NCT02651688

Study ID: ZA-205

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

Protocol Amendment 4 Date: 09 December 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.

ZA-205 Amendment 1 Protocol Summary of Changes

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

Changes From: From Original Protocol dated December 14, 2015 To: Protocol Amendment 1 dated February 2, 2016

Reason for Amendment: To add 24-hour T and enclomiphene steady state PK assessments after 12 weeks of treatment

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
PROTOCOL SYNOPSIS: **Study Purpose** **Study Design and Duration of treatment** **Number of Subjects** [redacted]		**Statement added:** [redacted]	[redacted]

ZA-205 Amendment 1 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted] **Statistical Methods**		[redacted] **Statement added:** [redacted]	
Tables 1 and 2		**Updated to include new assessments**	[redacted]
LIST OF ABBREVIATIONS		[redacted]	
7. TRIAL OBJECTIVES		**Statement added:** [redacted]	[redacted]
8. TRIAL DESIGN **8.1.1 Overview of Study Design**		**Statement added:** [redacted]	[redacted]
8.2.2 Exclusion Criteria	20. Enrolled and randomized (if applicable) in a previous enclomiphene study	**20.** Enrolled and randomized (if applicable) **to enclomiphe**ne in a previous enclomiphene study	
[redacted]		[redacted]	[redacted]

ZA-205 Amendment 1 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]		[redacted]	[redacted]
[redacted]		[redacted]	[redacted]
13. STATISTICAL METHODS [redacted]		**Statement added;** [redacted]	[redacted]

ZA-205 Amendment 1 Protocol Summary of Changes

[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	

ZA-205 Amendment 1 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		[redacted]	

ZA-205 Amendment 2 Protocol Summary of Changes

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

Changes From: From Original Protocol dated December 14, 2015 To: Protocol Amendment 2 dated July 1, 2016

Reason for Amendment: To add 24-hour T and enclomiphene steady state PK assessments after 12 weeks of treatment (selected sites) and new questionnaire

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
PROTOCOL SYNOPSIS: [redacted]		[redacted]	[redacted]
[redacted]		[redacted]	
Number of Subjects		**Statement added:** **Fifteen (15) of these subjects will be offered the opportunity to participate in the 24-hour testosterone and enclomiphene T subjects to be performed after 12 weeks of treatment.**	
[redacted]		[redacted]	

ZA-205 Amendment 2 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]		[redacted]	
[redacted]		[redacted]	Addition of PK assessments
LIST OF ABBREVIATIONS		**Updated to include PK parameters**	
[redacted]		[redacted]	[redacted]
8. TRIAL DESIGN **8.1.1 Overview of Study Design** **8.1.7 Subject Questionnaires**		[redacted]	[redacted]
8.2.2 Exclusion Criteria	20. Enrolled and randomized (if applicable) in a previous enclomiphene study	**20.** Enrolled and randomized (if applicable) **to enclomiphe**ne in a previous enclomiphene study	Clarification

ZA-205 Amendment 2 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
[redacted]		[redacted]	[redacted]
10. [redacted]		[redacted]	[redacted]
13. STATISTICAL METHODS [redacted]		[redacted]	[redacted]

ZA-205 Amendment 2 Protocol Summary of Changes

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
		[redacted]	

ZA-205 Amendment 2 Protocol Summary of Changes

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

ZA-205 Amendment 3 Protocol Summary of Changes

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

Changes From: From Protocol Amendment 2 dated July 1, 2016 To: Protocol Amendment 3 dated September 14, 2016

Reason for Amendment: To add fatigue assessment at each visit and subject interviews for PRO development at 36 weeks

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
Protocol Synopsis **Study Purpose** [redacted]	[redacted]	[redacted]	[redacted]
Table 1 [redacted]		[redacted]	[redacted]
8. TRIAL DESIGN **8.1.1 Overview of Study Design** [redacted]		[redacted]	[redacted]

ZA-205 Amendment 3 Protocol Summary of Changes

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

Repros
THERAPEUTICS INC

Protocol Number: ZA-205

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

Original Protocol: December 14, 2015
Amendment 1: February 2, 2016 (Selected Sites only)
Amendment 2: July 1, 2016
Amendment 3: September 14, 2016
Amendment 4: December 9, 2016

SPONSOR:

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

[redacted] IND 65,396

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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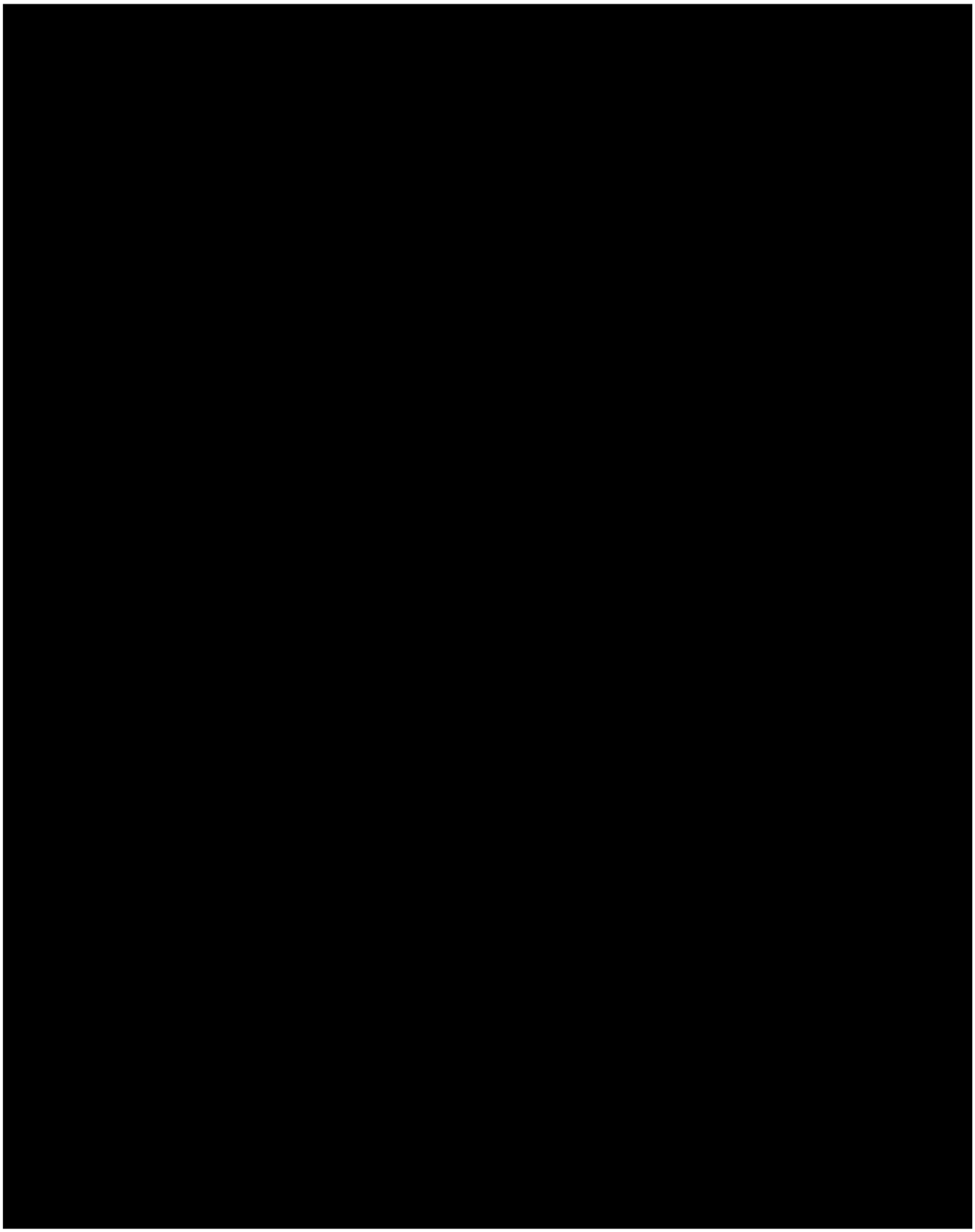
3. PROTOCOL SYNOPSIS

