding intensity score greater than 1 using the Daily Diary Card in Appendix 2 (spotting not requiring hygiene products) during the period.

12.2.3 Percentage Change in PBAC Scores

The percentage change in PBAC scores over each 28 day period of the course will be recorded and compared to baseline to determine onset of benefit. Additionally PBAC scores will be used to monitor the level of vaginal bleeding during the ODI.

Within treatment group paired t-tests will evaluate treatment effect. While the primary assessment will be after each 18 week treatment course, summaries will 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. Non-parametric methods will be employed as appropriate.

12.2.4 Percentage Change in Total and Individual Symptom Severity Scores for the UFSQOL

The UFSQOL has been validated as a three month look back

questionnaire. The survey will be administered at baseline and at the end of each course. Within group paired tests will be used to assess treatment effect. Non-parametric methods will be employed as appropriate. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

12.2.5 Percentage Change in Uterine Fibroid Volume by MRI

The percent change from baseline in total uterine fibroid volume will be determined at the end of treatment. This study will assess up to 3 fibroids present at baseline in each subject. The volume of these 3 fibroids will be summed to determine the total uterine fibroid volume at each assessment.

Within group paired tests will be used to assess treatment effect. Non-parametric methods will be employed as appropriate. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

[redacted]

12.3 General Statistical Issues

A Statistical Analysis Plan (SAP) will be finalized prior to unblinding the study. For the efficacy variables a last observation forward approach will be used to impute missing data to generate a complete ITT data. If there are no post-baseline efficacy data then a value of no change will be imputed for the

missing efficacy measure. Statistical significance will be declared if the two-sided p-value is ≤ 0.05. [redacted]

13. ETHICS

13.1 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.

13.2 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.

13.3 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.

13.4 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.

13.5 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.

13.6 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.

13.7 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.

14. INVESTIGATOR'S STATEMENT

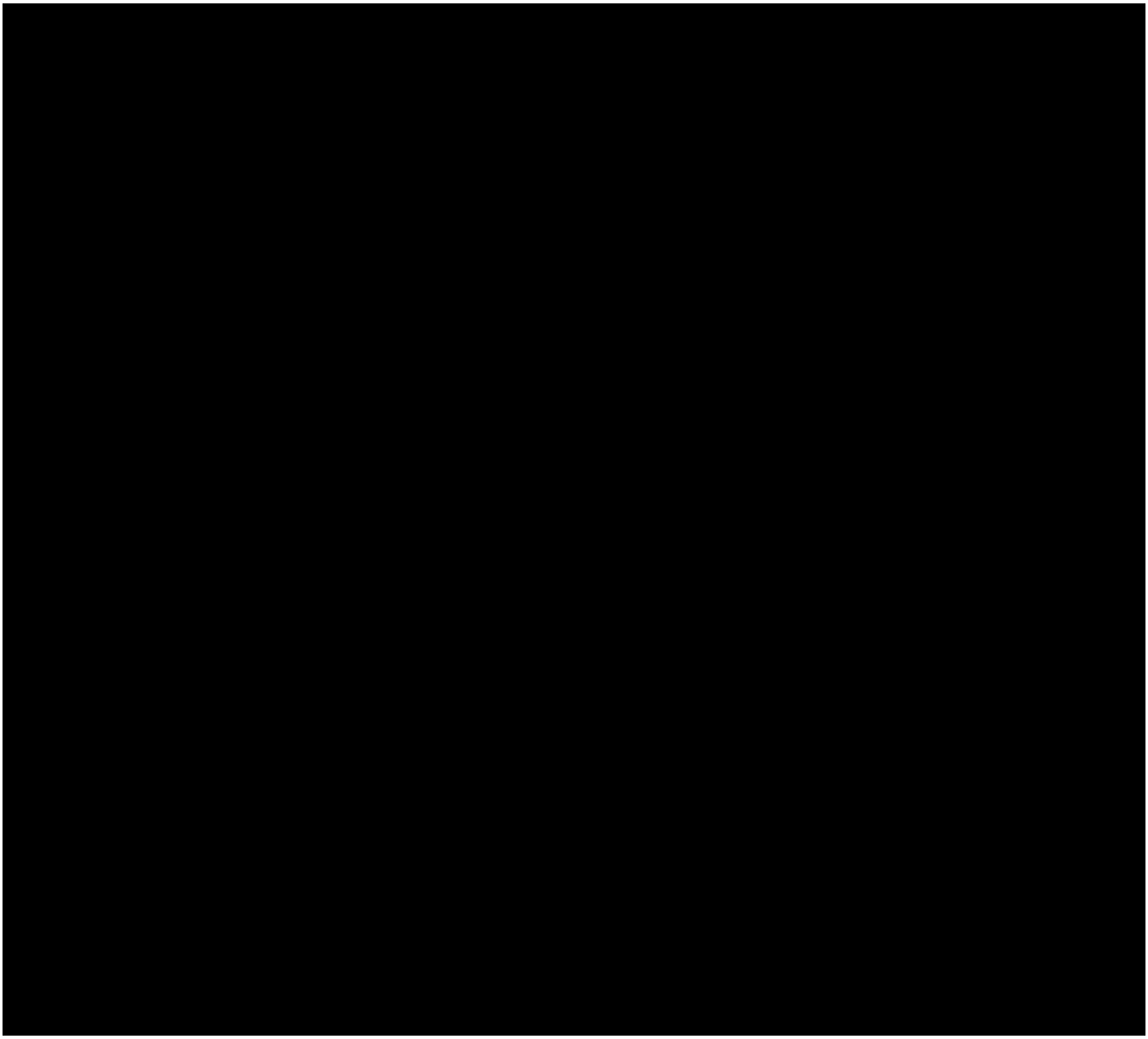
I have reviewed the ZPU-203EXT protocol and Investigator Brochure and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

