NCT02323646

Study ID: ZPV-201

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 4 Date: 20 June 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.

ZPV201 Protocol Amendment 1 Summary of Changes

Protocol 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

Changes From: From Original protocol, dated December 12, 2014 To: Protocol Amendment 1 dated February 24, 2015

Reason for Amendment: Change procedures, make corrections, add clarifications and change eligibility criteria

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
PROTOCOL SYNOPSIS: Study Population		**Subjects with evidence of prior heavy blood loss may be enrolled at the sponsor's discretion.**	Change in eligibility requirements
PROTOCOL SYNOPSIS: Study Procedures	An infectious disease screen will be conducted and a vaginal ultrasound will be performed [redacted] ~~and MRI~~ to confirm presence ~~and size~~ of uterine fibroids. Sanitary products and instructions for their collection will be provided and study questionnaires will be administered. [redacted] Subjects who meet the inclusion and exclusion criteria will be scheduled for Visit 2. [redacted]	An infectious disease screen will be conducted and a vaginal ultrasound will be performed [redacted] and to confirm presence of uterine fibroids. Sanitary products and instructions for their collection will be provided and study questionnaires will be administered. [redacted] Subjects who meet the inclusion and exclusion criteria will be scheduled for Visit 2. At visit 2, [redacted] **an MRI to confirm the presence and size of uterine fibroids**.	Correction
PROCEDURES AND	MRI of Uterine Fibroids	MRI of Uterine Fibroids **(no contrast)**	Correction

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
LABORATORY TABLES: Table 1	3.. Also ~~in the event of a finding of abnormal LFT~~ **7.** A historical PBAC looking back over the last 28 days will be used to determine eligibility (must be >120 mL, and verified by Alkaline Hematin as ≥80mL). 11. ~~For subjects who had finished bleeding 5 days or less before Visit 1~~, Visit 2 will occur within +4 days after end of bleeding in the~~ir~~ first menstrual event after Visit 1. ~~For everyone else Visit 2 will occur within + 4 days after end of bleeding in the second menstrual event after Visit 1~~.	**3.** Also **as necessary to evaluate possible hepatic abnormalities** **7.** A historical PBAC looking back over the last 28 days will be used to determine eligibility (must be >120 mL, **unless approved by sponsor**, and verified by Alkaline Hematin as ≥80mL). 11. **A complete menstrual event must be collected before Visit 2. If subject is bleeding at Visit 1, she must wait until the last day of bleeding of this cycle, then start collecting pads the following day until the last day of bleeding in the next menstrual event**. Visit 2 will occur within +4 days after end of bleeding in the first **complete** menstrual event after Visit 1.	Change in procedure
[redacted]	[redacted]	[redacted]	[redacted]
PROCEDURES AND LABORATORY TABLES: Table 3		Hypotension Questions …. **The investigator should report any of the above as adverse events.**	Clarification
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	
8. TRIAL DESIGN **8.2.1 Overview of study Design**	In the first stage, women will undergo a baseline assessment period, with no treatment, until 15-20 days after the start of their second ~~or third~~ menstrual event. [redacted]	In the first stage, women will undergo a baseline assessment period, with no treatment, until 15-20 days after the start of their second **complete** menstrual event. [redacted]	Change in procedures
8.3 Selection and Withdrawal of Subjects	• A need arises for concomitant medication prohibited by the protocol	• A need arises for concomitant medication prohibited by the protocol, **unless use of such medication is approved by the sponsor**	

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
8.3.1 Inclusion Criteria	• Subject has a history of at least 3 regular menstrual cycles in which menorrhagia is due to uterine fibroids  •  MBL of at least 80 mL by Alkaline Hematin Assay (during the baseline assessment period).	• Subject has a history of at least 3 regular menstrual cycles in which menorrhagia is due to uterine fibroids **(a past or concurrent diagnosis of uterine fibroids is acceptable).**  • MBL of at least 80 mL by Alkaline Hematin Assay (during the baseline assessment period). **Subjects with evidence of prior heavy blood loss may be enrolled at the sponsor's discretion.**	Clarification 
8.3.2 Exclusion Criteria	• 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) • ~~Known or suspected carcinoma of the breast or reproductive organs~~	• 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**) • **History or current diagnosis of**	Change in Exclusion Criteria Clarification Clarification

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted]	**malignancy other than curatively treated basal cell carcinoma** [redacted]	[redacted]
	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted] ~~their next cycle (first cycle after Visit 1).~~	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]	[redacted]	[redacted]	
12. Statistical Methods **12.2 Statistical and Analytical Plan**		**A Statistical Analysis Plan (SAP) will be prepared prior to unblinding the data. 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 in Stage 2. In this Phase 2 study there will be no statistical corrections for interim analyses or multiple comparisons.** **For the statistical analysis at the end of the first course of treatment, only statistical staff will be unblinded. All clinical operations staff and staff at investigative sites will remain blinded until completion of the study.**	Clarification

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

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

ZPV-201 Amendment 2 Protocol Summary of Changes

Protocol 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

Changes From: From Protocol Amendment 1 dated February 24, 2015 To: Protocol Amendment 2 dated September 4, 2015

Reason for Amendment: Changes study requirements for endometrial stripe ≥18mm.

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
8.3 Selection and Withdrawal of Subjects	• [redacted]	[redacted] • Any subject who experiences heavy bleeding (bleeding intensity of 4 or more per the Daily Diary Card in Appendix 4) for 7 consecutive days or more will be discontinued from the study. This does not	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		apply if heavy bleeding occurs in the first recovery menses after withdrawal of drug at the end of Course 1 or Course 2, or is no heavier than bleeding was prior to treatment.	
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]		

ZPV-201 Amendment 3 Protocol Summary of Changes

Protocol 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

Changes From: From Protocol Amendment 2 dated September 4, 2015 To: Protocol Amendment 3 dated April 8, 2016

Reason for Amendment: Addition of Alkaline Hematin Assay at the end of Course 2

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	Subjects will collect and return used sanitary materials for alkaline hematin assay for their first menstrual event during screening, for the recovery menses following Course~~s~~ 1 ~~and 2~~ and for the 2nd, 4th and 6th menstrual cycles after end of treatment in Course 2.	Subjects will collect and return used sanitary materials for alkaline hematin assay for their first menstrual event during screening, for the recovery menses following Course 1, **for the 28 days leading up to the end of treatment in Course 2**, and for the **1st**, 2nd, 4th and 6th menstrual cycles after end of treatment in Course 2.	Addition of Alkaline Hematin assay at the end of Course 2
8.2.1 Overview of Study Design		Statement added: Sanitary products will be collected for alkaline hematin assay during the following timepoints: • **From the 28 days leading up to end of treatment in Course 2 (Visit 18)**	Addition of Alkaline Hematin assay at the end of Course 2
8.2.6 Endometrial Biopsies		Statement added: [redacted]	Clarification

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

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

Charts and footnotes were updated to reflect the changes above.

Repros THERAPEUTICS INC

Protocol Number: ZPV-201

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

Original Protocol: December 12, 2014
Amendment 1: February 24, 2015
Amendment 2: September 4, 2015
Amendment 3: April 8, 2016
Amendment 4: June 20, 2016

SPONSOR:

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

IND 112,576

[redacted]

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3. PROTOCOL SYNOPSIS

Test Drugs:	Proellex® (Telapristone Acetate): 6 and 12 mg vaginal capsules and matching placebo
Protocol Number:	ZPV-201
Study Purpose:	To determine the safety and efficacy of two doses of Proellex in premenopausal women with symptomatic (menorrhagia) uterine fibroids confirmed by MRI.
Study Design and Duration of Treatment:	This study is a phase 2 3-arm-study with two 18-week dosing courses. The study will be conducted in two stages. In the first stage, women will undergo a baseline assessment period with no treatment, until 15-20 days after the start of their second complete menstrual event. During this phase a pictorial blood loss assessment chart will be utilized as well as sanitary products collected from their first menstrual event, for alkaline hematin assay, to determine menstrual blood loss and confirm eligibility. In the second stage, subjects will be randomized into one of 3 arms in a 1-1-1 fashion and receive two 18-week courses of treatment at their randomized dose (6 mg, 12 mg or placebo), separated by an off-drug interval (ODI). The start of the first 18-week course of treatment (Course 1) should commence 15-20 days after the start of their previous menses. Subjects should be instructed to continue vaginal dosing during their menses throughout the study and not to have sex or insert anything in the vagina for at least 1 hour after the capsule is inserted. Once dosing for Course 1 is stopped, subjects will be followed until menses return. The start of the second 18 week course of treatment (Course 2) will commence 15-20 days after the start of their menses following withdrawal of drug after Course 1 has been completed. During the ODI, subjects will continue to record study information in the daily paper diary and PBAC charts as well as collect sanitary products for alkaline hematin assay. After completion of stage 2 dosing (Courses 1 and 2), subjects will be followed through the subsequent 6 menses (recovery menses plus an additional 5 menstrual events), the subject may be offered the opportunity to enroll in an open-label extension study. Subjects who fail to achieve amenorrhea may enroll in the extension study at Visit 19. Amenorrhea is defined as any 28-day period during treatment (not including the ODIs) without a bleeding score >1. Throughout the study women will record study information in the diary, PBAC, and questionnaires as outlined in the study procedures. Subjects will collect and return used sanitary materials for alkaline hematin assay for their first menstrual event during screening, for the recovery menses menses following Course 1, for the 28 days leading

	up to the end of treatment in Course 2, and for the 1st, 2nd, 4th and 6th menstrual cycles after end of treatment in Course 2.
Subject Population:	The study will enroll healthy adult, pre-menopausal women with confirmed uterine fibroids via MRI and confirmed menorrhagia (>120 mL blood loss per menstrual cycle by historical PBAC assessment, nominal 28 days to ensure a MBL of at least 80 mL by Alkaline Hematin Assay). Subjects with evidence of prior heavy blood loss may be enrolled at the sponsor's discretion.
Number of Subjects:	Up to 45 female subjects, 15 per dose arm
Number of Sites	Approximately 10 sites
Study Duration:	Total participation in the study is approximately 18 months.
[redacted]:	[redacted]
Study Endpoints	The primary endpoint will be: • Percentage of subjects who become amenorrheic after one course of treatment Secondary endpoints will be: • Percentage of subjects who become amenorrheic after 2 courses of treatment

	• Change and percentage change in PBAC score over the course of the study. Specifically comparing the baseline menstrual cycle to the matching end-of-study period leading up to Week 18 and the end of treatment as well as comparing the baseline PBAC to the ODI time periods. • Percentage change in UFSQOL Symptom Severity score (UFS-SSS) comparing Week 18 to Baseline (three month look back) and for the ODI. • Percentage change in the individual UFS-SSS sub scores • Percentage change from baseline in total uterine fibroid volume measured by MRI [redacted]
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 in Stage 2. 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. Continuous efficacy endpoints, such as the change from baseline in the alkaline hematin assay will assess treatment effect using a t-test or appropriate non-parametric technique. Pairwise comparisons between treatment groups will also be conducted with the same methods. Other continuous efficacy variables will be treated similarly. The percentage of subjects becoming amenorrheic within each treatment and dose group will be compared by Chi-square test or appropriate non-parametric method. Safety and tolerability will be assessed by evaluating physical exams, colposcopy findings and reported AEs as well as changes in values from baseline of clinical chemistry variables, hematology variables, hormone variables, and liver function variables. No formal hypothesis testing will be performed to compare the treatment groups. For the quantitative physical exam variables, laboratory variables and bone mineral density the statistical significance of the change from baseline to each of the post-baseline visits will be determined using a paired t-test.

[redacted]

1. Any LFT >ULN will be repeated.

   Subjects must be discontinued if 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, jaundice (skin or sclera) and/or eosinophilia (>5%)

Cases of liver transaminases that increase above 3 times the upper limit of normal must be reported as SAEs regardless of whether the SAE criteria specified in Section 10.1.2 are met.

5. LIST OF ABBREVIATIONS

AE	Adverse event
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
LSC	Least Significant Change
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-SSS	Uterine Fibroid Symptom Quality of Life Survey Symptom Severity Score (first 8 questions)
WBC	White blood cell

6. BACKGROUND INFORMATION

6.1 Rationale for Current Study

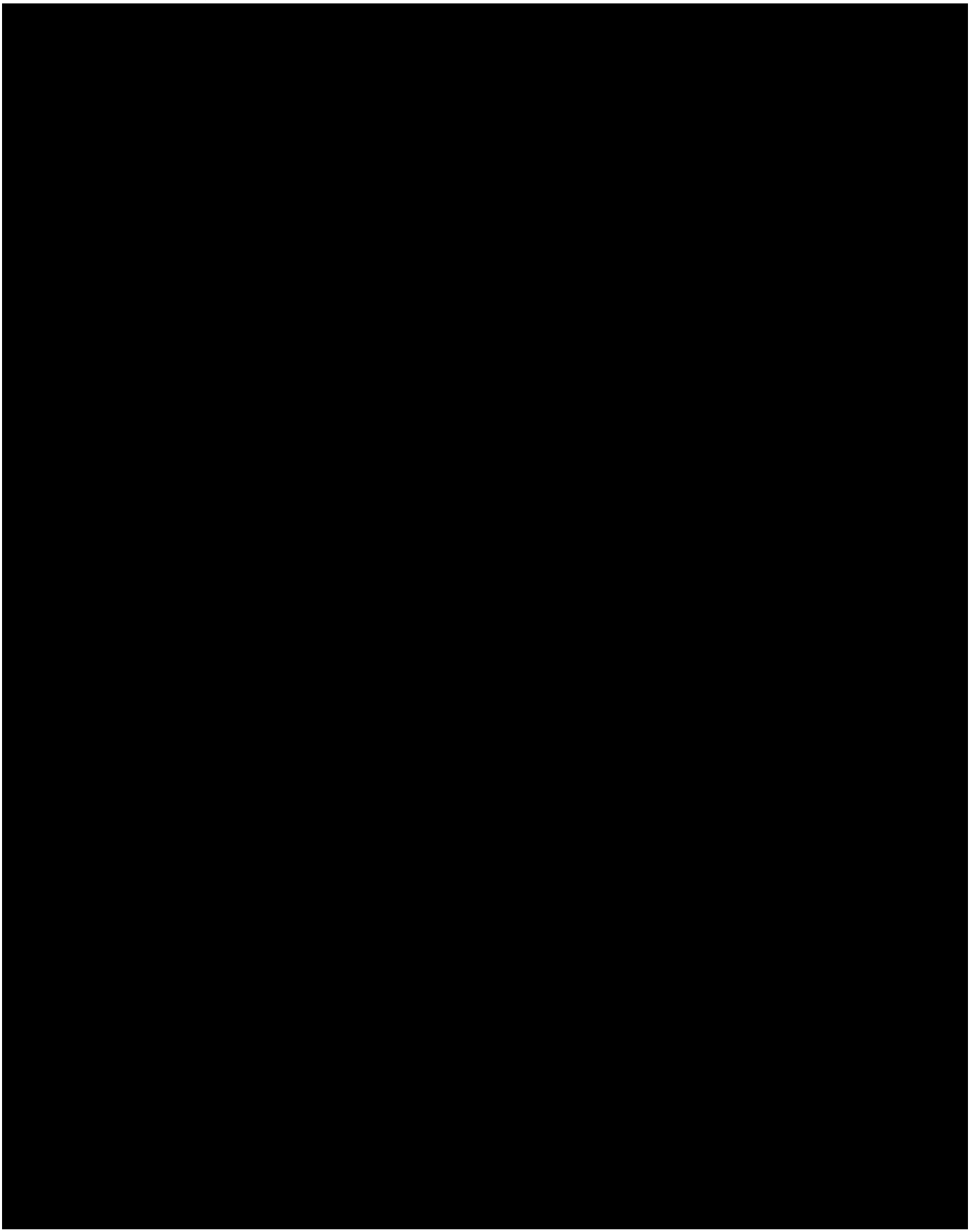
Repros believes telapristone offers the potential to provide significant symptomatic relief to women that suffer from a variety of reproductive disorders in which progesterone may be implicated. [redacted]