Test Drugs:	Enclomiphene 12.5 and 25 mg capsules, and placebo
Protocol Number:	ZA-205
Study Purpose:	To compare the effects of 12 months of treatment with enclomiphene 12.5 mg, 25 mg, or placebo capsules on body composition and metabolic parameters in overweight men with acquired hypogonadotropic hypogonadism (confirmed morning T≤300 ng/dL) following a 6 month diet and 15 month exercise program. Subjects must not have been treated with testosterone products in the 6 months prior to the study and must not ever have used testosterone products for a year or longer. [redacted]
Study Design and Duration of Treatment:	Protocol ZA-205 is a randomized, double-blind, placebo-controlled multi-center study to compare changes in metabolic parameters following treatment with 12.5 mg or 25 mg of enclomiphene or placebo in conjunction with a 6-month diet and 15 month exercise program, in overweight men with acquired hypogonadotropic hypogonadism. Subjects will receive a 15-month gym membership with personal trainer for 12 months, a Fitbit and a 6 month commercial diet program. The study requires 7 clinic visits and is approximately 15 months in duration. Subjects will be treated with enclomiphene or placebo for 12 months. [redacted] The study will enroll 45 male subjects, 15 randomized to treatment with enclomiphene 12.5 mg, 15 randomized to treatment with 25 mg enclomiphene, and 15 randomized to Placebo, in a 1:1:1 ratio. Eligible subjects must have 2 consecutive assessments of morning testosterone ≤300 ng/dL. LH must be >1.4 mIU/mL and below 9.4 mIU/mL at Screening. Waist circumference must be ≥ 40 inches (101.6 cm). Efficacy assessments will include weight, BMI, waist circumference, lean body mass, and metabolic parameters. [redacted]
Subject Population	The study will enroll overweight males, aged 18-60, with secondary hypogonadism and confirmed morning testosterone levels ≤300ng/dL, with a waist circumference ≥ 40 inches (101.6 cm), who must not have been treated with testosterone products in the 6 months prior to the study and must not ever have used testosterone products for a year or longer.

Number of Subjects:	45 male subjects, 15 randomized to the 12.5 mg enclomiphene group, 15 to the 25 mg enclomiphene group and 15 in the Placebo group, meeting the inclusion/exclusion criteria. Fifteen (15) of these subjects will be offered the opportunity to participate in the 24-hour testosterone and enclomiphene T subjects to be performed after 12 weeks of treatment.
Study Duration:	Total participation in the study is approximately 15 months.
[redacted]	[redacted]
Test Drugs:	Enclomiphene 12.5 and 25 mg, and matching placebo capsules will be supplied by the sponsor.
Study Endpoints	The efficacy endpoints will be: • Changes in Lean Body Mass (LBM), assessed using DXA • Changes in waist circumference, comparing enclomiphene to placebo • Changes from baseline in testosterone, comparing enclomiphene to placebo • Values and changes in values from baseline in LH, HbA1c, FPG, C-reactive protein, Interleukin-6, tumor necrosis factor (TNF-α) receptor 2, and leptin compared to placebo • Change in strength assessed from maximum chest and leg press weight achieved, using an inclined plane leg press and vertical chest press • Changes in insulin resistance determined by HOMA-IR and Quantose IR™ (Metabolon Inc) compared to placebo

	• Change in weight and BMI compared to placebo • Values for dihydrotestosterone (DHT) and estradiol (E2), and the ratios of DHT:testosterone and testosterone:E2 [redacted]
Statistical Methods:	Although this study is considered hypothesis generating, a Statistical Analysis Plan (SAP) will be prepared prior to the unblinding of the study that documents all planned analyses and data assumptions. Interim analyses will be conducted after all subjects have been assessed for 6 and 12 months. 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. Analyses will focus on descriptive statistics for each efficacy endpoint with between and within treatment comparison conducted. It is hypothesized that subjects treated with enclomiphene will have additional improvements in testosterone, body composition, weight, waist circumference and assessments of metabolic parameters. Safety and tolerability [redacted] will be summarized for each treatment group separately. 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. Where applicable, statistical testing of the safety data to compare the treatment groups is anticipated. [redacted]

[redacted]



5. LIST OF ABBREVIATIONS

AE	adverse event
CRF	case report form
[redacted]	
DHT	dihydrotestosterone
dL	deciliter
DVT	deep vein thrombosis
ECG	electrocardiogram
FSH	follicle-stimulating hormone
g	grams
GCP	Good Clinical Practice
HbA_{1c}	hemoglobin A_{1c}
hCG	human chorionic gonadotrophin
Hct	hematocrit
Hgb	hemoglobin
HOMA-IR	Homeostasis Model of Assessment – Insulin Resistance
ICH	International Conference on Harmonization
IND	investigational new drug
IRB	Institutional Review Board
kg	kilogram(s)
LBM	lean body mass
LH	luteinizing hormone
m	meters
mg	milligram(s)
mL	milliliter
ng	nanograms
PRO	Patient Reported Outcome
PSA	prostate specific antigen
RBC	red blood cell
SAE	serious adverse event
SHBG	sex hormone binding globulin
T	testosterone
TE	thromboembolic
Total T	total testosterone
$t_{½}$	Apparent elimination half life
T_{max}	Time of the maximum measured plasma concentration
λz	Terminal elimination rate constant
VTE	venous thromboembolism
WBC	white blood cell

6. BACKGROUND INFORMATION

The sponsor has completed a full Phase III development program demonstrating the safety and efficacy of enclomiphene for the treatment of secondary hypogonadism. Details of non-clinical findings are provided in the Investigator Brochure.

[redacted]

6.3 Ethical Conduct of the Study

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

7. TRIAL OBJECTIVES AND PURPOSE

The primary objective of this study is to compare the effects of treatment with enclomiphene to placebo, upon anthropometric and metabolic parameters in hypogonadal men undergoing a 6-month diet and 15 month exercise program.

Additional study objectives are to document the differences in testosterone and LH and changes from baseline in symptoms using a selection of subject questionnaires in enclomiphene-treated men compared to placebo. [redacted]

8. TRIAL DESIGN

8.1 Study Design

8.1.1 Overview of Study Design

Protocol ZA-205 is a randomized, double-blind, placebo-controlled multi-center study to compare changes in weight, lean body mass (using DXA), waist circumference, glycemic parameters and scores using various subject questionnaires following treatment with 12.5 or 25 mg enclomiphene or placebo in overweight men with acquired hypogonadotropic hypogonadism and waist circumference ≥ 40 inches (101.6 cm). The study requires 7 clinic visits and is approximately 15 months in duration. Subjects will be provided with a 15 month gym membership and personal trainer, and will exercise for 30-45 minutes three times a week. They will also receive a 6 month commercial diet program. Subjects will be treated for 12 months. [redacted]

The study will enroll 45 male subjects, 15 randomized to treatment with enclomiphene 12.5 mg, 15 randomized to enclomiphene 25 mg and 15 randomized to placebo, in a 1:1:1 ratio.

Eligible subjects must have 2 consecutive assessments of morning T at Visit 1 (screening). The assessments must be 2-4 days apart and both must be 300 ng/dL or less. Subjects must also have LH >1.4 and < 9.4 mIU/mL at Screening. Waist circumference must be ≥ 40 inches (101.6 cm). Subjects must not have been treated with testosterone products in the 6 months prior to the study. They must not have used testosterone products for 12 months or longer at any time in the past. Subjects will follow a commercial diet plan and exercise with a personal trainer at least 3 times a week. At clinic visits, clinical laboratory assessments will be performed and subject questionnaires will be administered. Subjects will be called every 2 weeks to check on compliance with their exercise regimen and diet, and solicit adverse events. [redacted]

8.1.2 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 unused study medication with dispensing records to the Sponsor for final accountability and disposal.

8.1.3 Randomization and Blinding

Subjects will be randomized, in a double-blinded manner, in a 1:1:1 ratio to enclomiphene 12.5 mg, enclomiphene 25 mg, or placebo.

8.1.4 Study Medication

All study drugs will be supplied by Repros Therapeutics Inc. Enclomiphene 12.5 mg and 25 mg capsules, or placebo capsules, [redacted] by a clinical supplies contract vendor designated by Repros Therapeutics Inc. Each bottle will have a label indicating the identification number, the number of capsules, expiration date, a statement "Caution: New Drug – Limited by Federal Law (US) to Investigational use" and instructions to take 1 capsule daily in the morning. Subjects will take one capsule with approximately 8 ounces of water.

Subjects should be instructed not to dose on the mornings of clinic visits.

Subjects will record study medication date and time on subject Drug Diary Cards. [redacted]

8.1.6 Lean Body Mass Assessment

Lean body mass will be assessed by DXA. For further details reference the Study Procedures Manual.