_____ _____

Investigator Date

_____

Printed name



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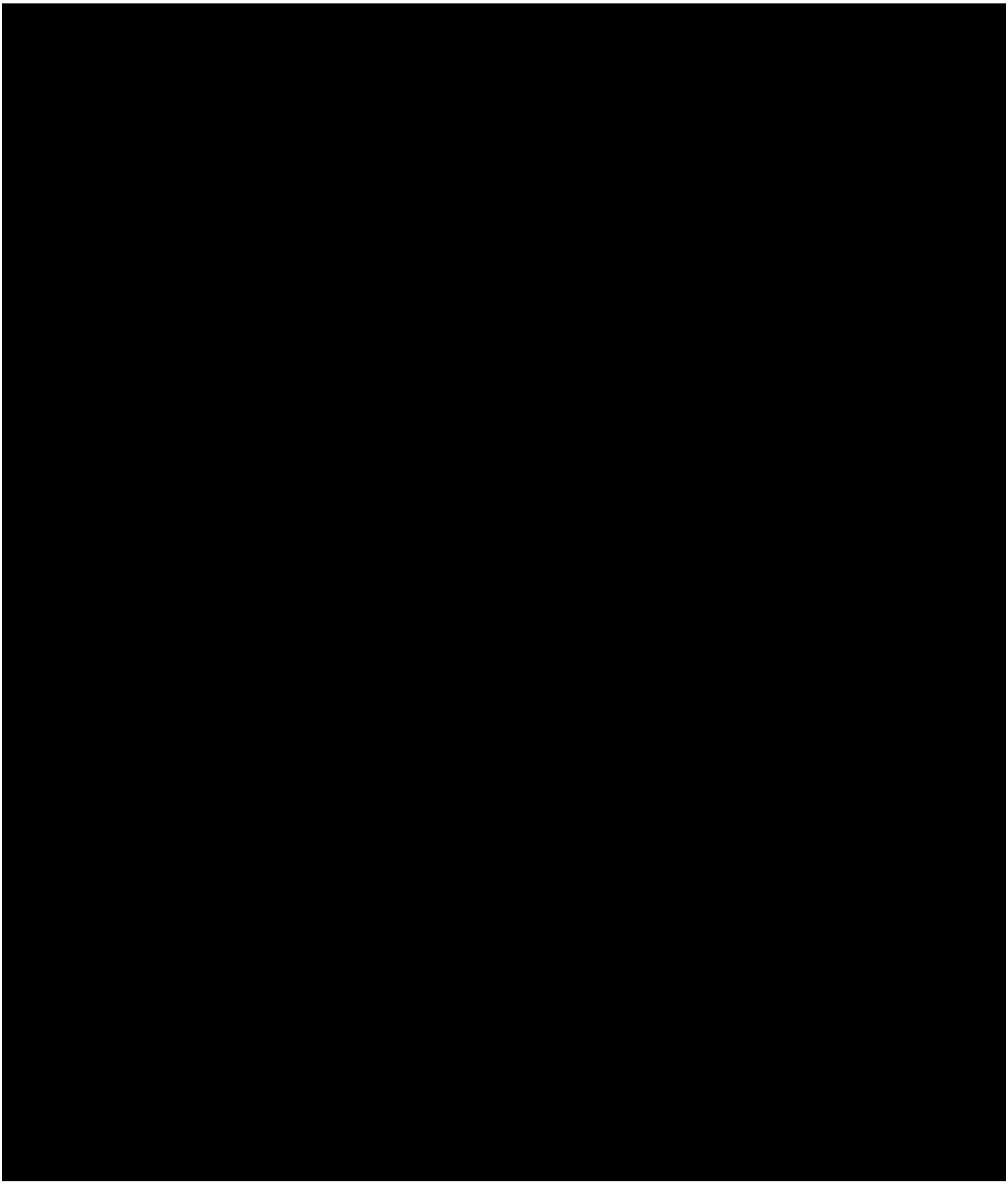