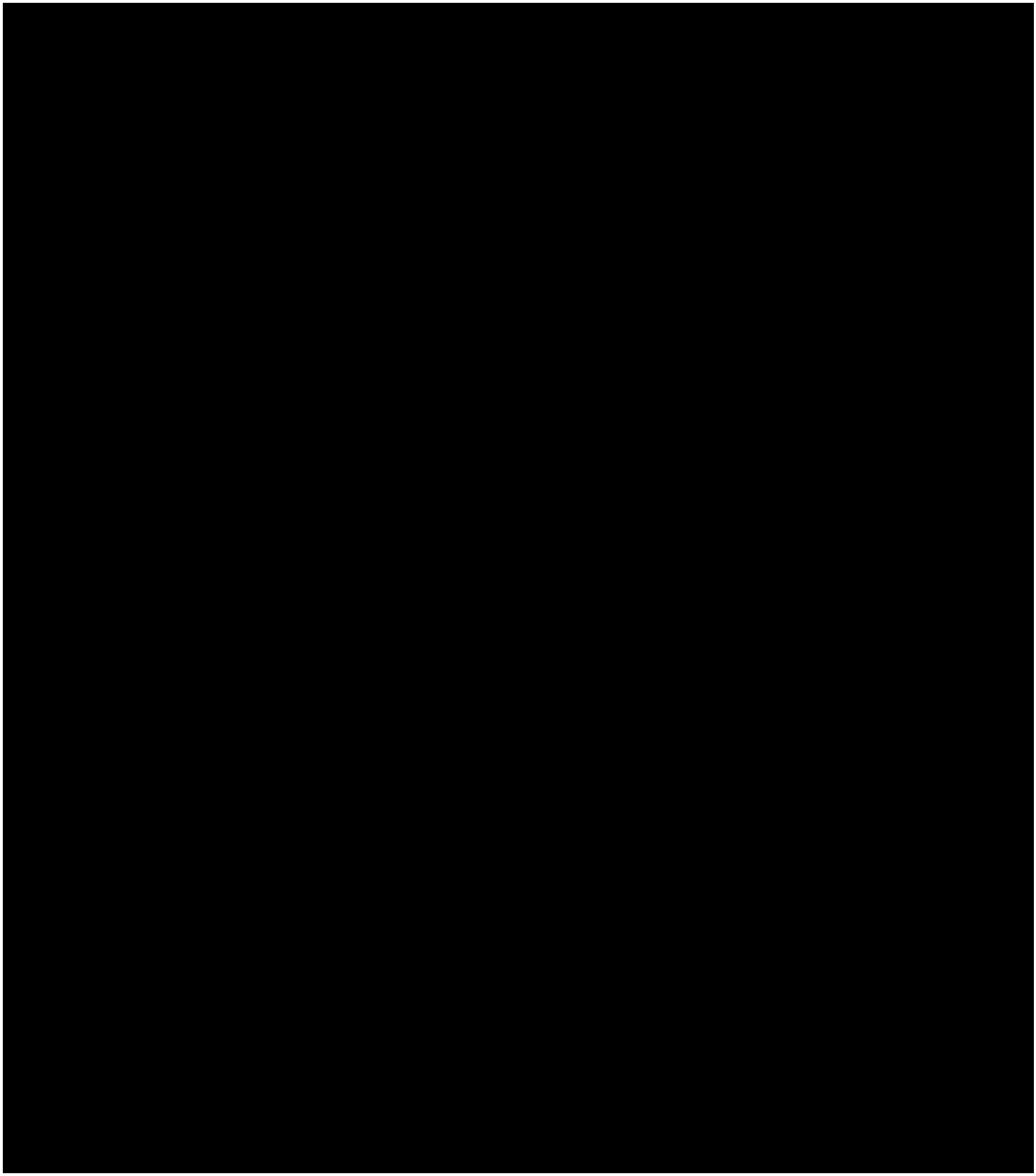
Based on recent findings in rabbit and dog studies the sponsor believes vaginal administration of Telapristone will bypass the liver, achieve higher local concentrations and better effects in utero while significantly reducing safety margin.

[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]

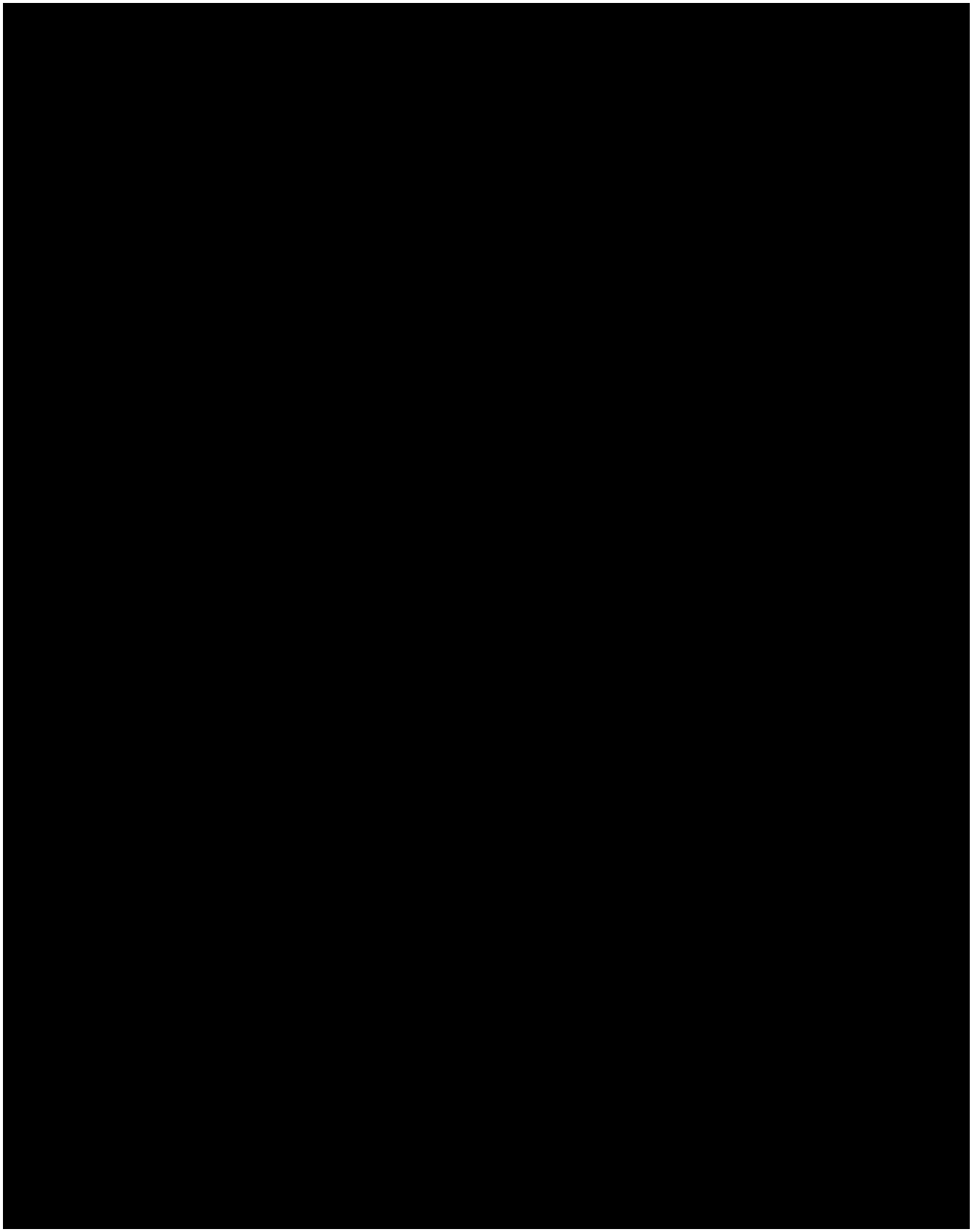


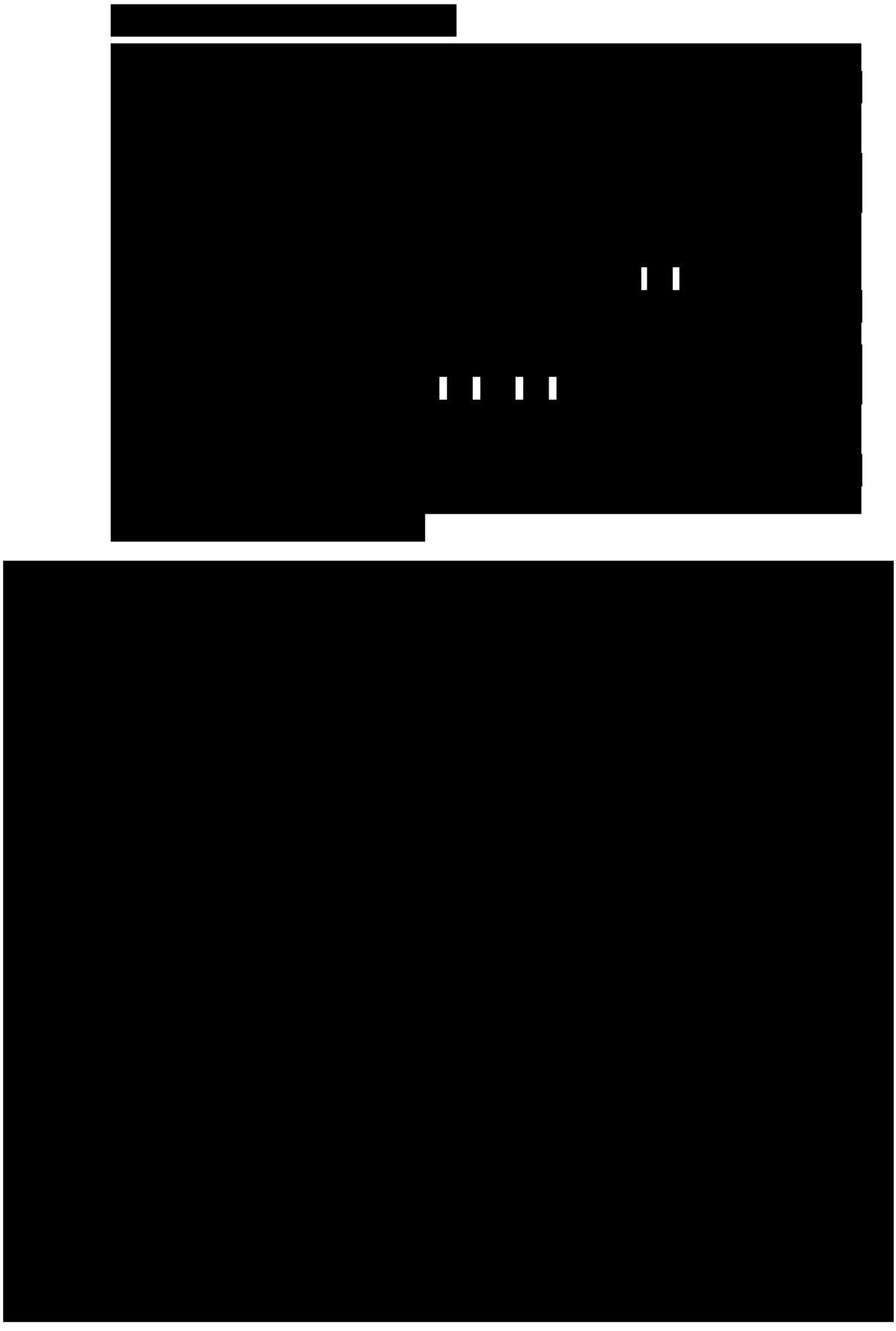


Endometrial Proliferation

BioQual also used a scoring system that assessed several uterine sections from the five rabbits in each dose group. [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 has 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).