[redacted]

8.1.8 Waist Circumference Measurement

Waist circumference should be measured at the level of the navel to the nearest 0.5 cm. The tape should be held level. Subject should take 3 breaths and on the last exhale (normal exhale) the measurement should be taken.

[redacted]

8.1.11 Diet and Exercise Programs

These programs are described in more detail in the Study Procedures Manual.

The sponsor is providing a 15 month gym membership that will commence when subjects start treatment and conclude at the 3-Month follow up visit. Subjects will be assigned a personal trainer for 12 months and will be instructed to exercise for at least 30-45 minutes 3 times each week. The workout will be 60% cardiovascular training and 40% resistance training. Strength progress will be assessed from changes in leg press and chest press weights. Subjects will receive a signed letter from the investigator stating that the subject has been cleared to participate in an exercise program that the subject can provide to their trainer prior to starting their program.

Subjects will also receive a 6-month commercial diet program that they will start when they start treatment, and follow until their 6 month visit. The diet plan provides about 1500 calories/day comprised as follows: 25% of calories from lean protein, less than 30% of calories from fat, about 50% carbohydrates, low sodium (less than 2,300 mg/day) and 25-35 g fiber /day. Subjects will select the plan of their choice from those available and modify it to individual needs, if necessary, with the help of a plan dietician. The program includes counseling from a plan counselor.

After completion of the commercial diet program subjects will be counseled at each visit to continue with healthy eating habits. Subjects will be called every 2 weeks (except on days of clinic visits), to check on compliance with their diet and exercise programs and solicit any adverse events.

8.2 Selection and Withdrawal of Subjects

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

- Unacceptable adverse events considered by the investigator to be associated with use of the study drug occur
- Hematocrit >54% and confirmed upon repeat
- The subject requests to be withdrawn from the study
- A need for concomitant medication prohibited by the protocol arises

- The Principal Investigator decides that it is in the subject's best interest
- The subject is noncompliant with the protocol at Sponsor/Investigator discretion

8.2.1 Inclusion Criteria

Subjects must meet the following criteria:

1. Overweight (BMI 30 to 42 kg/m^2 inclusive) males age 18 to 60 inclusive
2. Waist circumference ≥ 40 inches (101.6 cm)
3. Previously or concurrently diagnosed as having secondary hypogonadism.
4. Must have 2 morning testosterone assessments at Visit 1, collected before 10 AM, 2-4 days apart, and both of which must be ≤ 300ng/dL.
5. LH >1.4 and < 9.4 mIU/mL (at Visit 1 only)
6. HbA1c ≤7.5
7. Stable weight for last 3 months (+/- 10 pounds)
8. Lives or works within 10 miles of the gym that will be used for the study
9. Must be fit enough to participate in the fitness program
10. Ability to complete the study in compliance with the protocol requirements
11. Ability to understand and provide written informed consent

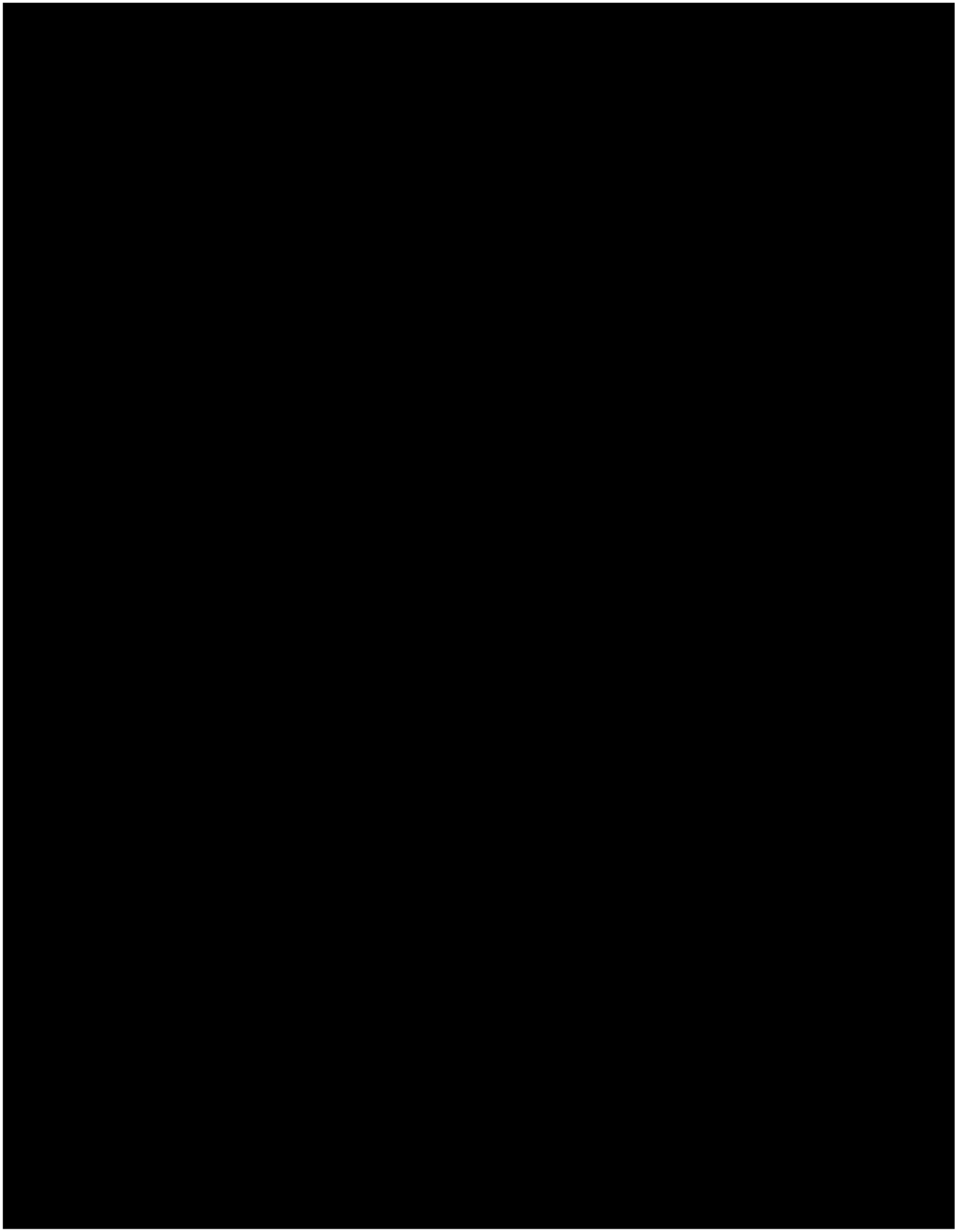
8.2.2 Exclusion Criteria

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

1. Any use of testosterone products (injectable, pelleted, transdermal or sublingual) in the 6 months prior to the study or any prior use of testosterone products for 12 months or longer at any time.
2. Use of testosterone, Clomid, 5α-reductase inhibitors, hCG, androgen, estrogen, anabolic steroid, DHEA, or herbal hormone products during the study
3. Use of Clomid in the past year
4. Known hypersensitivity to Clomid
5. Allergy to soy, peanuts or latex
6. Chronic use of glucocorticoids (chronic use of inhaled or topical glucocorticoids is acceptable)
7. History of drug abuse or chronic narcotic use including methadone
8. A recent history of alcoholism or illegal substance or steroid abuse (<2 years) or presence of moderate alcohol use (>21 drinks per week)
9. Use of an investigational drug or product, or participation in a drug or medical device research study within 30 days prior to receiving study medication
10. A hematocrit >54%

11. Presence or known history of hyperprolactinemia with or without a tumor (prolactin >20 ng/mL)
12. Current or history of prostate cancer or a suspicion of prostate disease unless ruled out by prostate biopsy, or a PSA>3.6
13. Current or history of breast cancer
14. Uncontrolled hypertension based on the Investigator's assessment at screening
15. History of bulimia nervosa or binge eating
16. Subject has (had) a lap band or undergone gastric bypass surgery
17. Subject has celiac disease or gluten intolerance
18. Subject has Type I diabetes
19. Subject has any condition which in the opinion of the investigator would interfere with the participant's ability to provide informed consent, comply with study instructions, possibly confound interpretation of study results, or endanger the participant if he took part in the study
20. Enrolled and randomized (if applicable) to enclomiphene in a previous enclomiphene study

[redacted]



[redacted]

10. STUDY ENDPOINTS

The efficacy endpoints will be:

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

[redacted]

11. ASSESSMENT OF SAFETY

[redacted]

11.1 Adverse Events

11.1.1 Reporting Adverse Experiences

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

11.1.2 Definitions

Adverse Event – Any untoward medical occurrence in a clinical investigation subject administered a drug and does not necessarily have a causal relationship with this treatment. An AE can therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding if the investigator considers this finding to be an adverse event), 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.