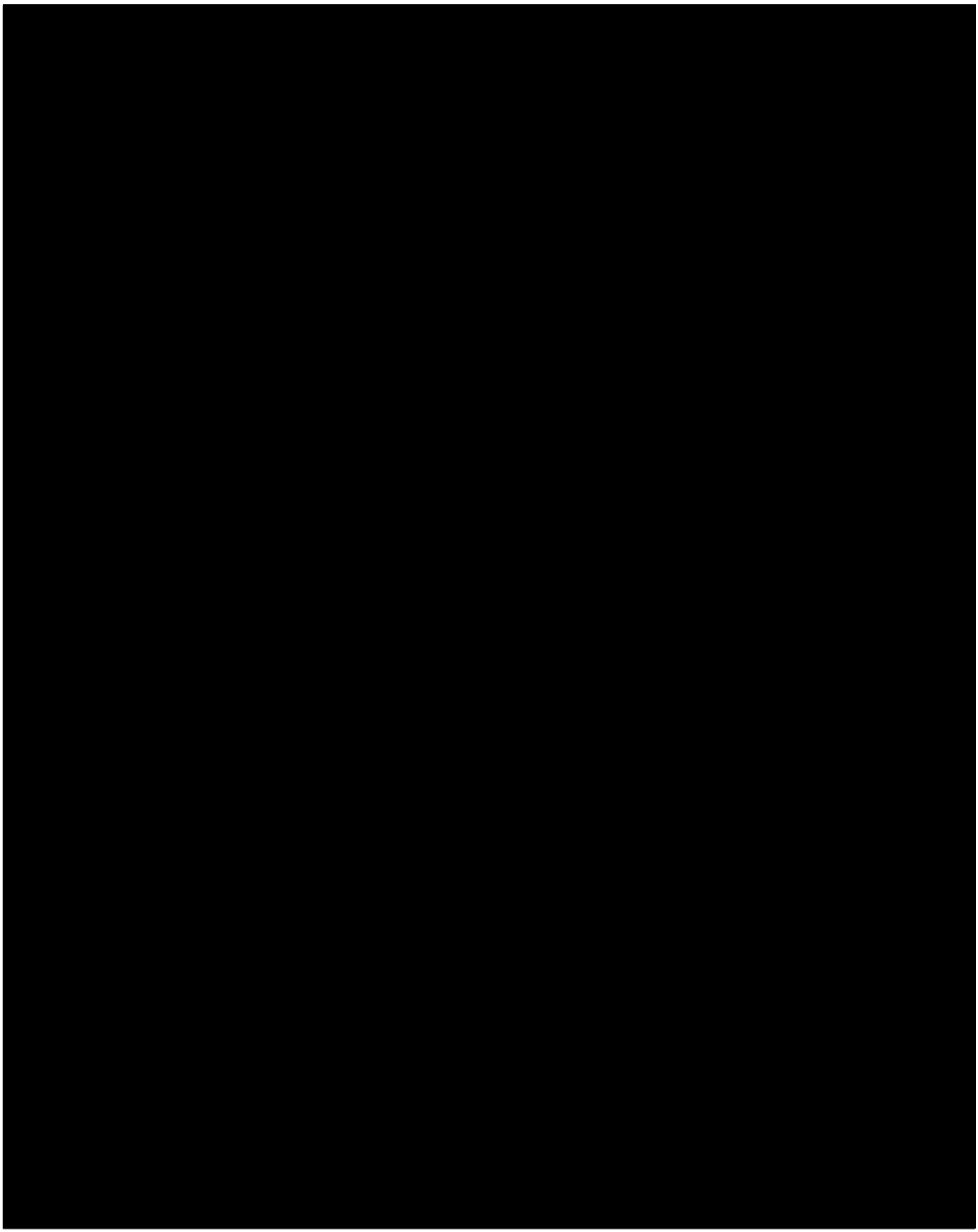

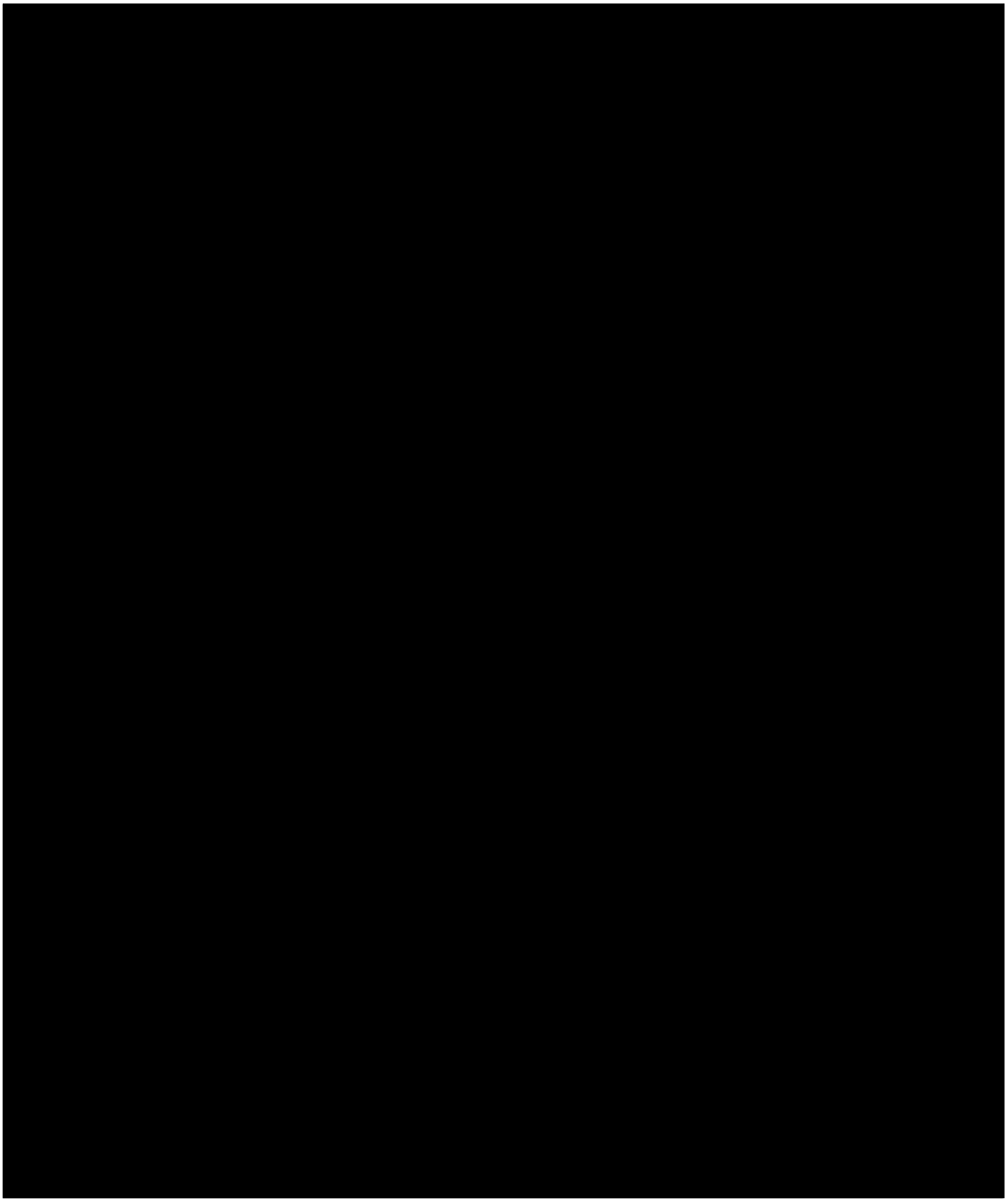

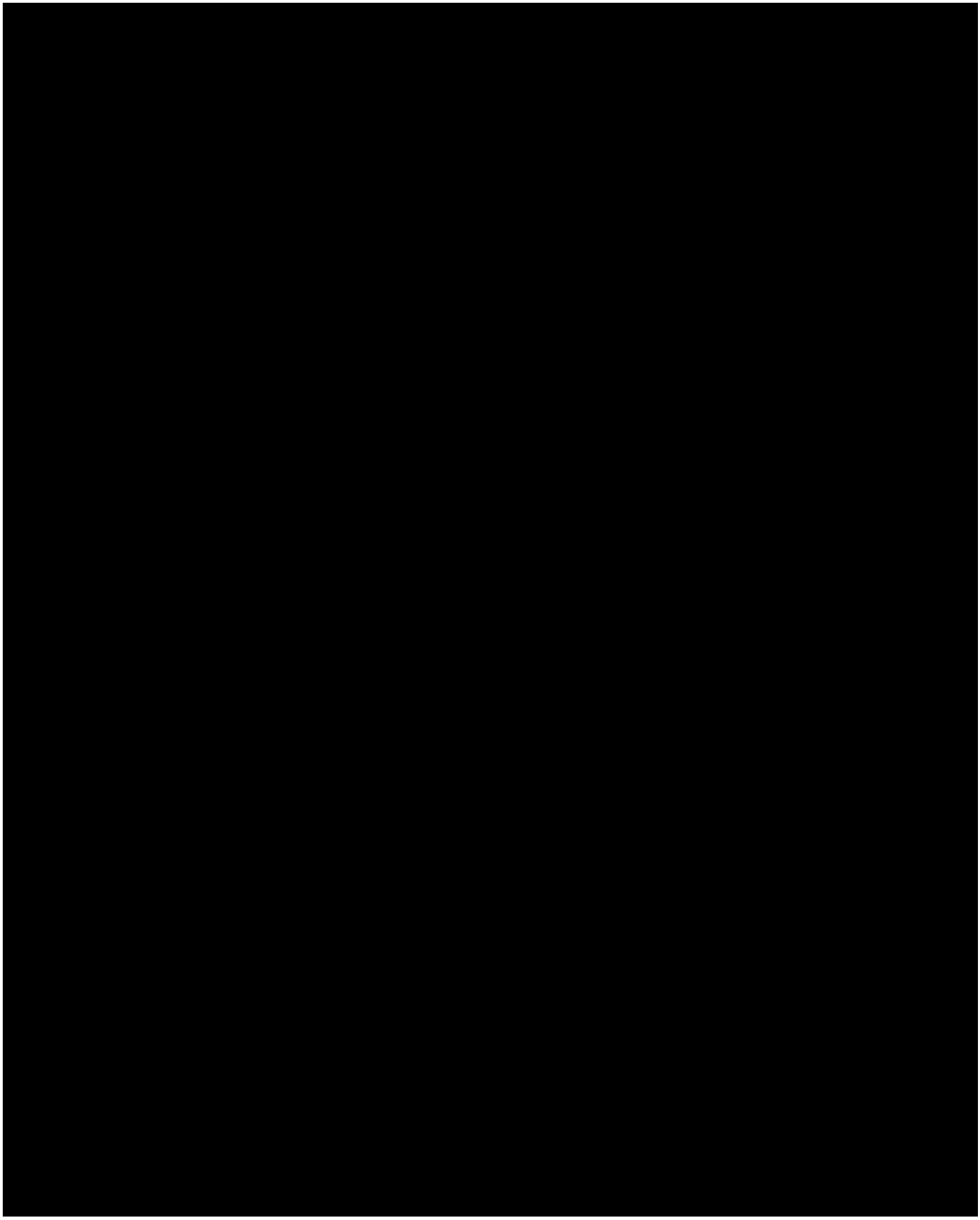