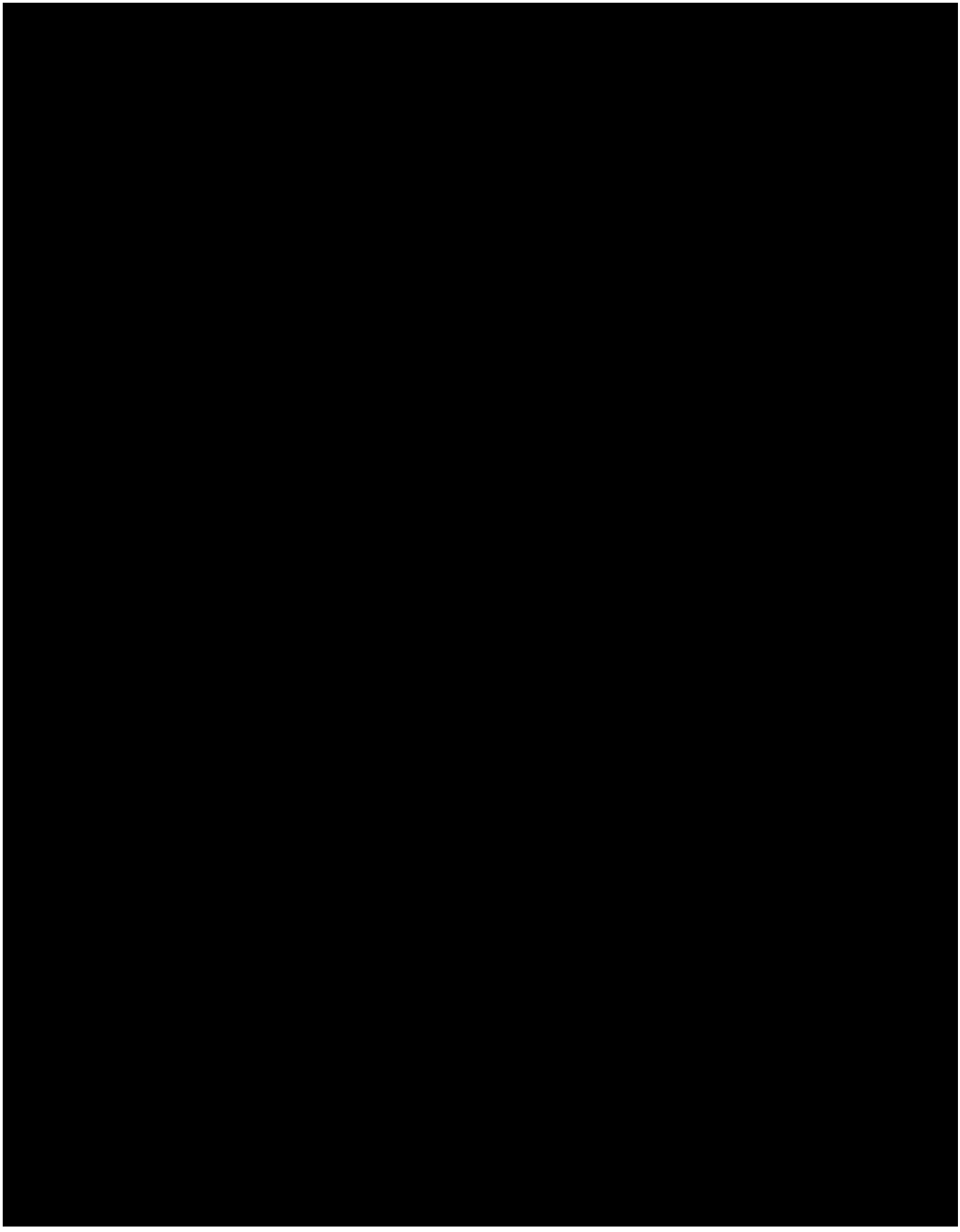
[redacted]

6.4 Safety Data

[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 Data From ZPV-200

This study included an initial two week exposure of vaginal administration of 12mg telapristone acetate in six women with uterine fibroids to determine the length of time it takes for the drug to reach steady state and the overall systemic exposure of both the parent compound and the primary metabolite. The purpose of this first cohort was to determine whether the systemic exposure of 12mg vaginal for both the parent molecule and primary metabolite was less than that which had been safely tested in the previously completed low dose oral study ZP-204.

[redacted]

[redacted]

6.6 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, 3001 S. Lamar Blvd., Suite 210, Austin, Texas 78704, will serve as an Institutional Review Board (IRB) for clinical sites who will accept their review.

7. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this study is to determine the safety and efficacy of two vaginal doses of Proellex administered for up to 2 courses of treatment (18 weeks each), each separated by an Off-Drug Interval (ODI), to premenopausal women with symptomatic uterine fibroids.

8. TRIAL DESIGN

8.1 Study Endpoints

8.1.1 Primary Efficacy Endpoint

- Percentage of subjects who become amenorrheic after one course of treatment

8.1.2 Secondary Endpoints

- Percentage of subjects who become amenorrheic after 2 courses of treatment
- Change and percentage change in PBAC score over the course of the study. Specifically comparing the baseline menstrual cycle to the matching end-of-study period leading up to Week 18 and the end of treatment as well as comparing the baseline PBAC to the ODI time periods.
- Percentage change in UFSQOL Symptom Severity score (UFS-SSS) comparing Week 18 to Baseline (three month look back) and for the ODI.
- Percentage change in the individual UFS-SSS subscores
- Percentage change from baseline in total uterine fibroid volume measured by MRI

8.2 Study Design

8.2.1 Overview of Study Design

This study is a phase 2 3-arm-study with a 36 week active dosing period. The study will be conducted in two stages.

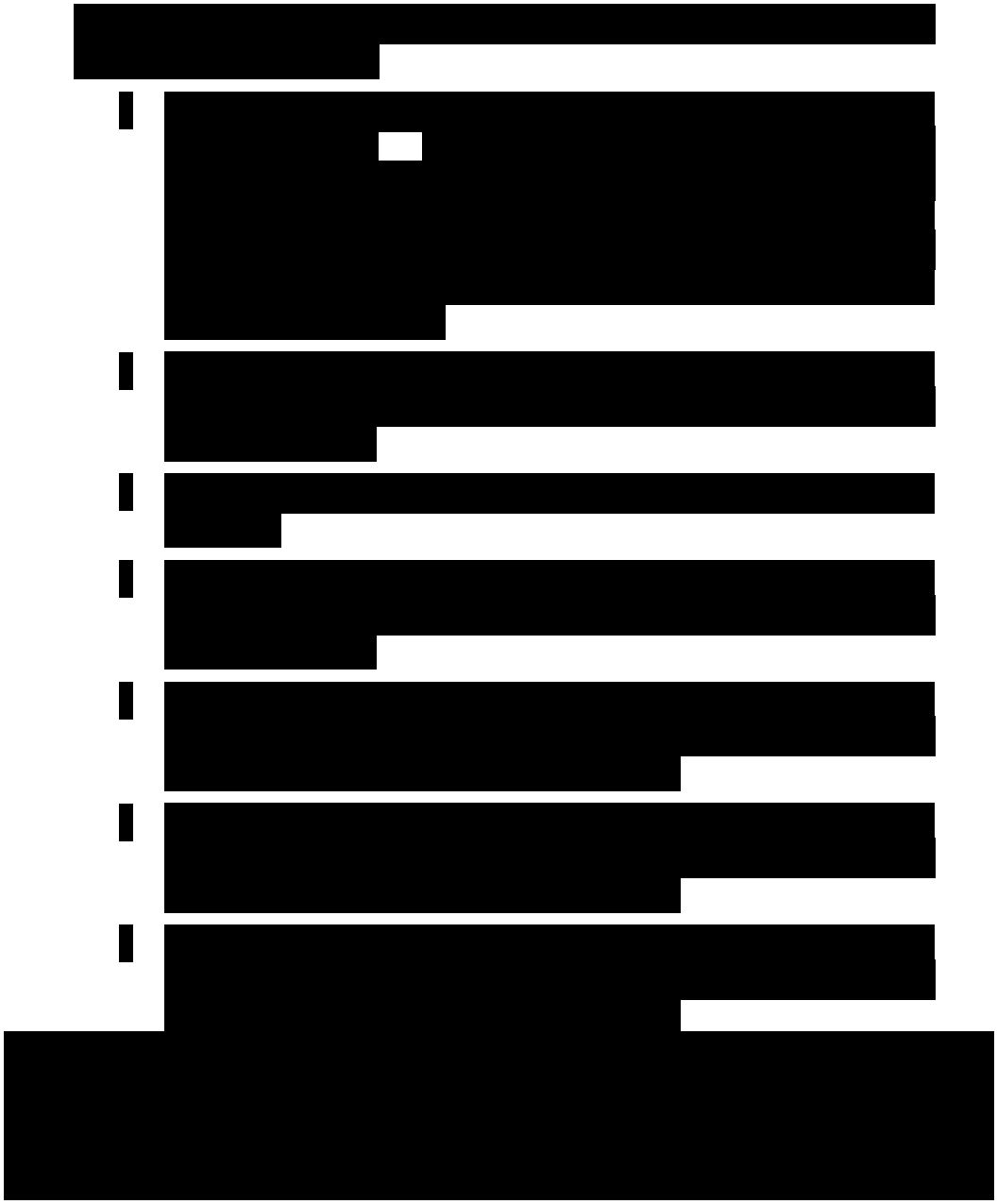
In the first stage, women will undergo a baseline assessment period, with no treatment, until 15-20 days after the start of their second complete menstrual event. During this phase a pictorial blood loss assessment chart and daily diaries will be utilized. Used sanitary products from the first menstrual event will be collected and returned to the clinic for alkaline hematin assay. This assay will confirm subject eligibility (MBL must be 80 mL or greater by alkaline hematin assay for subjects to qualify).

In the second stage, subjects will be randomized into one of 3 arms in a 1-1-1 fashion. The start of the 18 week dosing period (Course 1) in this stage of the study should commence 15-20 days after the start of their first menses after Visit 2. Once active dosing is stopped, subjects will be followed until menses returns. The start of the second 18 week dosing period (Course 2) will commence 15-20 days after the start of their menses following withdrawal of drug after Course 1 has been completed. During the non dosing off-drug interval (ODI), subjects will continue to record study information in the daily paper diary and PBAC charts.

After end of dosing in Course 2, subjects will be followed through the subsequent recovery menses and for an additional 5 menstrual events, after which the subject may be offered the opportunity to enroll in an extension study. Subjects who fail to achieve amenorrhea may enroll in the extension study at Visit 19. Amenorrhea is defined as any 28-day period during treatment (not including the ODIs) without a bleeding score >1. Throughout the study women will record study information in the diary, PBAC and questionnaires as outlined in the study procedures.

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 and second 18 week dosing periods.



The primary efficacy analysis will be conducted when all subjects complete the first cycle of treatment. A second analysis will summarize the subject's second treatment cycle which will be conducted after all subjects complete study treatment and follow-up.

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

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 a total of 36 weeks (two 18 week courses separated by an ODI) before the 6 cycle follow up is started. After the second treatment course is completed the subjects will be followed for 6 menstrual events to determine durability of effect of treatment, after which they may be offered the opportunity to enroll in an open-label extension study. Subjects who fail to achieve amenorrhea may enroll in the extension study at Visit 19. Amenorrhea is defined as any 28-day period during treatment (not including the ODIs) without a bleeding score >1. Each treatment course will be separated by an ODI. Blinded treatments kits will be randomized and distributed by the packaging company.

For the statistical analysis at the end of the first course of treatment, only statistical staff will be unblinded. 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 supplied as placebo, 6, and 12 mg vaginal capsules, in blister packs of 10 capsules, by a clinical supplies contract vendor designated by Repros Therapeutics Inc. [redacted] instructions to administer 1 capsule vaginally each day at the same time using the applicator provided. Subjects should be instructed to refrain from vaginal intercourse or putting anything in the vagina for 48 hours prior to clinic visits 2, 3, 12, and 18. Study medication should be taken at the same time of day every day, and clinic visits should be scheduled according to each subject's administration schedule. [redacted]

8.2.5 [redacted]

8.2.6 [redacted]

8.3 [redacted]

[redacted]

8.3.1 Inclusion Criteria

Subjects must meet the following criteria:

- Otherwise healthy adult females between 18 and 47 years
- Subject has a history of at least 3 regular menstrual cycles in which menorrhagia is due to uterine fibroids (a past or concurrent diagnosis of uterine fibroids is acceptable).
- Screening ultrasound confirms presence of uterine fibroids

[redacted]

- Agreement not to attempt to become pregnant during the trial

[redacted]

- Agreement to use only sanitary pads provided throughout the course of the study, tampon use is prohibited
- Ability to complete a daily subject diary and study procedures in compliance with the protocol

[redacted]

- Has a negative pregnancy test at the Screening and Baseline visits
- A Body Mass Index (BMI) between 18 and 45 inclusive
- Subject is available for all treatment and follow-up visits

[redacted]

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 the entire study period

[redacted]

- 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, including the [redacted]

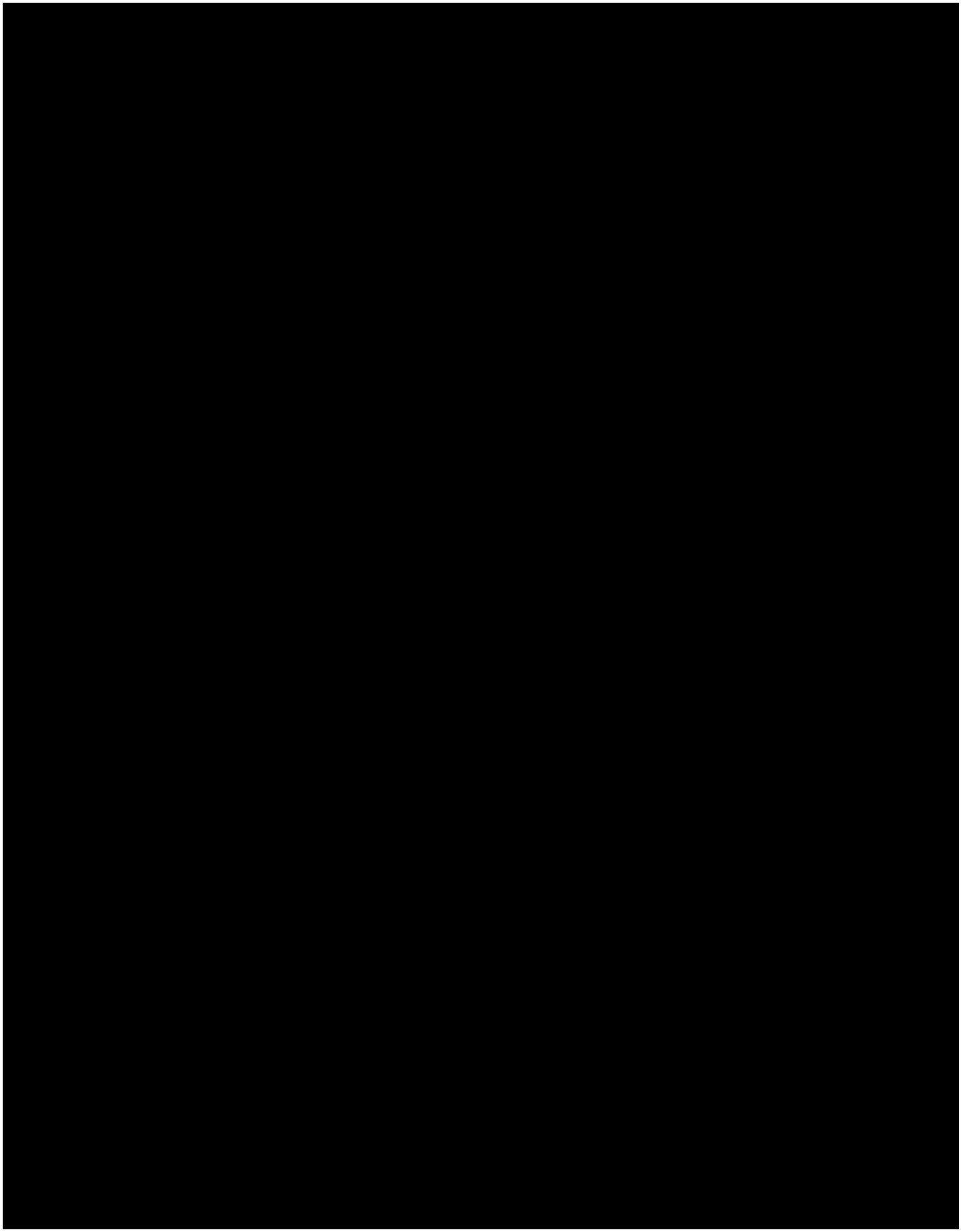
- Use of oral contraceptives in the30 days preceding screening. Use of Depo-Provera® in the preceding 10 months.
- Use of GnRHas (e.g. Lupron Depot) within 3 months prior to screening (Lupron Depot must have a wash-out period of 3 months prior to screening)
- Has an IUD in place
- History or current diagnosis of malignancy other than curatively treated basal cell carcinoma