Venous thromboembolic events (VTE) should also be reported to the sponsor as Serious Adverse Events regardless of whether the above-defined SAE requirements are met.

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

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

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

Intensity, to be graded as:

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

Relationship to study medication, to be graded as:

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

11.1.3 Serious Adverse Events (SAEs)

The Principal Investigator shall document all SAEs in a subject receiving study drug or during 30 days following the last dose and must be reported to the Repros Therapeutics Inc. Safety Monitor within 24 hours by Fax or telephone, even if the SAE does not appear to be drug-related. This report should include all available information at the time of notification. This notification should be followed with submitting a SAE Report Form provided by Repros Therapeutics Inc. All additional follow-up reports must be reported to the Repros Therapeutic Inc. monitor as soon as available.

Venous Thromboembolic Events

Venous thromboembolic events (VTE) should be reported to the sponsor as Serious Adverse Events regardless of whether the above-defined SAE requirements are met.

12. Concomitant Medications

Any prescription or over-the-counter medication taken during the study will be recorded in the appropriate section of the CRF. Subject must be on a stable dosage of approved concomitant medications at least 48 hours prior to initial drug administration. Unless medically necessary the dosage of chronic medications should not be changed. Unless medically necessary the addition of new medications should be avoided.

12.1 Prohibited Medications

Use of any of the following medications during the study is prohibited:

- Any testosterone products other than the randomized study treatment
- Aromatase inhibitors (e.g. Anastrazole)
- Clomid
- 5α-reductase inhibitors
- hCG
- Androgen
- Estrogen
- Anabolic steroid
- DHEA
- Herbal hormone products
- Chronic systemic steroid use (short term use is acceptable)

13. STATISTICAL METHODS

13.1 Determination of Sample Size

As this is a hypothesis-generating study sample size was not determined based on statistical assumptions and calculations. [redacted]

13.2 Statistical and Analytical Plan

A Statistical Analysis Plan will be prepared prior to study unblinding which will fully describe the analyses planned for this study.

13.2.1 Interim Analysis

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

13.2.2 Demographics and Subject Characteristics

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

13.2.3 Efficacy Analyses

The analysis of each efficacy endpoint will be conducted in the intent-to-treat (ITT) population, defined as all subjects randomized to treatment with enclomiphene or placebo. The ITT population will be determined prior to unblinding the study data and reasons for any subjects excluded will be explained in the clinical study report. Handling of missing data will be described in the Statistical Analysis Plan (SAP) [redacted] t will be of interest to investigate various prognostic factors, such as age and diet compliance, to determine how these affect treatment response. Those factors will be noted in the SAP.

13.2.3.1 Lean Body Mass

Lean Body Mass (LBM) will be determined by DXA at baseline, 6 months and end of study. The change from baseline in lean body mass will be investigated with at least two measurements:

- Percentage change in LBM
- Change in LBM percentage (%LBM)

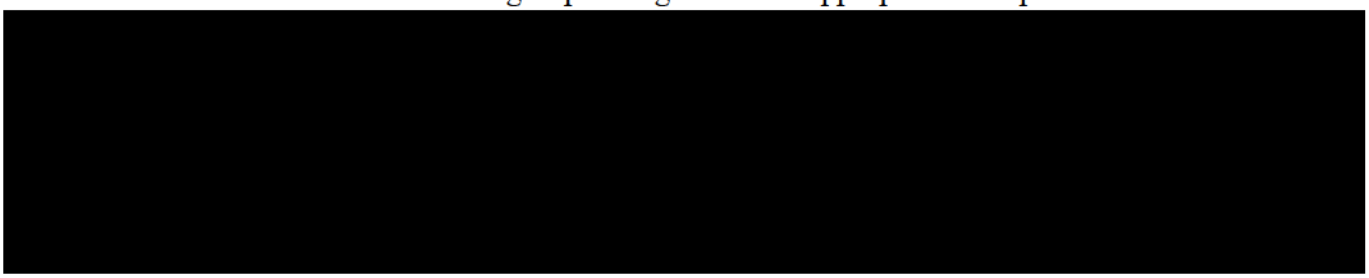
Subjects are expected to gain LBM and percentage LBM. Within and between treatment group t-tests or appropriate non-parametric methods will assess treatment affect. Descriptive statistics will summarize the results.

13.2.3.2 Body Strength

Strength will be assessed over the course of the study by assessments of the maximum Leg and Chest Press weight obtained. These values will be assessed at baseline and weekly. The baseline assessment will be determined at the subject's first gym visit. Analyses will compare the periodic assessments to the subject's baseline. Within and between treatment group t-tests or appropriate non-parametric methods will assess treatment affect. Descriptive statistics will summarize the results.

13.2.3.3 Waist Circumference

Careful assessments of waist circumference will detect change in body composition. The change in waist circumference over the duration of the study will be calculated and summarized using descriptive statistics. The change from baseline will be compared within and between treatment groups using a t-test or appropriate non-parametric method.



13.2.3.5 Testosterone

For each treatment group, the T and change from baseline in T (visit value minus baseline value) will be summarized at each treatment visit using descriptive statistics (sample size, mean, median, standard deviation, minimum and maximum). The change from baseline in T will be compared within and between treatment groups using a t-test or appropriate non-parametric method.

13.2.3.6 LH

For each treatment group, the LH and change from baseline in LH (visit value minus baseline value) will be summarized at each treatment visit

using descriptive statistics (sample size, mean, median, standard deviation, minimum and maximum). The change from baseline in LH will be compared within and between treatment groups using a t-test or appropriate non-parametric method.

13.2.3.7 Metabolic Parameters

For each treatment group, the HbA1c, FPG, Insulin, HOMA-IR and Quantose IR assessment of insulin sensitivity and change from baseline will be summarized at each treatment visit using descriptive statistics (sample size, mean, median, standard deviation, minimum and maximum). The change from baseline will be compared within and between treatment groups using a t-test or appropriate non-parametric method.

13.2.3.8 Change in BMI

For each treatment group, the weight and change from baseline in BMI (visit value minus baseline value) will be summarized at Week 16 using descriptive statistics (sample size, mean, median, standard deviation, minimum and maximum). The change from baseline in BMI will be compared within and between treatment groups using a t-test or appropriate non-parametric method.

[redacted]

[redacted]

[redacted]

13.3 General Statistical Issues

For the efficacy variables, a last observation forward approach will be used to impute missing data in some analyses. 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]