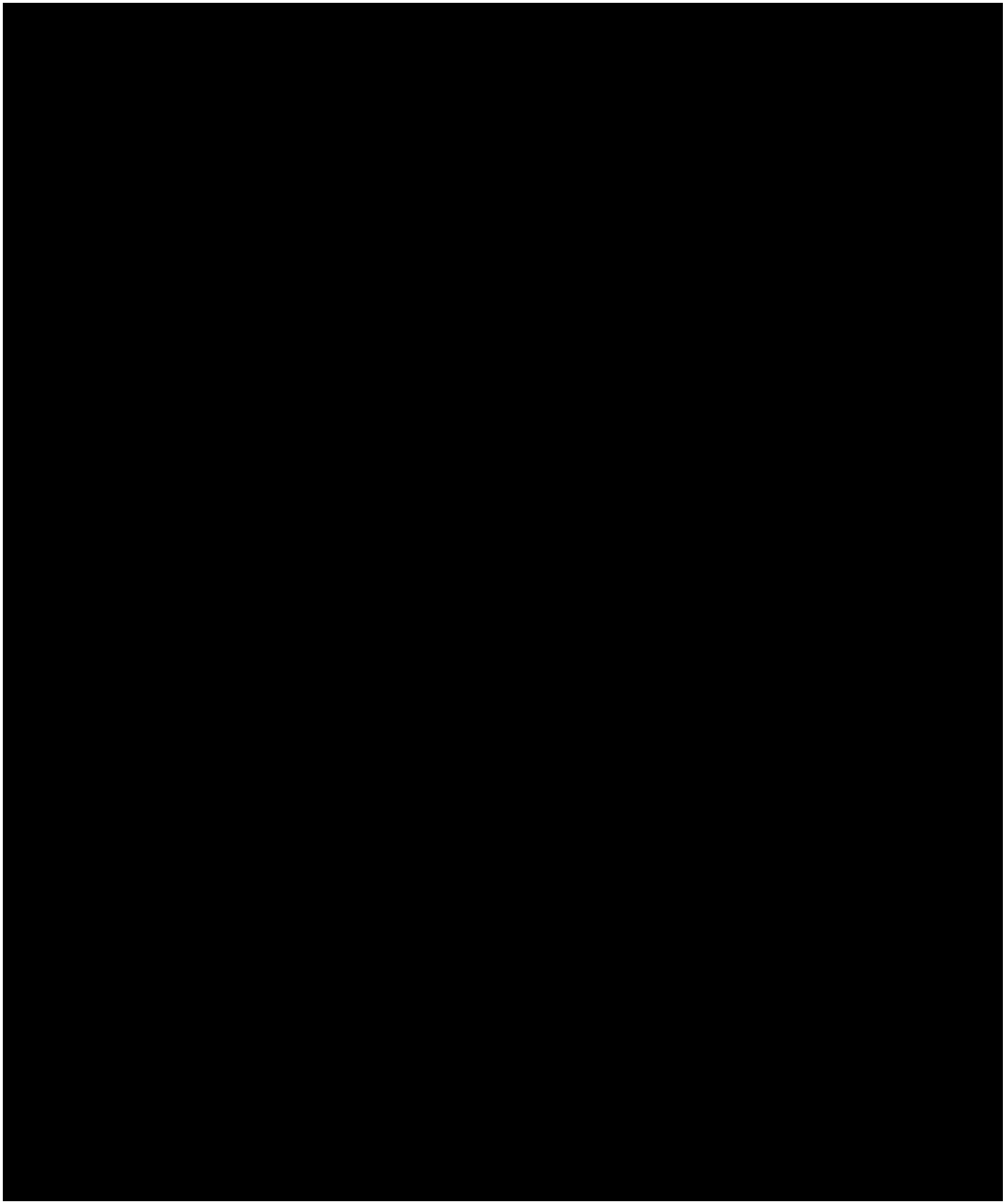

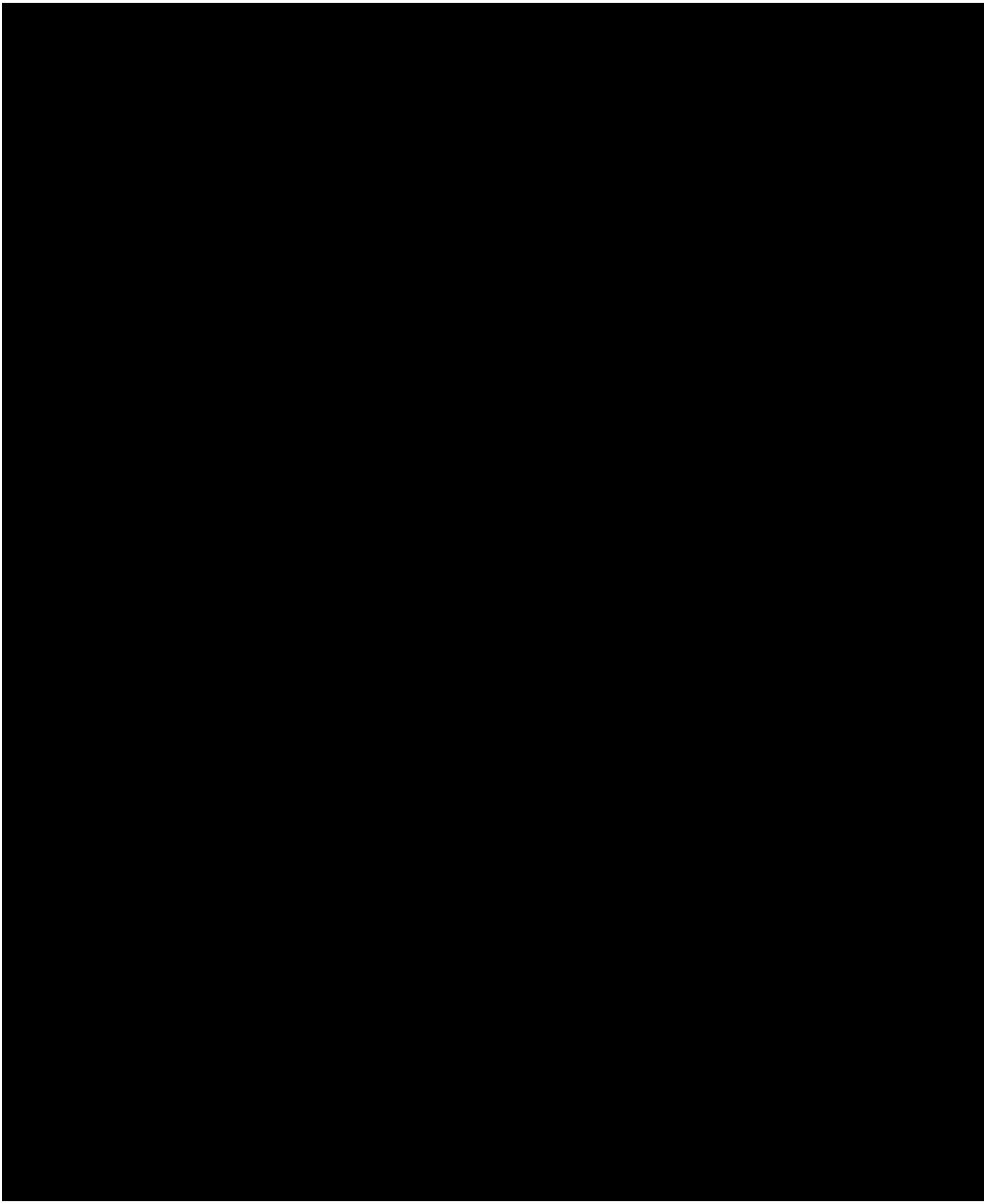

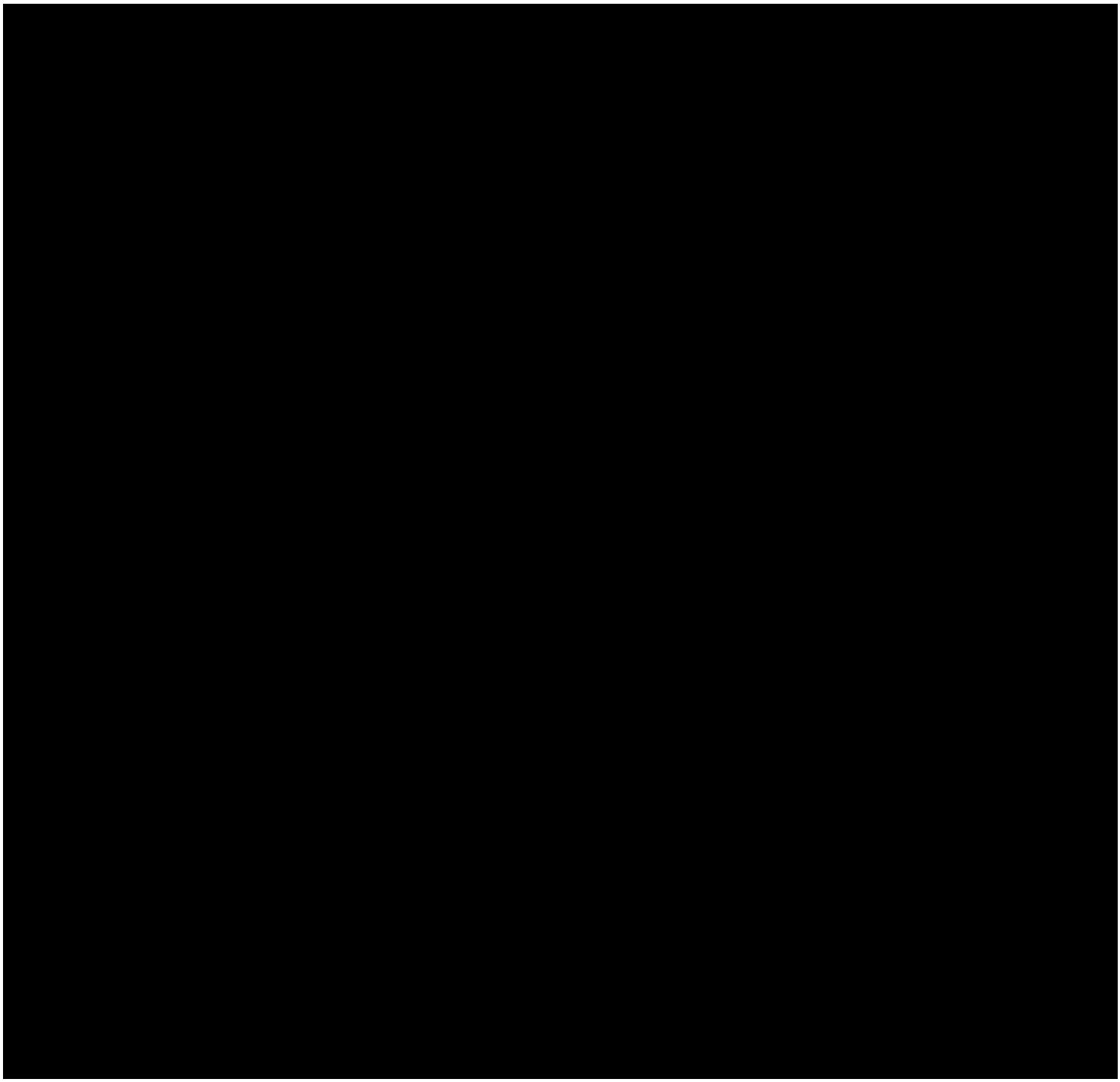

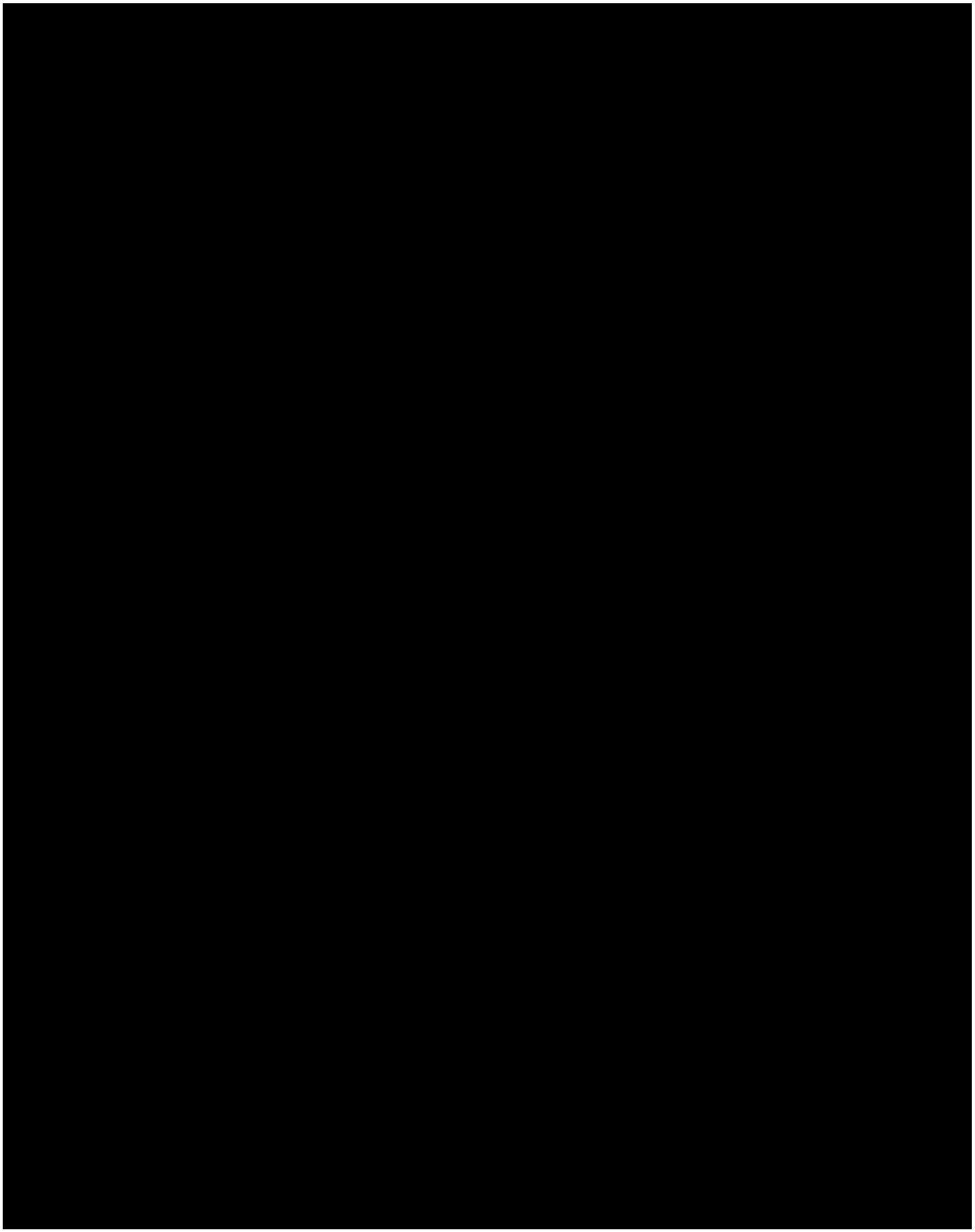