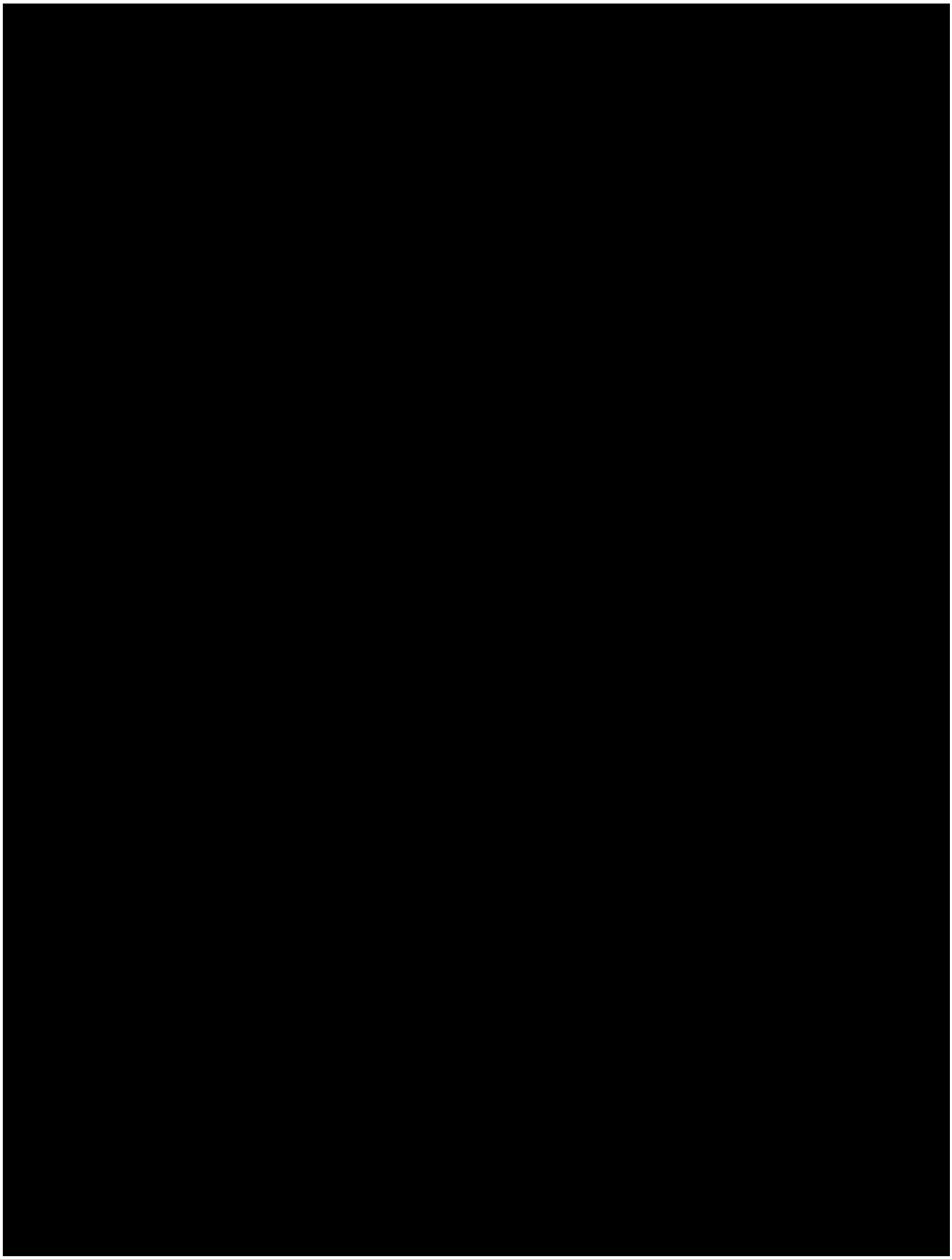
[redacted]

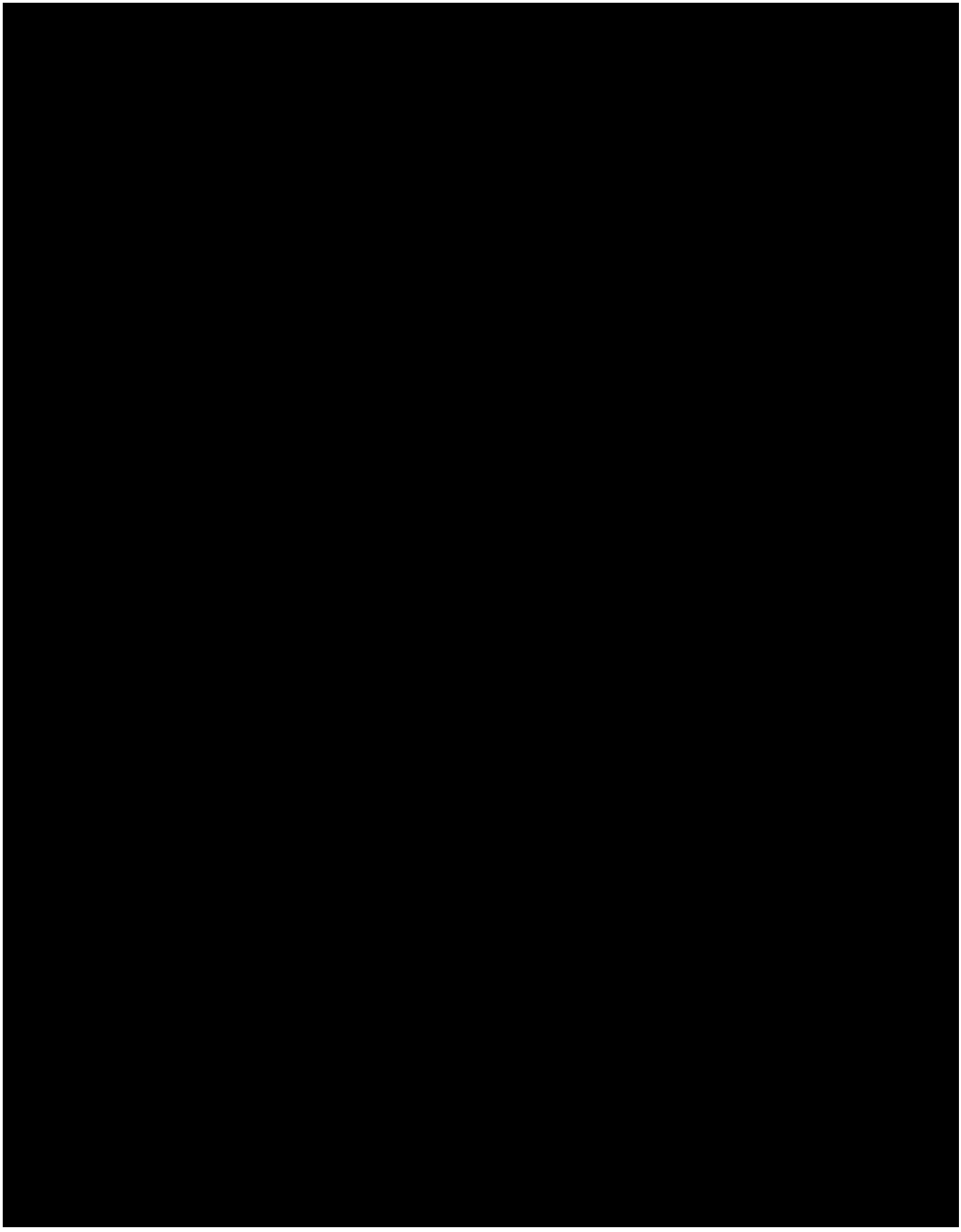
- Recent history (within past 6 months) of alcoholism or drug abuse

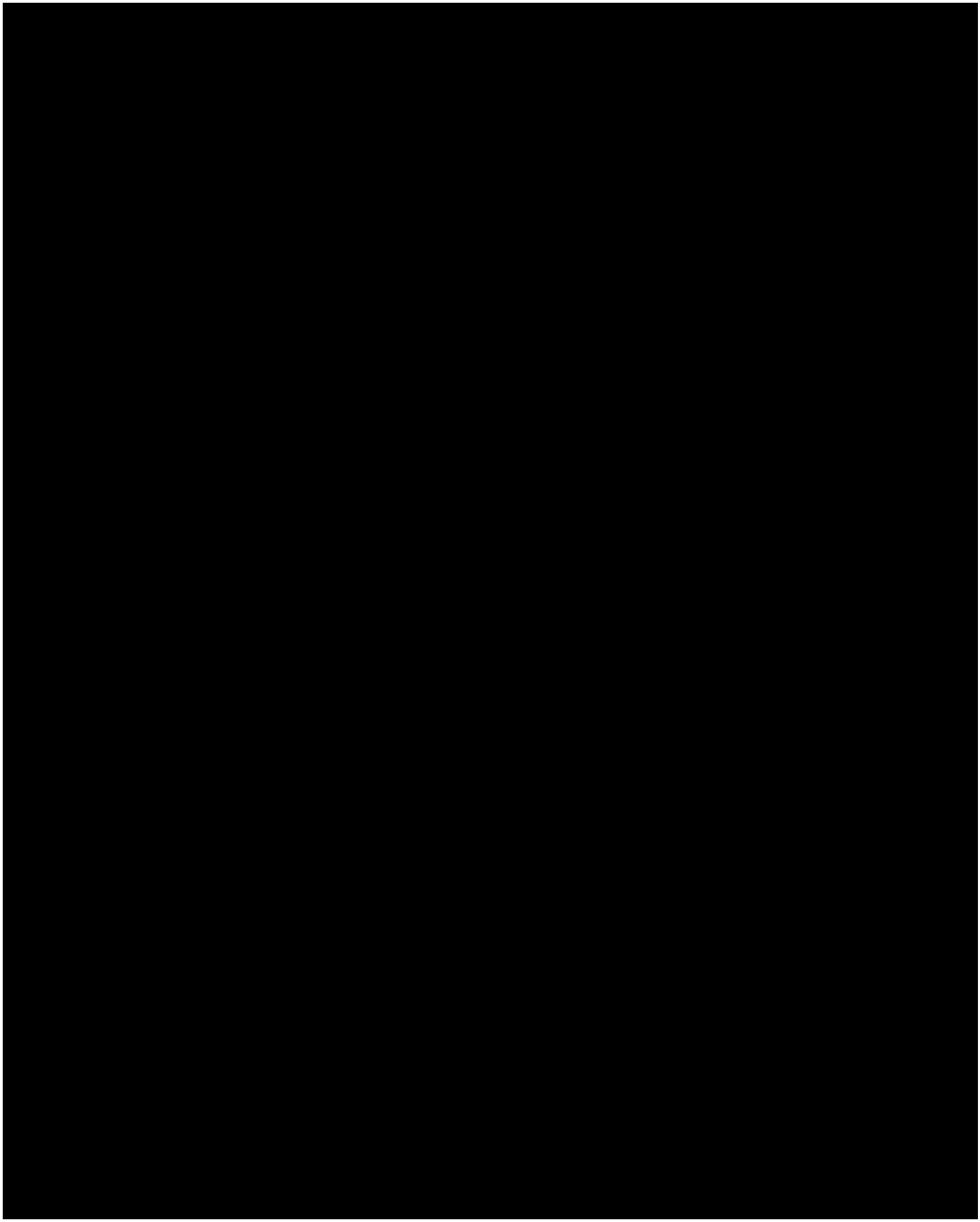
[redacted]

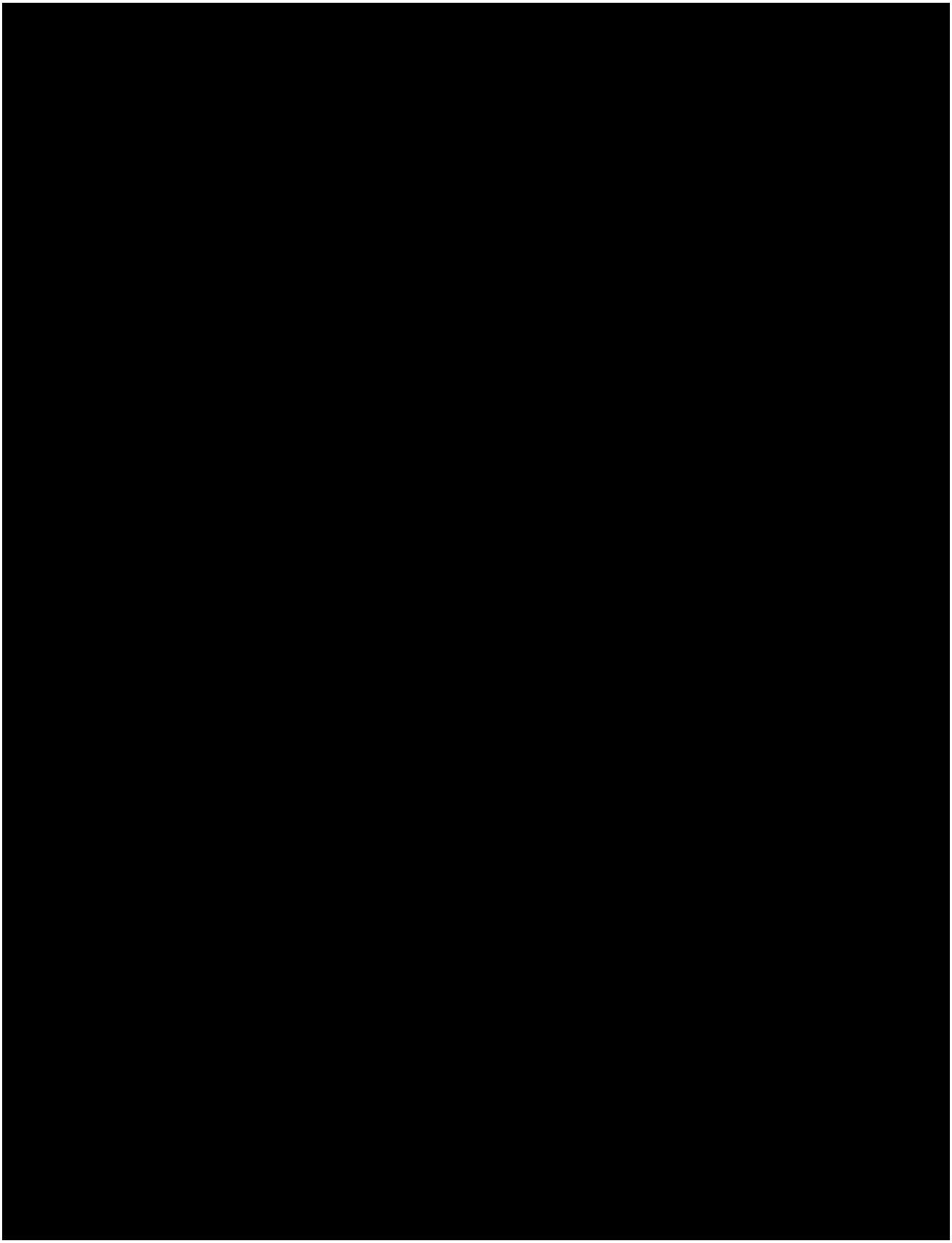
- Clinically significant abnormal findings on screening examination and laboratory assessments or any condition which in the opinion of the investigator would interfere with the participant's ability to comply with the study instructions or endanger the participant if she took part in the study