14. ETHICS

14.1 Subject Information and Consent

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

14.2 Institutional Review Board

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

14.3 Monitoring Case Report Forms

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

14.4 Study Record Retention

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

14.5 Data Quality Assurance

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

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

14.6 Confidentiality

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

14.7 Publications

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

15. INVESTIGATOR'S STATEMENT

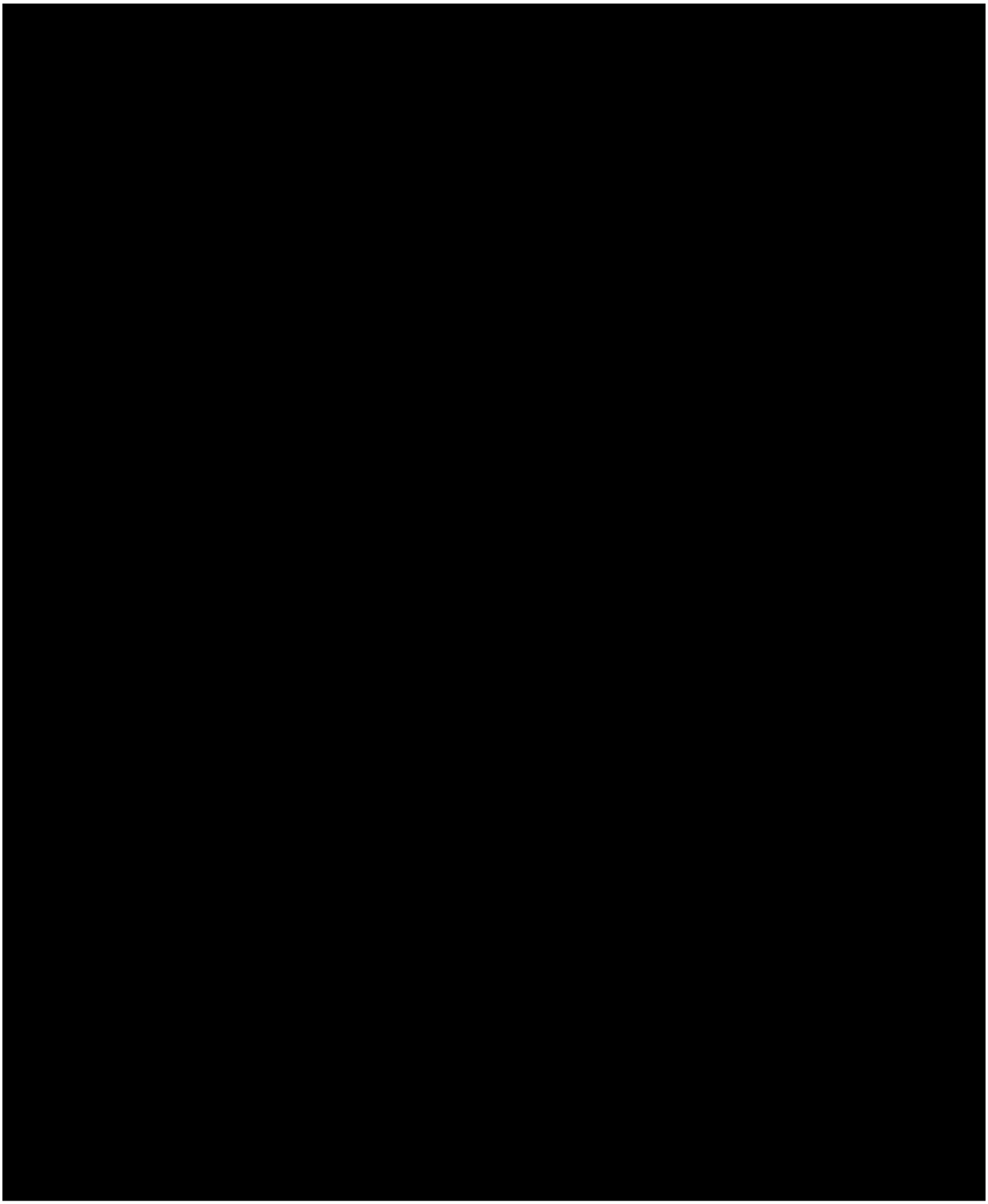
I have reviewed the ZA-205 protocol and Investigator Brochure and agree to conduct this study as outlined in the protocol and in compliance with ICH/GCP Guidelines.