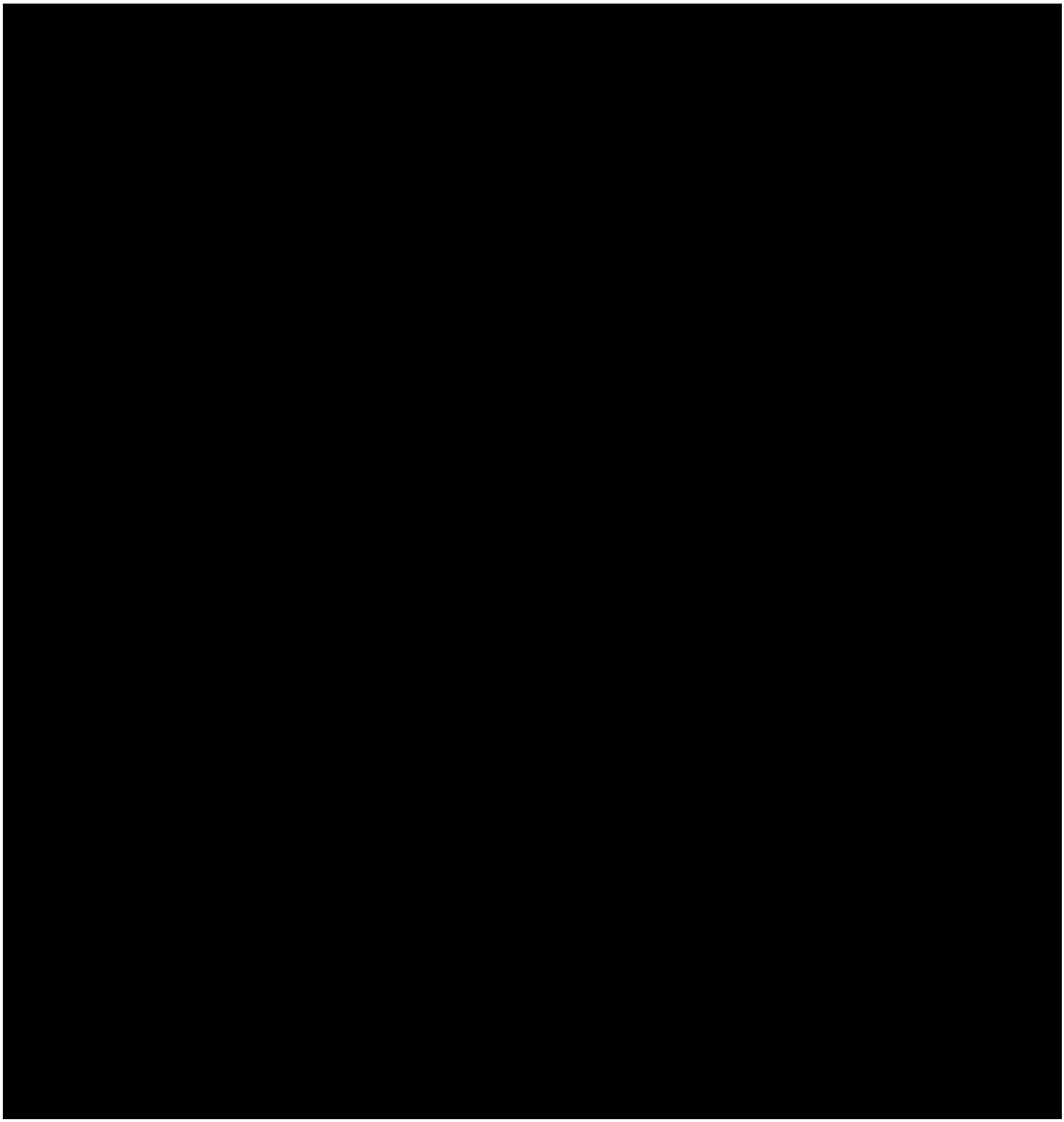

ZPU-203EXT Amendment 1 Protocol Summary of Changes

Protocol Title: An Open-Label Extension Study of 12 mg Proellex® (Telapristone Acetate) Administered Orally in the Treatment of Premenopausal Women with Confirmed Symptomatic Uterine Fibroids

Changes From: From Original Protocol dated June 22, 2016 To: Protocol Amendment 1 dated July 13, 2016