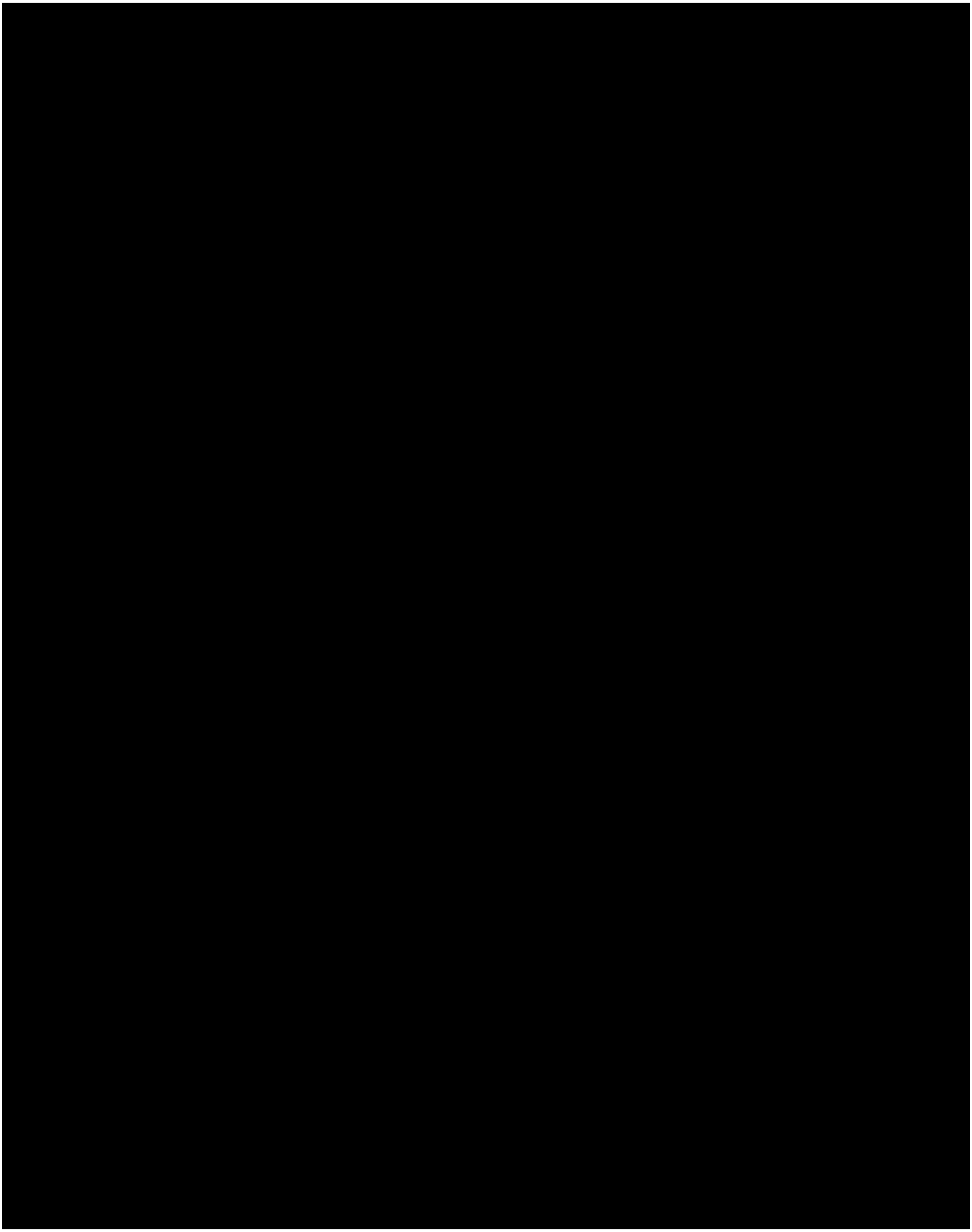


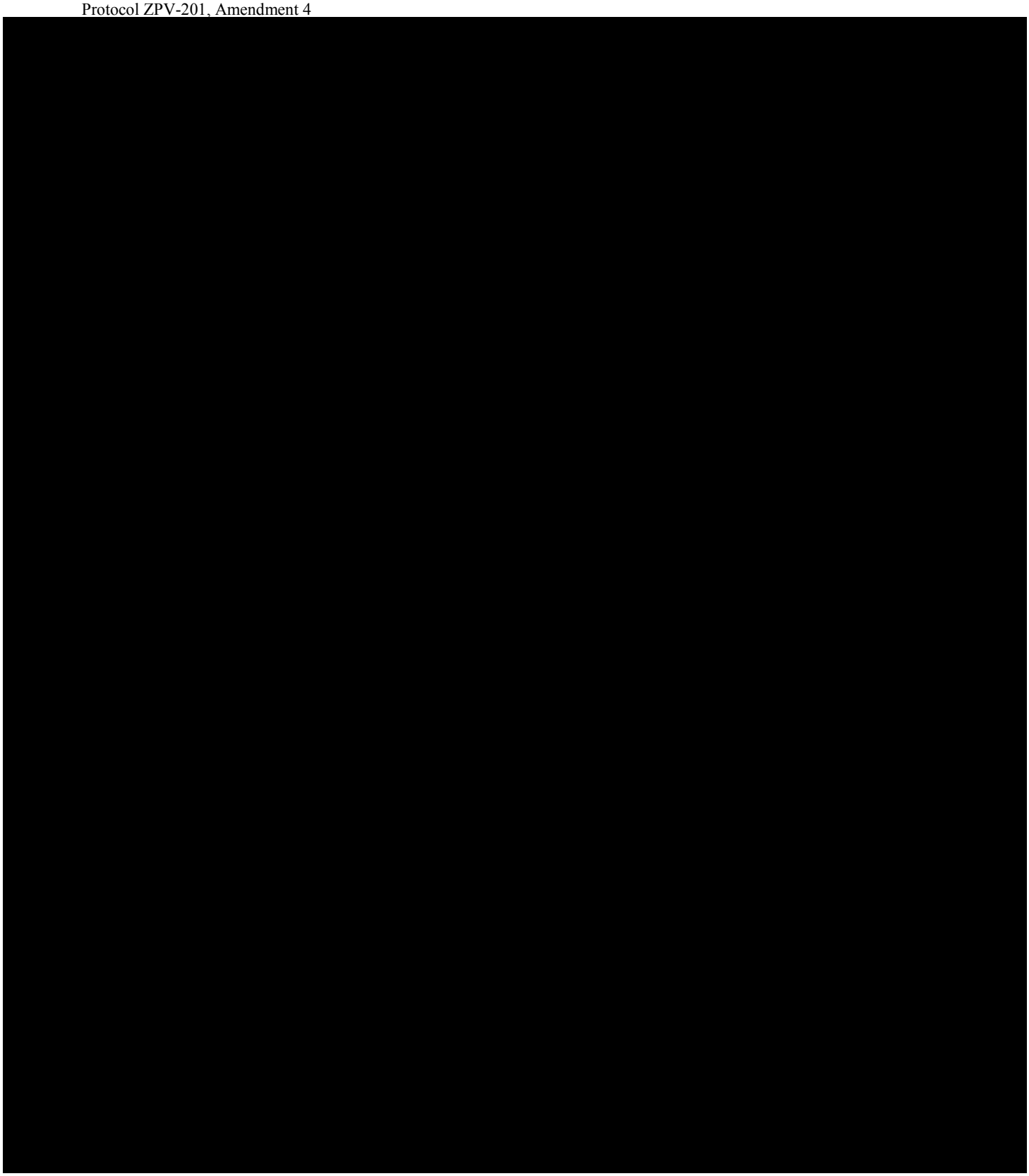












10. ASSESSMENT OF SAFETY

[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. 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. 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.
Not Related	There is evidence of exposure to the study drug; there is another more likely 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 and during the 6-month follow up after discontinuation of study medication:

- 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

Up to 50 female subjects, 15 per dose arm, meeting the inclusion/exclusion criteria will be randomized in a 1-1-1 fashion with the expectation that approximately 45 will be fully eligible for efficacy analyses. The primary endpoint is amenorrhea. [redacted]

12.2 Statistical and Analytical Plan

A Statistical Analysis Plan (SAP) will be prepared prior to unblinding the data. 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 in Stage 2. In this Phase 2 study there will be no statistical corrections for interim analyses or multiple comparisons.

For the statistical analysis at the end of the first course of treatment, only statistical staff will be unblinded. All clinical operations staff and staff at investigative sites will remain blinded until completion of the study.

12.2.1 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.

12.2.2 Efficacy Analyses

A Statistical Analysis Plan (SAP) will be prepared prior to unblinding of the study data. 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.

12.2.2.1 Primary Endpoint: Incidence of Amenorrhea

The percentage of subjects who become amenorrheic during the 28 days leading up to the last day of dosing at Week 18 will be compared by Chi-Square test. Amenorrhea after a second course of treatment will be analyzed as a secondary endpoint. Testing will evaluate the pooled Proellex doses compared to placebo, each Proellex dose compared to Placebo as well as compare the active dose groups. A Fisher's Exact test will be utilized if the cell sizes are small.

A subject is deemed amenorrheic if they have no bleeding intensity score greater than 1 using the Daily Diary Card in Appendix 3 (spotting not requiring hygiene products) during the 28 day period.

12.2.2.2 Secondary Endpoints

Percentage Change in PBAC scores

The percentage change in PBAC scores over each 28 day period for each menstrual cycle 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 and the time to return to baseline vaginal bleeding to determine duration 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 as compare the pooled Proellex doses to placebo. While the primary assessment will be after 18 weeks of treatment, 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.

Percentage change in total and individual symptom severity scores for the UFS-SSS

The UFS-SSS is an 8 question symptom severity score and has been validated as a three month look back questionnaire. The survey will be administered at the baseline of each dosing course and at the end of each course. An analysis of UFS-SSS scores will compare the pooled Proellex dose results to the placebo group with a t-test. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. Within group paired tests will also be used to assess treatment effect. Non-parametric methods will be employed as appropriate. The primary assessment will be based on Visit 12 (after 18 weeks of treatment). If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

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 and after the 6 months of recovery menses (Visit 24). 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.

An analysis of percentage change in uterine fibroid volume will compare the pooled Proellex doses to the placebo group with a t-test. Pairwise comparisons of the treatment groups will be made using a two-sample t-test. Within group paired tests will also be used to assess treatment effect. Non-parametric methods will be employed as appropriate. The primary assessment will be based on Visit 12 (after 18 weeks of treatment). However, analyses will continue for each volume assessment. If data are missing, a last observation carried forward procedure will be used, including the baseline, if necessary.

[redacted]

[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

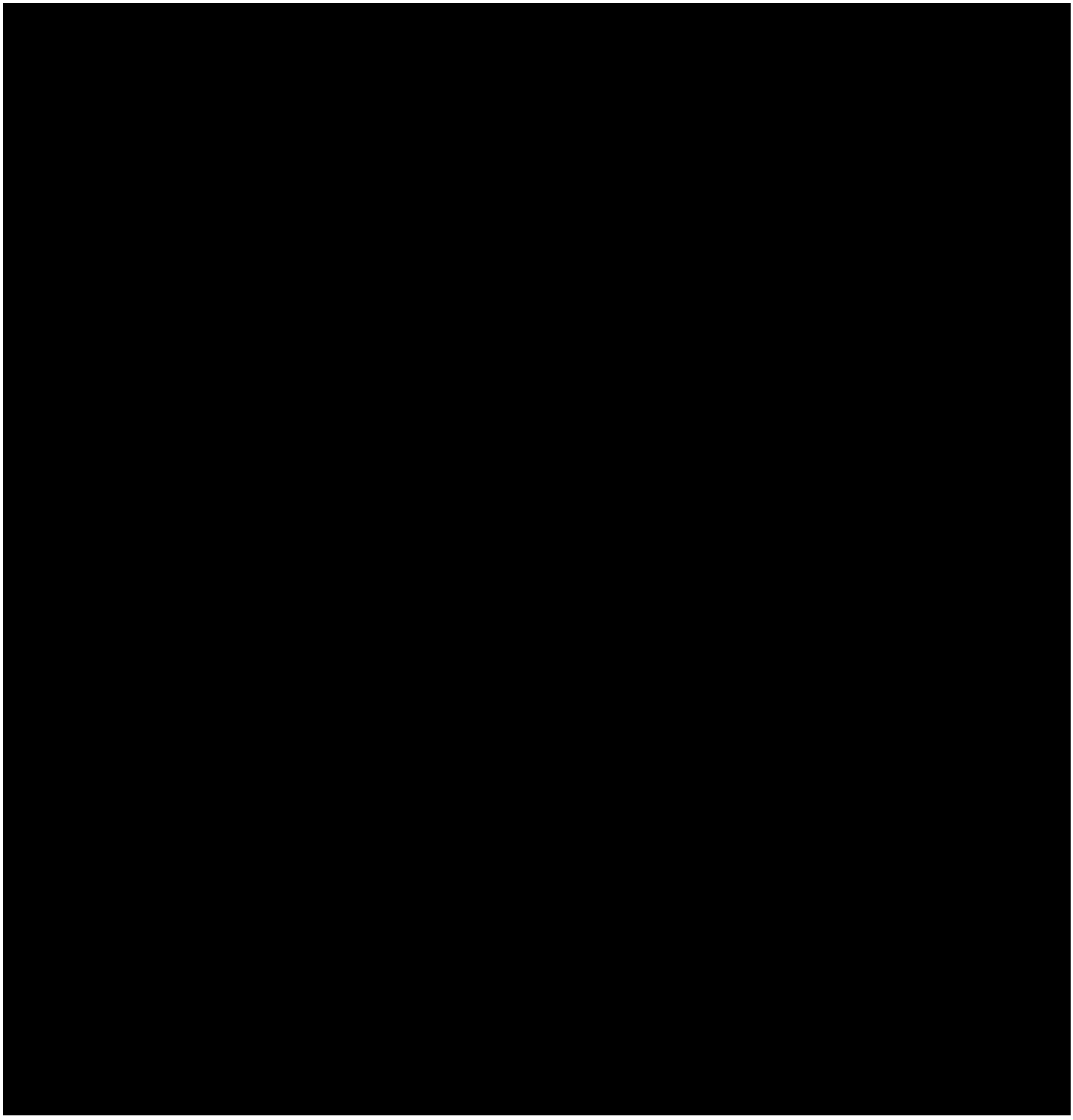
I have reviewed the ZPV-201 protocol and Investigator Brochure and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