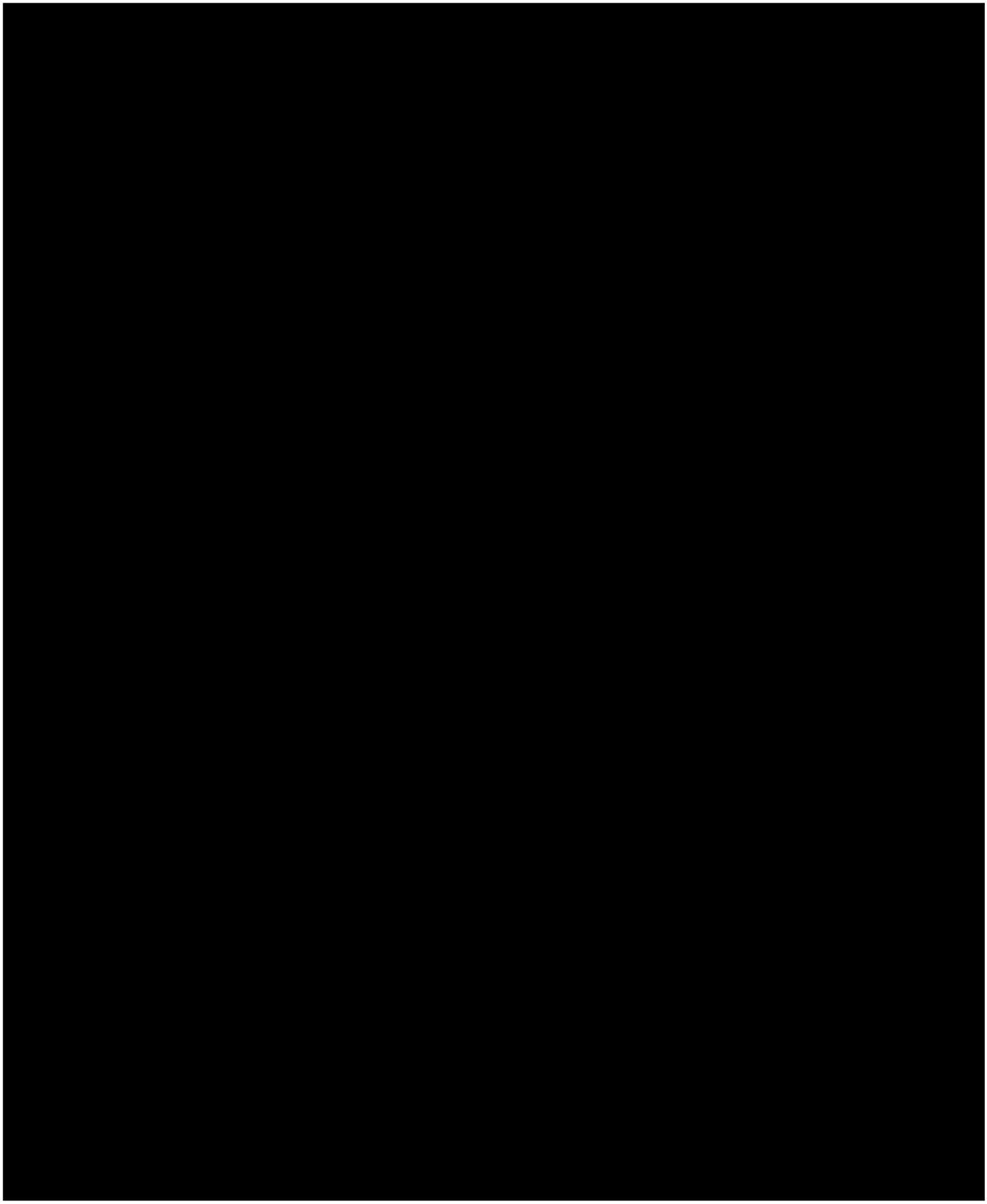
_____ _____

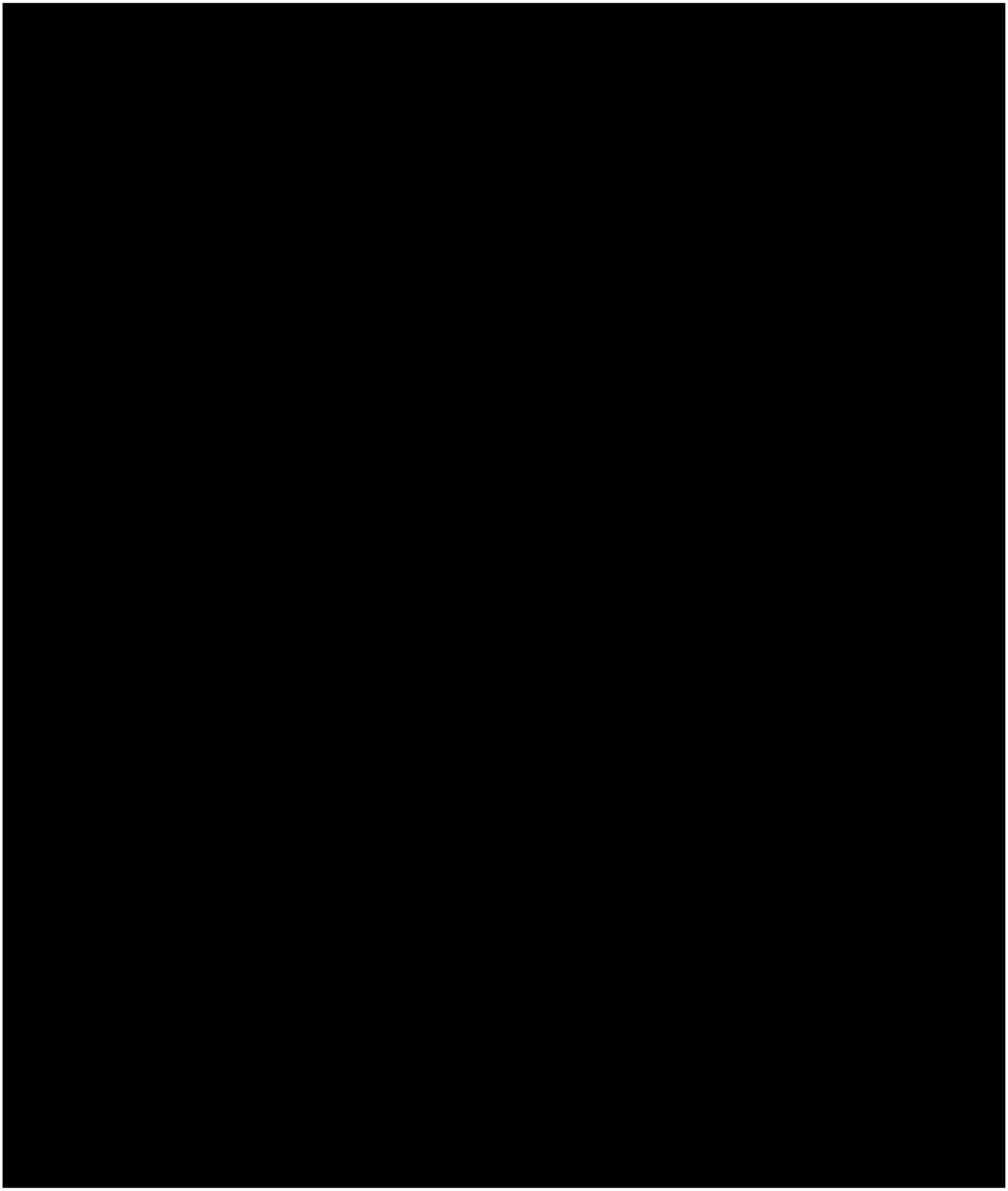
Investigator Date

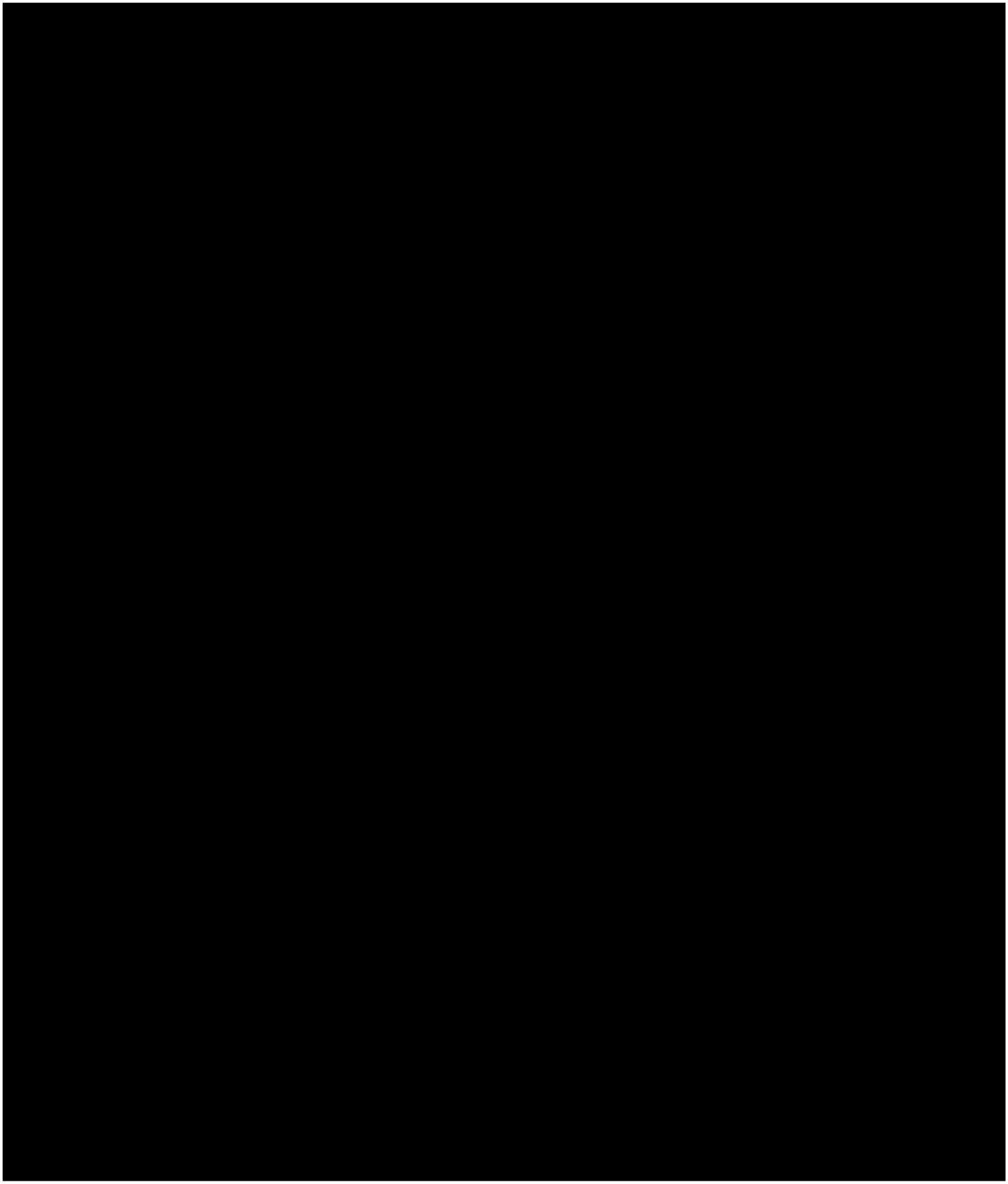
_____

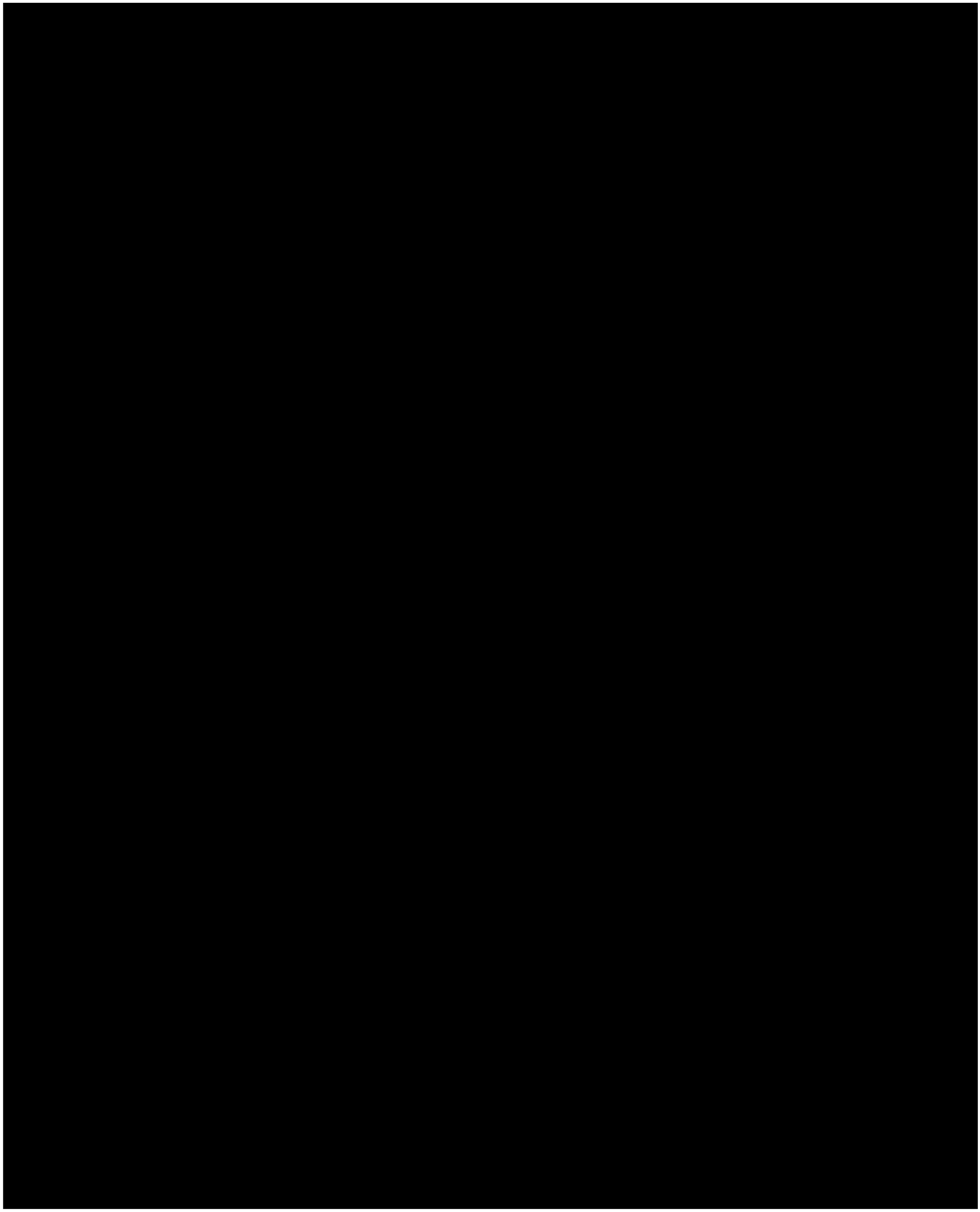
Printed name

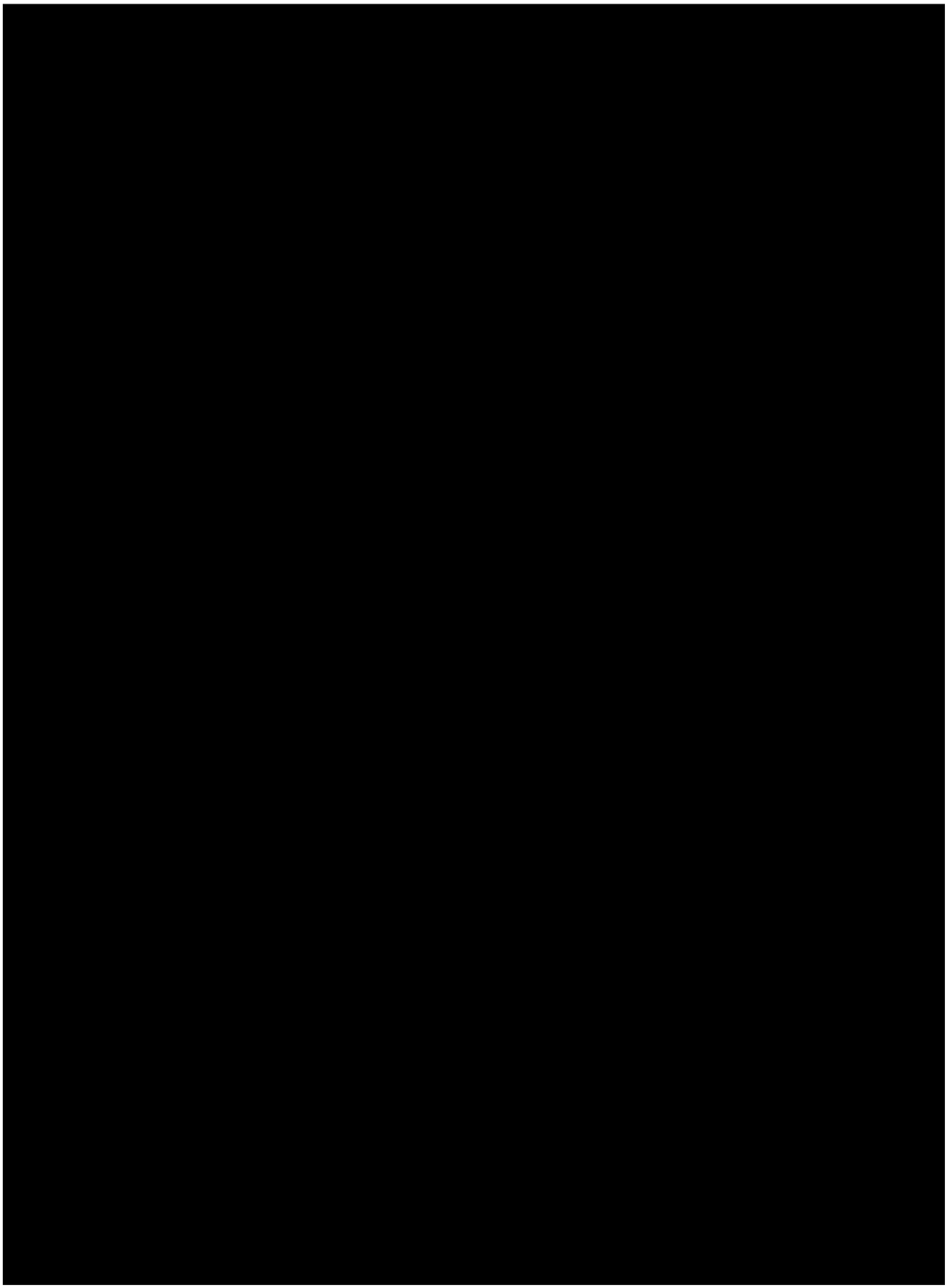


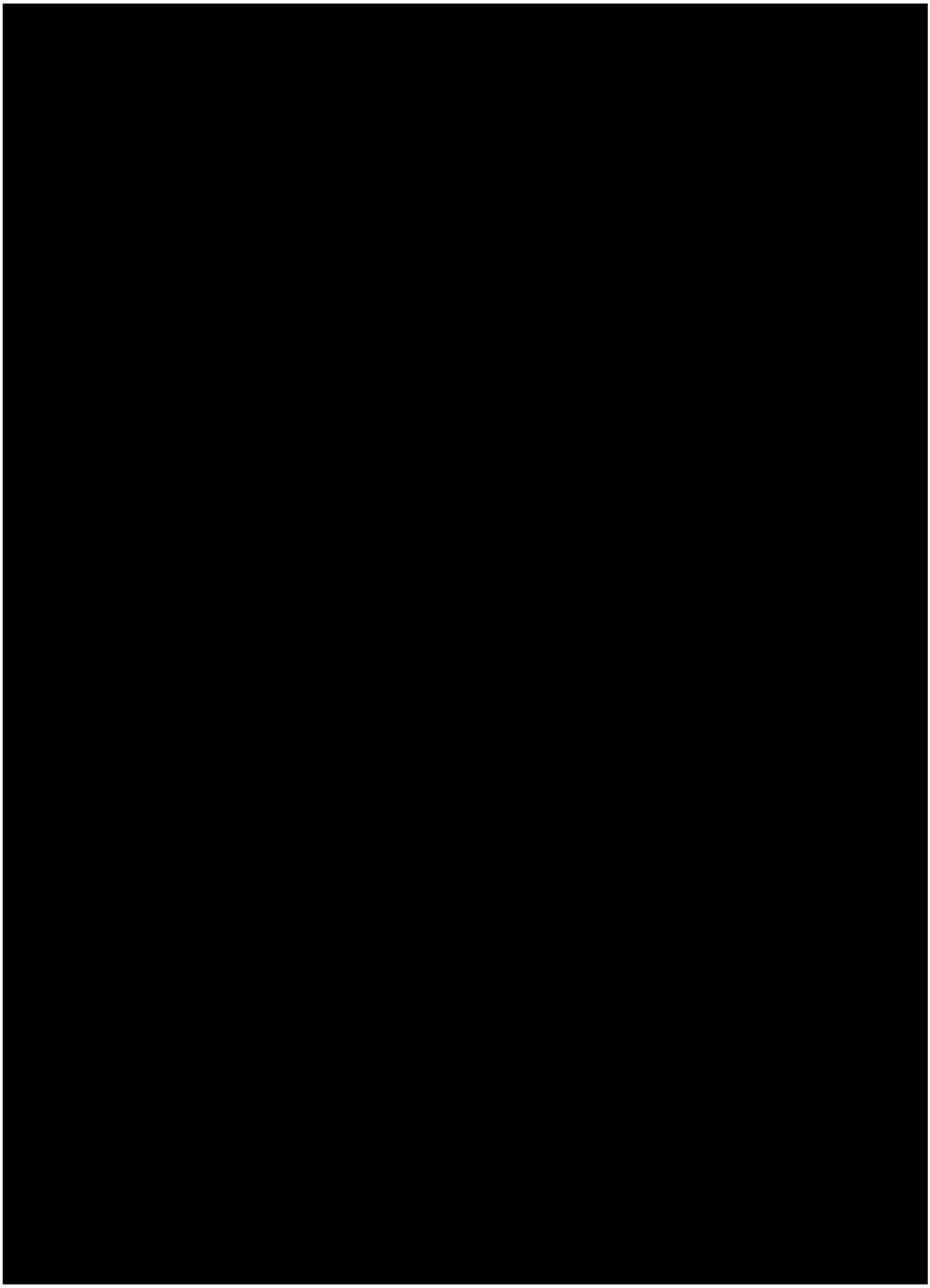


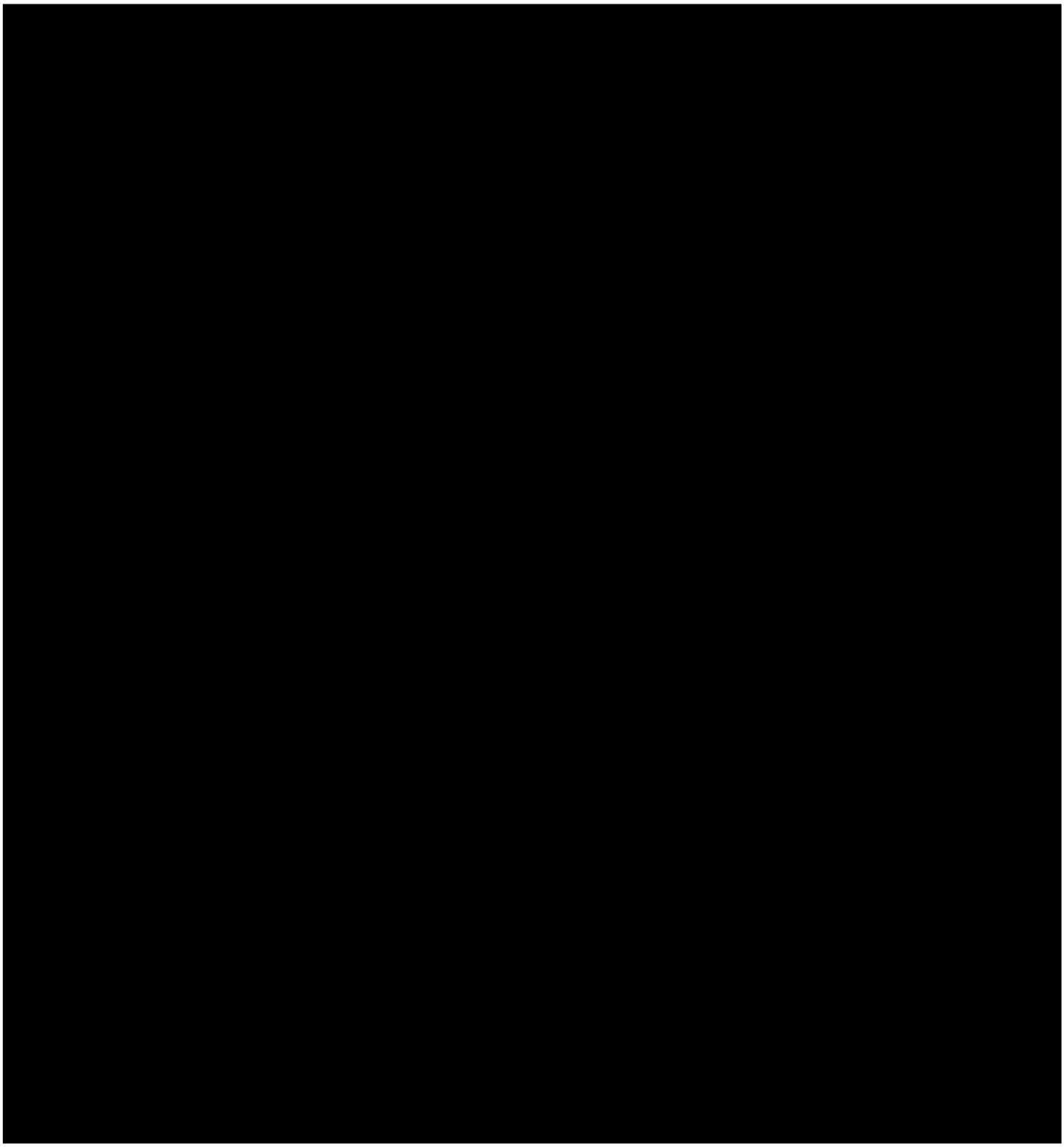