Reason for Amendment: To add a different start of dosing date for selected sites

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
PROTOCOL SYNOPSIS: Study Design and Duration of Treatment	The study requires 16 visits and is approximately 13 months in duration	**Statement added:** The study requires 16 visits and is approximately 13 months in duration **(up to 15 months for selected sites).** **At *selected sites* subjects will commence dosing on the first day of bleeding in their next menstrual cycle after Visit 19 or Visit 24 (about 3 weeks after V19 or 24). The start of the second and third courses of treatment will start on the first day of bleeding in the subject's second menses following withdrawal of study drug.**	Change in design to investigate change in start of dosing
PROTOCOL SYNOPSIS Study Endpoints	• Changes in clinical laboratory results ~~to values significantly outside of normal range~~ • Changes in liver function ~~to~~ values ~~outside the normal range~~ • ~~Change in~~ Endometrial thickness assessed using vaginal ultrasounds • ~~Changes in~~ the endometrium o~~ver the~~	• Changes in clinical laboratory results • Changes in liver function values • Endometrial thickness assessed using vaginal ultrasounds • **Pathology of** the endometrium **assessed by biopsies**.	Corrections

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	~~course of the treatment and ODI period (half of the subjects will be assigned to biopsy on the last day of treatment and half will undergo a biopsy after recovery menses).~~		
PROTOCOL SYNOPSIS Statistical Methods	Continuous efficacy endpoints, such as the change from baseline in uterine tumor volumes will assess treatment effect using a within-group t-test or appropriate non-parametric technique. ~~Other continuous efficacy variables will be treated similarly.~~ The percentage of subjects becoming amenorrheic will be determined. Safety and tolerability will be assessed [redacted]	Continuous efficacy endpoints, such as the change from baseline in uterine tumor volumes will assess treatment effect using a **within-group** t-test or appropriate non-parametric technique. The percentage of subjects becoming amenorrheic will be determined. [redacted]	Corrections
7. TRIAL OBJECTIVES		**Statement added:** **To further investigate the effect of the timing of**	Change in design to

ZPU-203EXT Amendment 1 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
AND PURPOSE		**start of dosing upon the onset of amenorrhea, at selected sites the start of dosing in each cycle will be on the first day of bleeding rather than 0-4 days after stopping bleeding.**	investigate change in start of dosing
8. TRIAL DESIGN **8.1 Study Endpoints**	[redacted]	[redacted]	Corrections
8.2.1 Overview of Study Design		**Statement added:** **At *selected sites* subjects will commence dosing on the first day of bleeding in their next menstrual cycle after Visit 19 or Visit 24 (about 3 weeks after V19 or 24). The start of the second and third courses of treatment will start on the first day of bleeding in the subject's *second* menses following withdrawal of drug.**	Change in design to investigate change in start of dosing
[redacted]	[redacted]	[redacted]	[redacted]

ZPU-203EXT Amendment 1 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted]	[redacted]	
8.3.2 Exclusion Criteria	• Subject had a significant decrease in bone mineral density while participating in ZPV-201 or ZPU-203 (total hip or spine measurement decreased by ~~5% or more~~)	• Subject had a significant decrease in bone mineral density while participating in ZPV-201 or ZPU-203 (total hip or spine measurement decreased by **more than 5%)**	Correction
[redacted]	[redacted]	[redacted]	[redacted]

ZPU-203EXT Amendment 1 Protocol Summary of Changes

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

ZPU-203EXT Amendment 1 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]			

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted]		
10.1.1 Reporting Adverse Experiences	~~After Visit 20, all SAEs and any adverse events that the investigator considers to be due to the study drug (e.g. hepatotoxicity) and not those considered to be due to withdrawal of the drug (e.g. vaginal bleeding), will be collected.~~		Correction
12. STATISTICAL METHODS **12.2 Statistical and Analytical Plan**		**Statement added:** **Analyses in this study will focus on comparison to two baseline assessments. One baseline is associated with the original parent study baseline and the other is associated with the 28-day period prior to the start of this extension study. Reference to baseline in this section refers to each baseline definition.**	Clarification
12.2.2 Incidence of Amenorrhea	The percentage of subjects who become amenorrheic during the 28 days leading up to the last day of dosing in each course will be determined.	The percentage of subjects who become amenorrheic during the 28 days leading up to the last day of dosing in each course will be determined. **The incidence of amenorrhea during the entire course and after the 11th day of the course will also be investigated.**	Clarification
12.2.3 Percentage Change in PBAC scores	The percentage change in PBAC scores over each 28 day period ~~for each menstrual cycle~~ will be recorded …. …..~~and the time to return to baseline vaginal bleeding to determine duration~~	The percentage change in PBAC scores over each 28 day period **of the course** will be recorded ….	Correction Correction

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	~~of benefit during the five menstrual cycle follow-up after dosing Course 2~~. Within treatment group paired t-tests will evaluate treatment effect. ~~Pairwise comparisons of the treatment groups will be made using a two-sample t test as well to compare the pooled Proellex doses to placebo.~~ While the primary assessment will be after 18 week ~~of treatment~~, summaries will be prepared for each of the other visits.	Within treatment group paired t-tests will evaluate treatment effect. While the primary assessment will be after **each** 18 week **treatment course**, summaries will be prepared for each of the other visits.	Correction
12.2.5 Percentage Change in Uterine Fibroid Volume by MRI	The percent change from baseline in total uterine fibroid volume will be determined at the end of ~~each 18 week dosing course~~	The percent change from baseline in total uterine fibroid volume will be determined at the end of **treatment**	Correction
[redacted]	[redacted]	[redacted]	[redacted]

ZPU-203EXT Amendment 1 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
12.3 General Statistical Issues	A Statistical Analysis Plan (SAP) will be finalized prior to ~~unblinding the study.~~	A Statistical Analysis Plan (SAP) will be finalized prior to **database lock.**	Correction
[redacted]	[redacted]		[redacted]