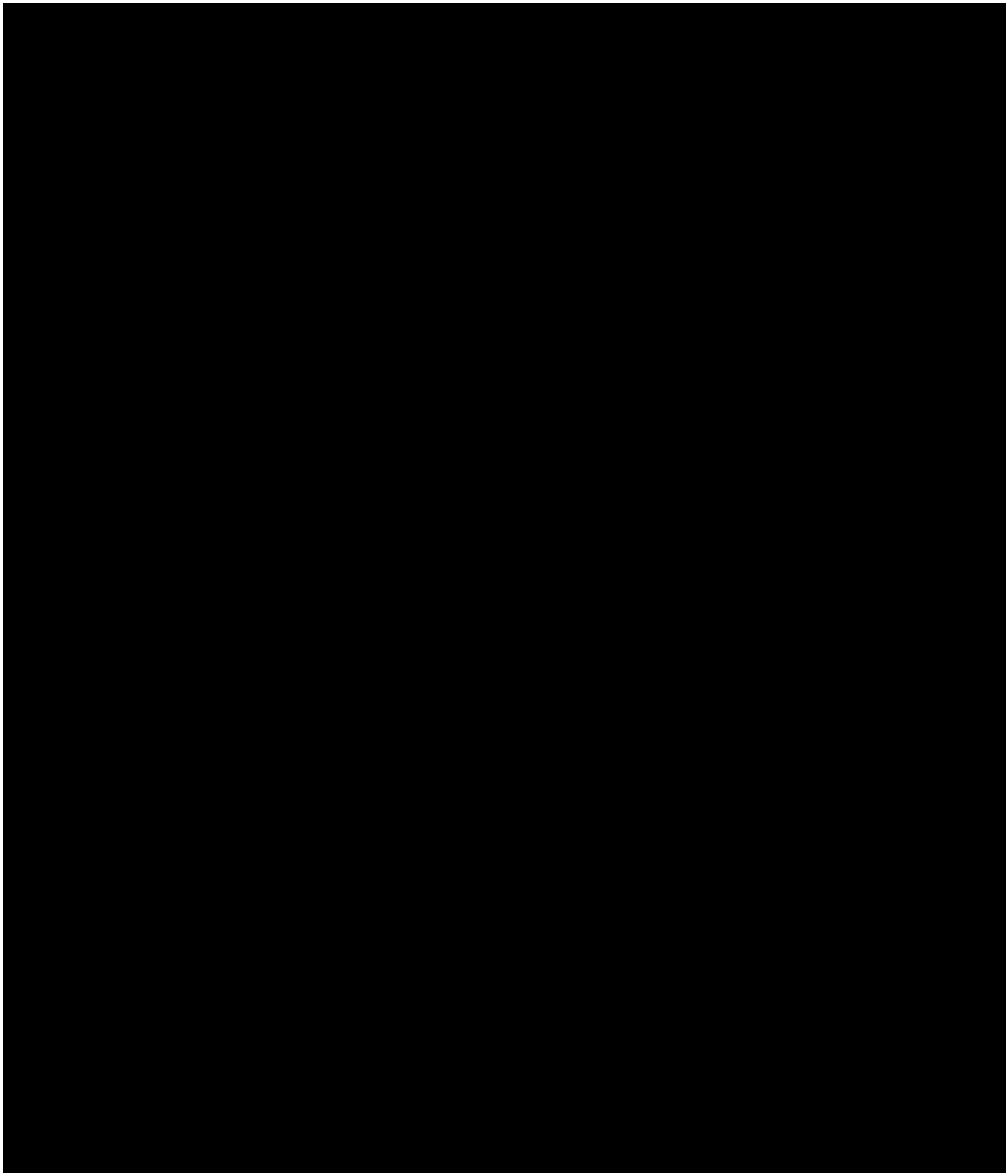
_____ _____

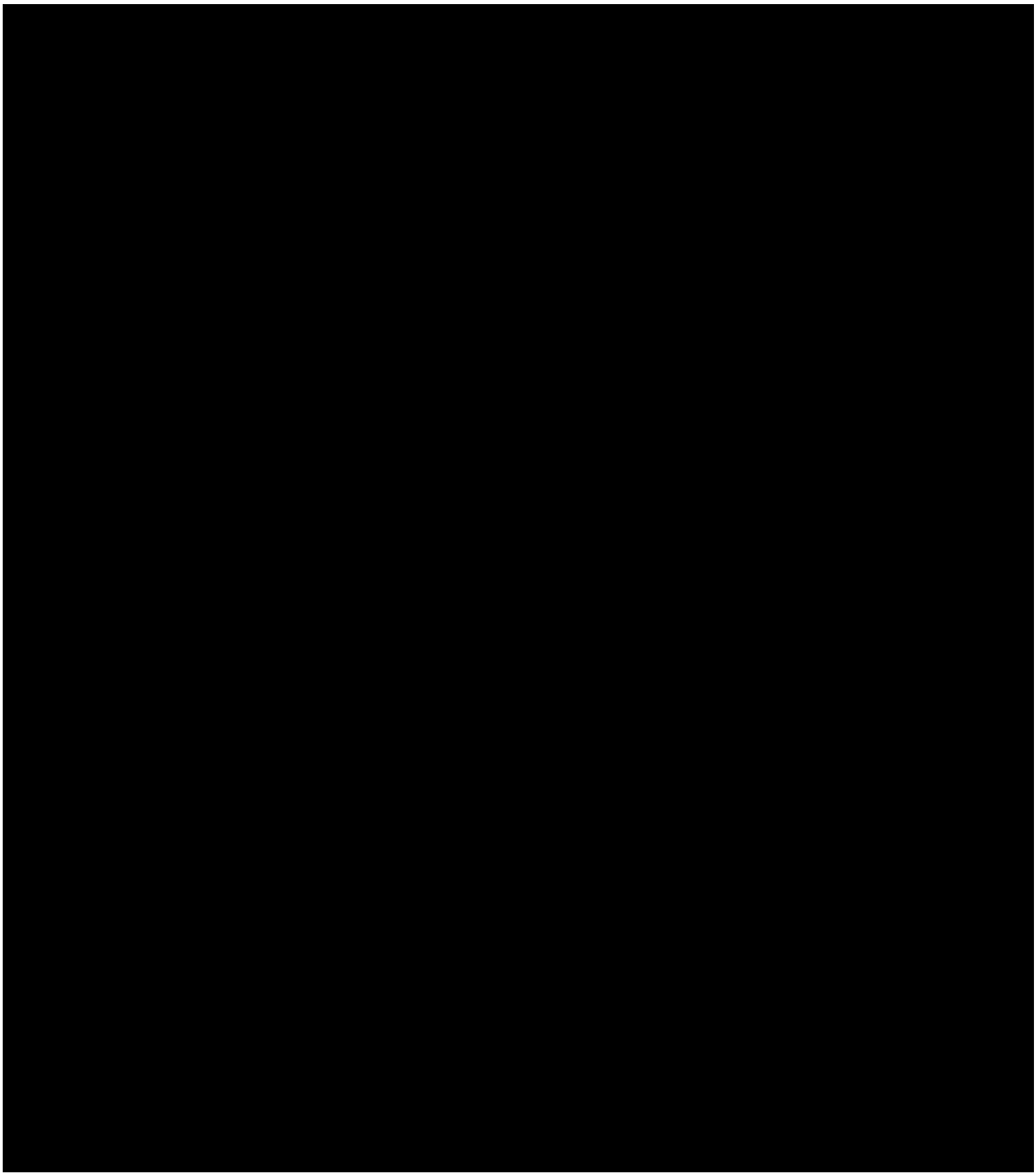
Investigator Date

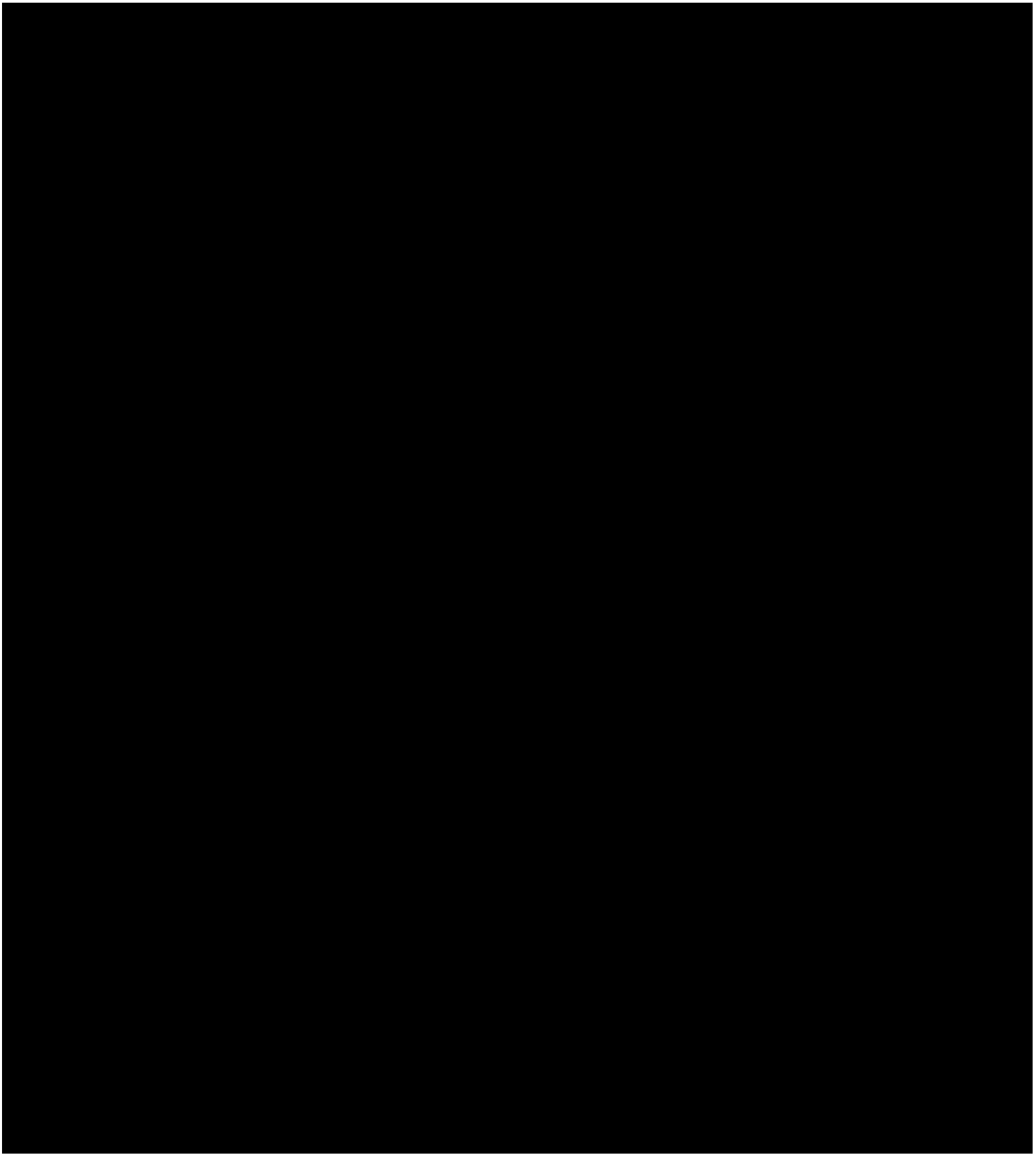
_____

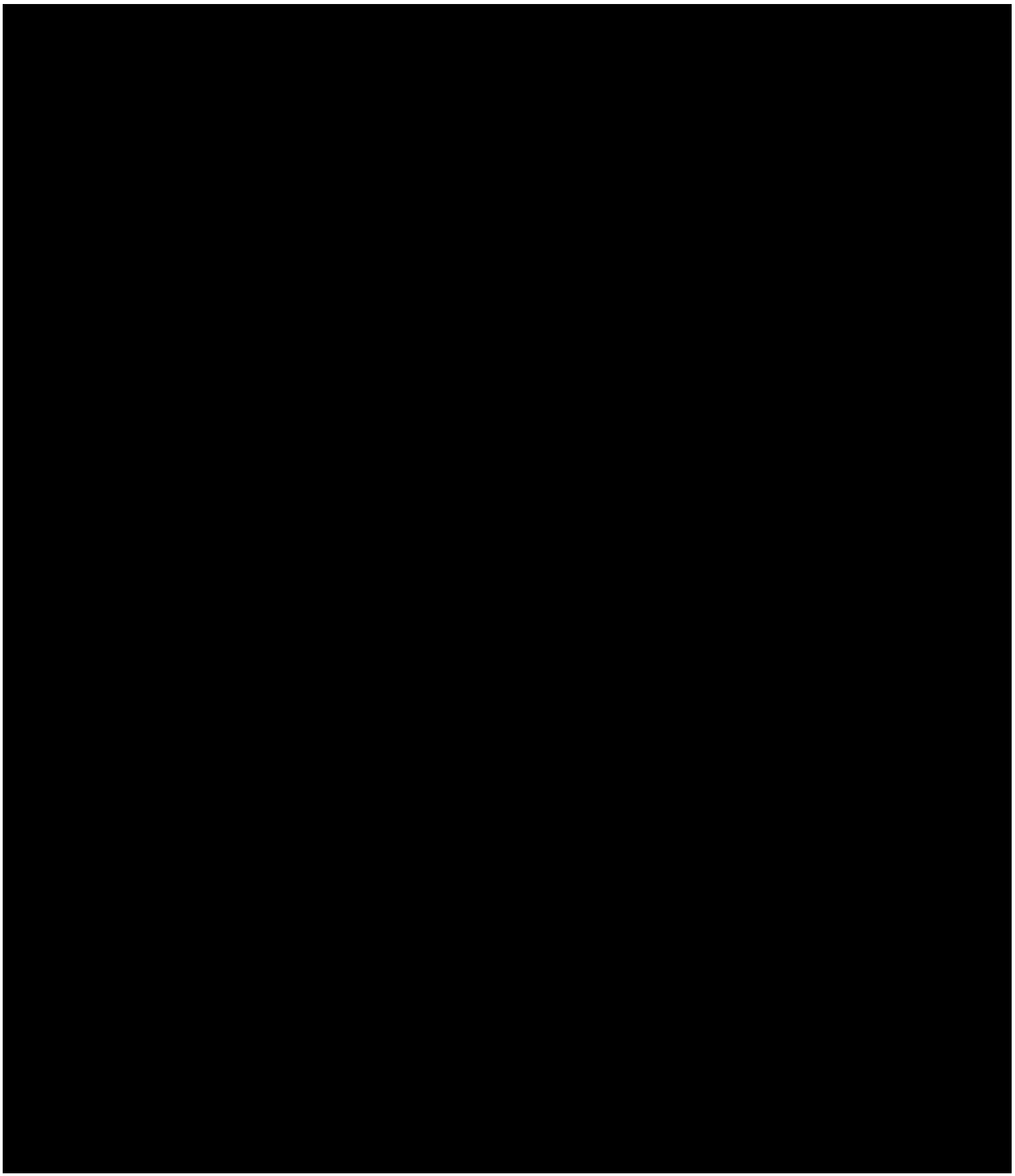
Printed name

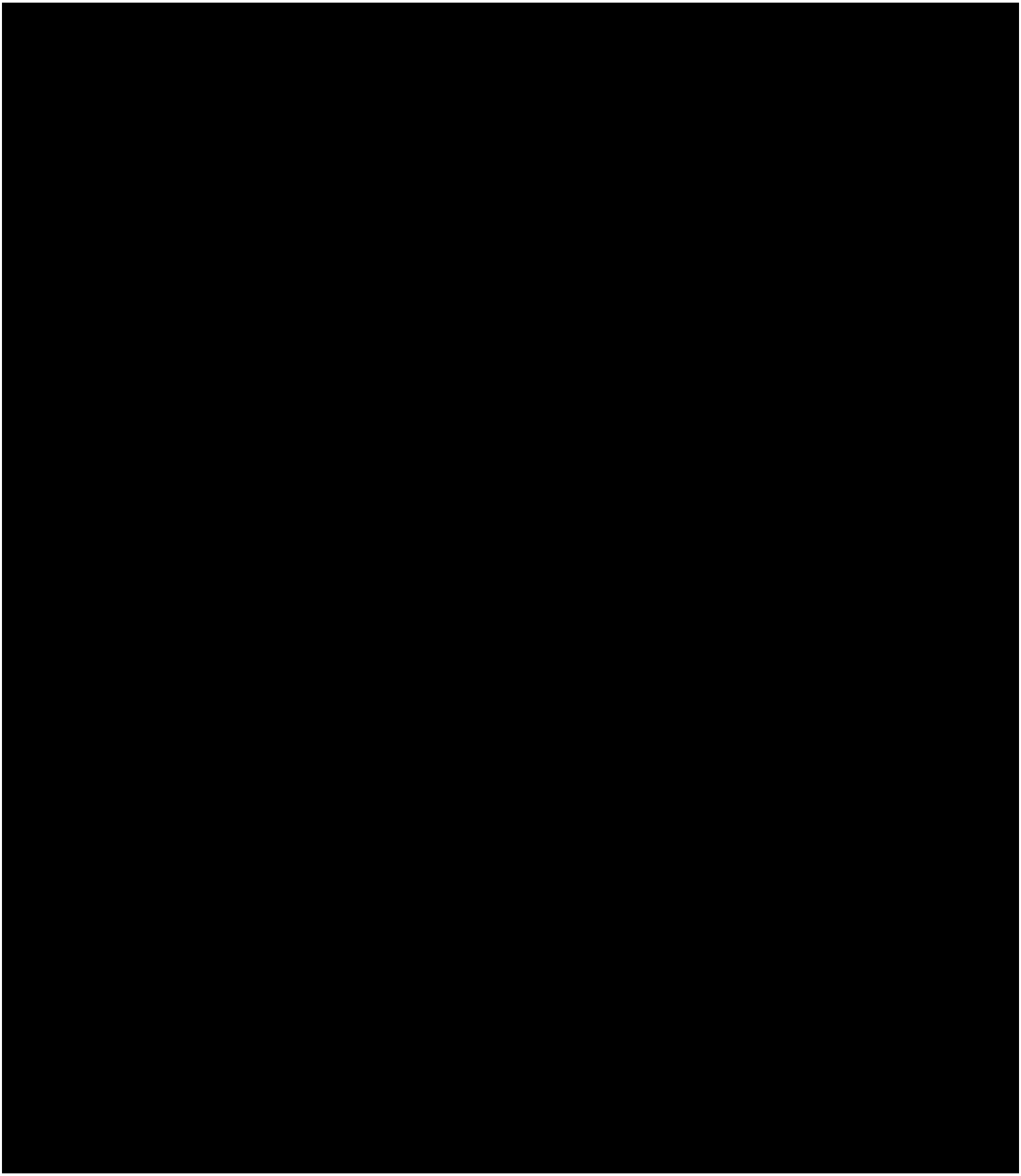


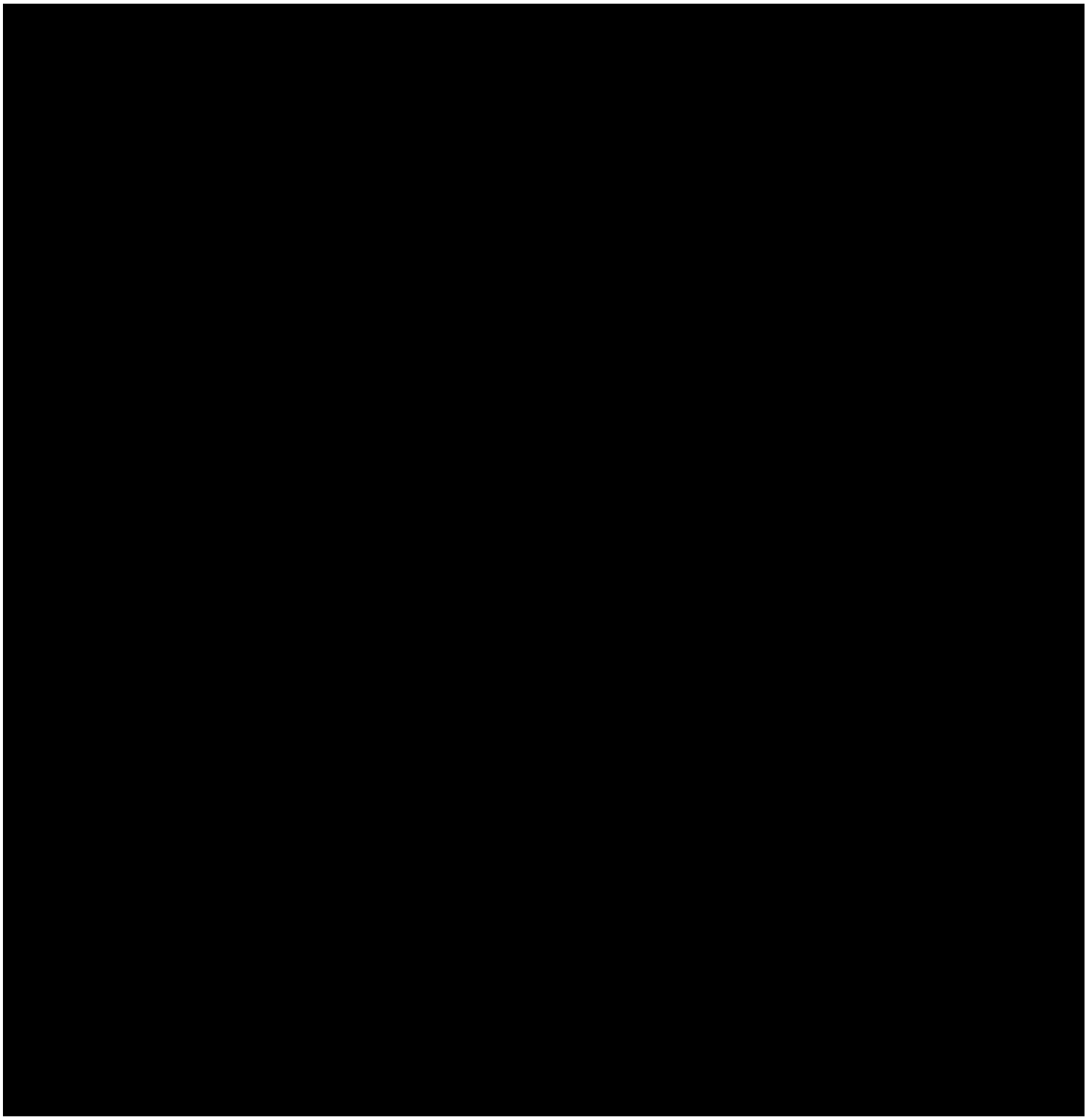


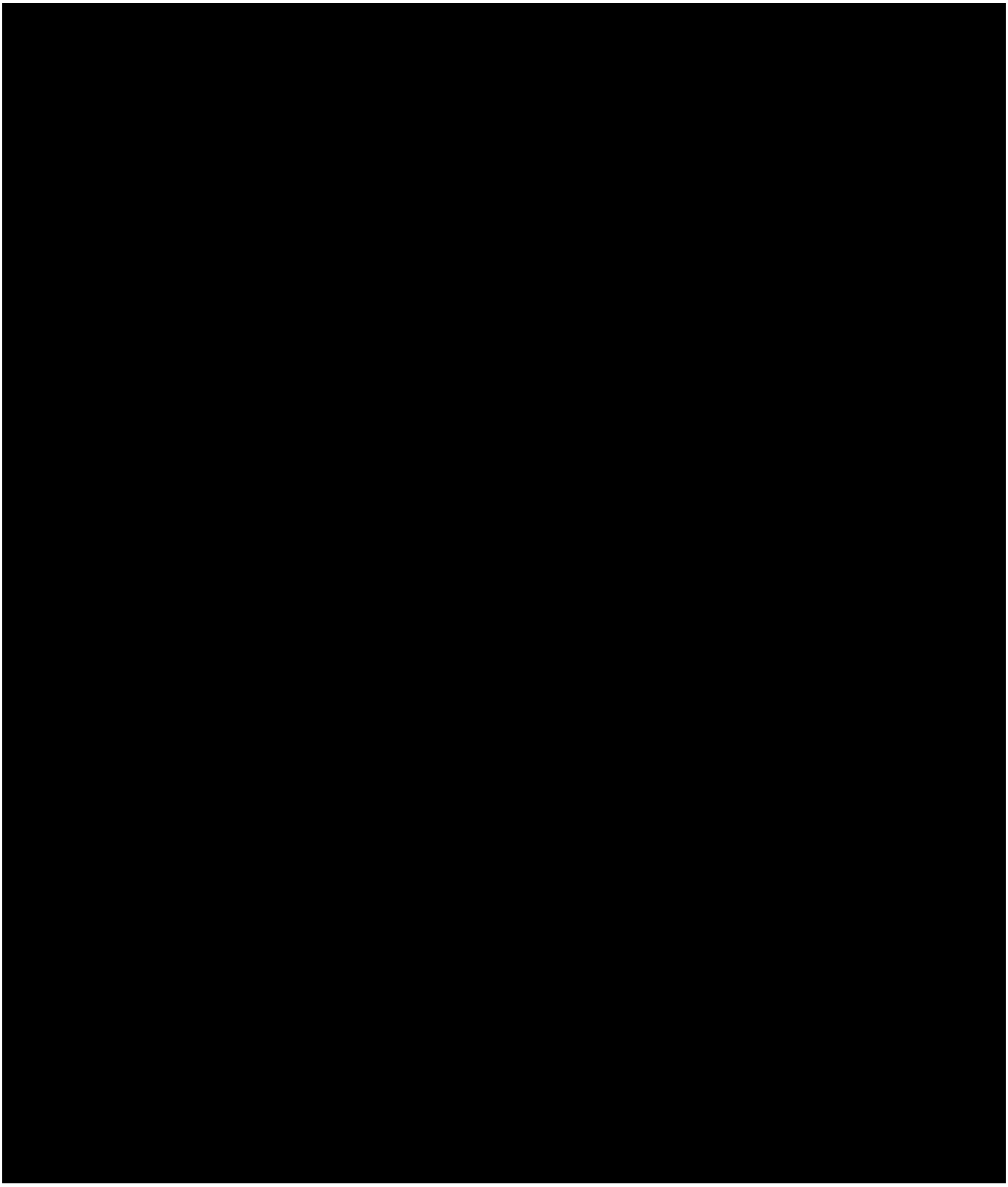


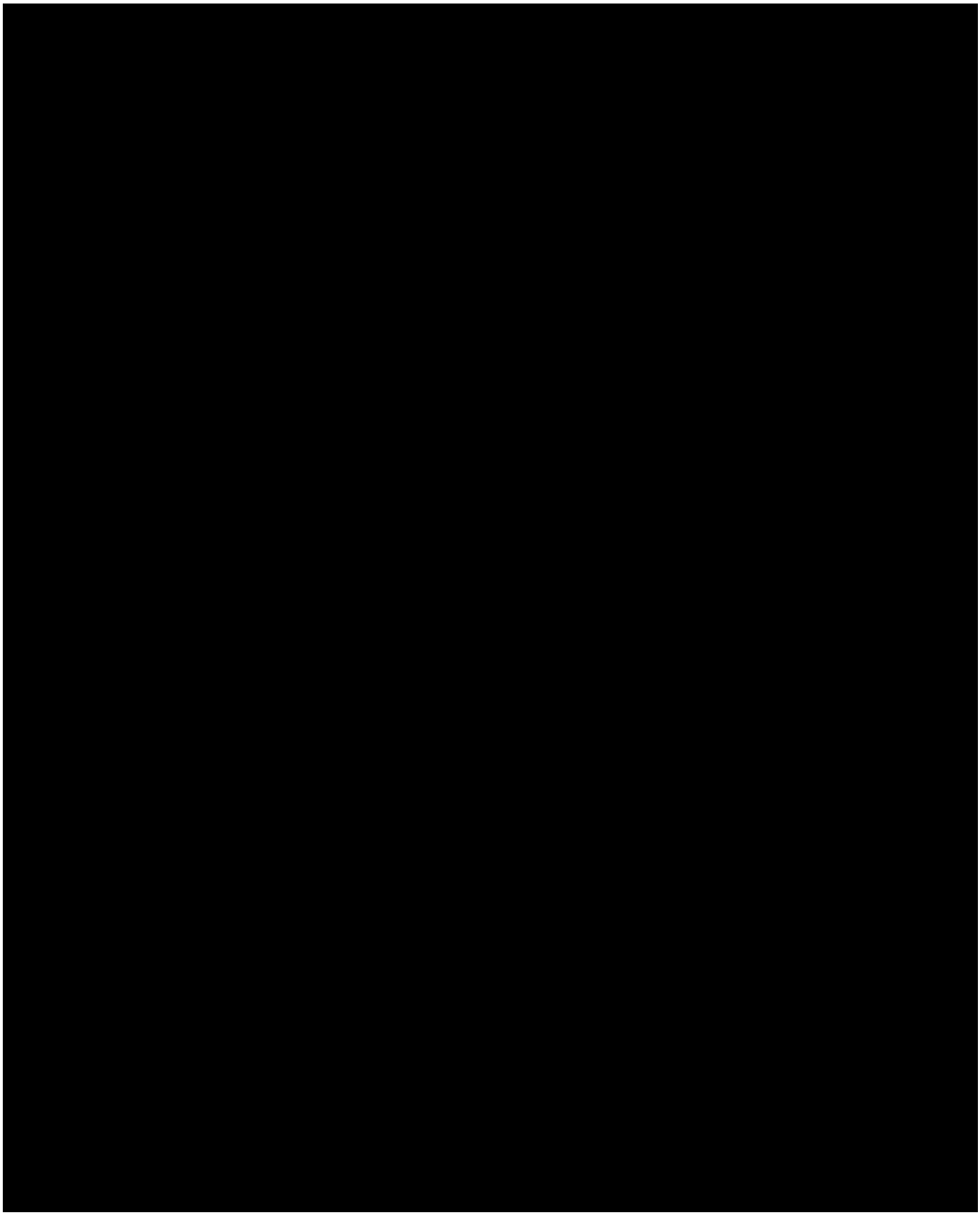


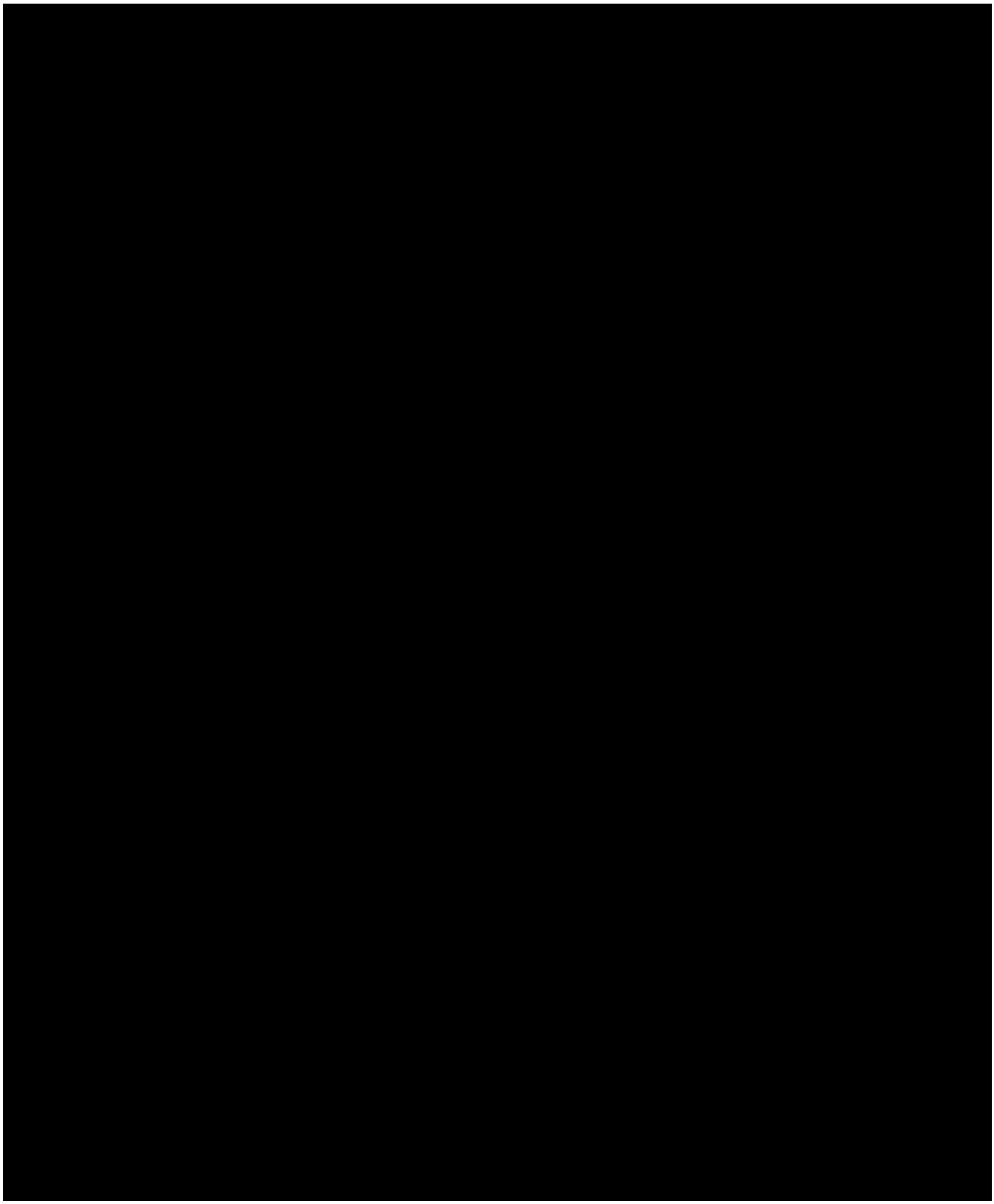


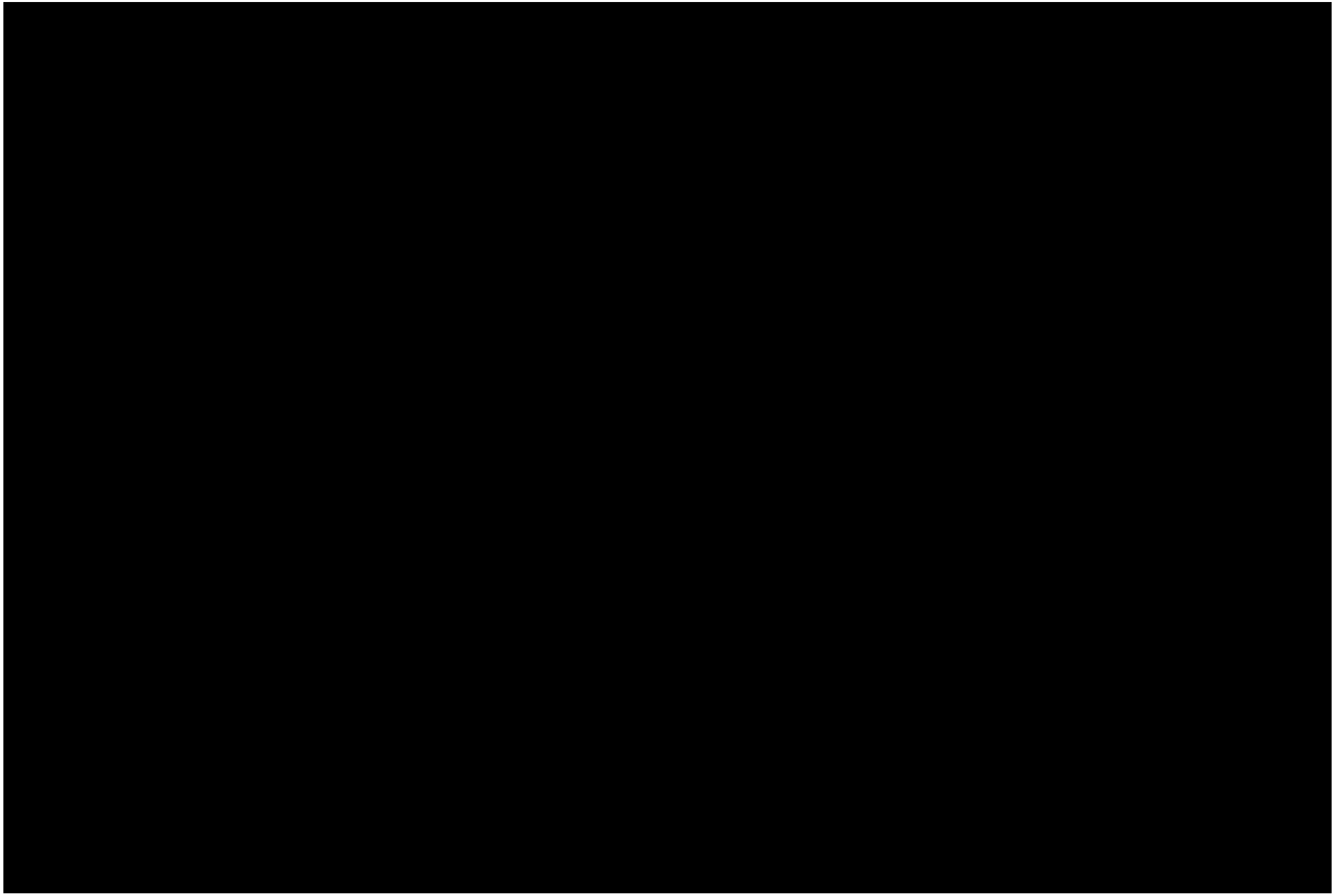


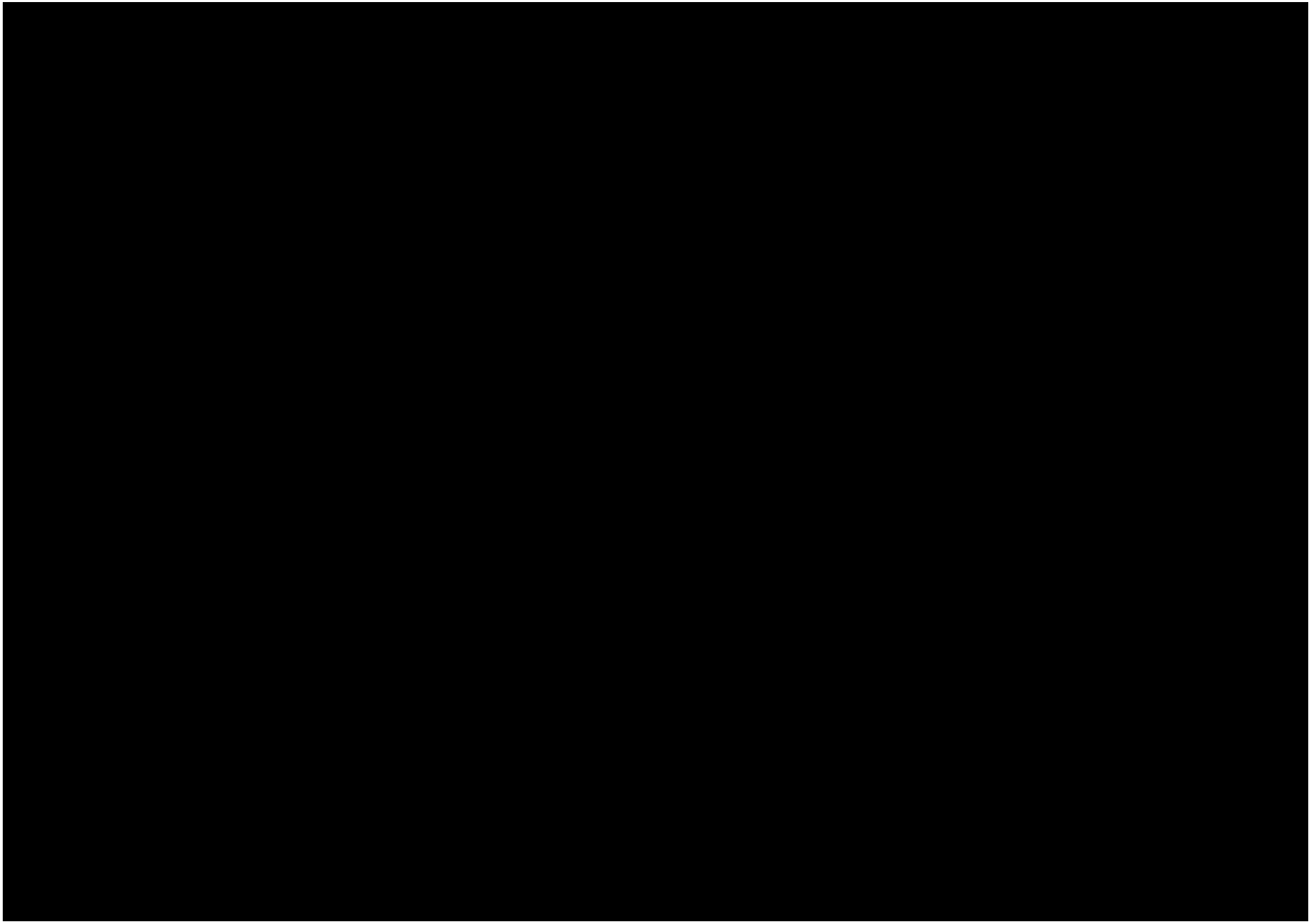












ZPV-201 Amendment 4 Protocol Summary of Changes

Protocol 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

Changes From: From Protocol Amendment 3 dated April 8, 2016 To: Protocol Amendment 4 dated June 20, 2016

Reason for Amendment: Addition of MRI at Visit 24, addition of requirements for enrollment in Extension Study

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	After completion of stage 2 dosing (Courses 1 and 2), subjects will be followed through the subsequent 6 menses (recovery menses plus an additional 5 menstrual events). ~~In the event that a subject's menstrual bleeding returns to ≥80mL (assessed by alkaline hematin assay) at the end of this period~~, the subject may be offered the opportunity to enroll in an extension study.	After completion of stage 2 dosing (Courses 1 and 2), subjects will be followed through the subsequent 6 menses (recovery menses plus an additional 5 menstrual events), **after which (at Visit 24)** the subject may be offered the opportunity to enroll in an **open-label** extension study. **Subjects who fail to achieve amenorrhea may enroll in the extension study at Visit 19. Amenorrhea is defined as any 28-day period during treatment (not including the ODIs) without a bleeding score >1.**	Change in study design
8.2.1 Overview of Study Design	After end of dosing in Course 2, subjects will be followed through the subsequent recovery menses and for an additional 5 menstrual events. ~~In the event that a subject's menstrual bleeding returns to >80 mL (assessed by alkaline hematin assay) at the end of this period~~ the subject may be offered the	After end of dosing in Course 2, subjects will be followed through the subsequent recovery menses and for an additional 5 menstrual events, **after which** the subject may be offered the opportunity to enroll in an extension study. **Subjects who fail to achieve amenorrhea may enroll in the extension study at Visit 19.**	Requirements for roll-over into Extension Study added

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	opportunity to enroll in an extension study.	**Amenorrhea is defined as any 28-day period during treatment (not including the ODIs) without a bleeding score >1.**	
8.2.3 Randomization and Blinding	After the second treatment course is completed the subjects will be followed for 6 menstrual events to determine durability of effect of treatment. ~~If subjects return to a MBL score of ≥80 mL at the end of this period, assessed by alkaline hematin assay~~, they may be offered the opportunity to enroll in an extension study.	After the second treatment course is completed the subjects will be followed for 6 menstrual events to determine durability of effect of treatment, **after which** they may be offered the opportunity to enroll in an **open-label** extension study. **Subjects who fail to achieve amenorrhea may enroll in the extension study at Visit 19. Amenorrhea is defined as any 28-day period during treatment (not including the ODIs) without a bleeding score >1.**	Requirements for roll-over into Extension Study added
[redacted]		[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
	[redacted]		Study changed
[redacted]	[redacted]	[redacted]	[redacted]
12. STATISTICAL METHODS **12.2.2.2 Secondary Endpoints**	*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.	*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 **and after the 6 months of recovery menses (Visit 24).**	New procedure added
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	
[redacted]		[redacted]	

Charts and footnotes were updated to reflect the changes above.