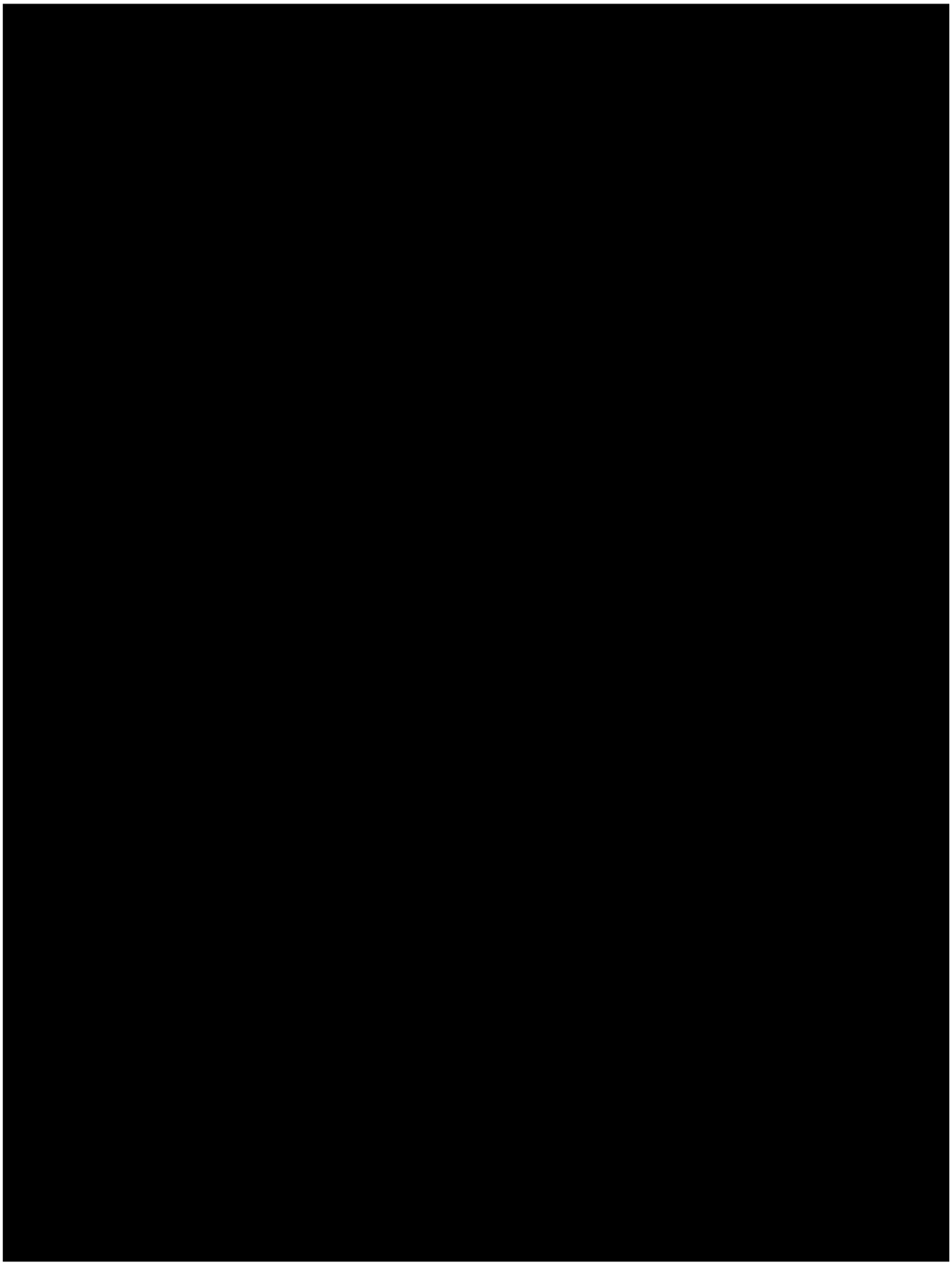












ZA-205 Amendment 4 Protocol Summary of Changes

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

Changes From: From Protocol Amendment 3 dated September 14, 2016 To: Protocol Amendment 4 dated December 9, 2016

Reason for Amendment: To add depression assessment (PHQ-9) at Visits 6 and 7

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

SECTION	CHANGED FROM	CHANGED TO	REASON FOR CHANGE
Table 1		**Footnote 6 added to include depression assessment**	New study assessment
8. TRIAL DESIGN **8.1.7 Subject Questionnaires**	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]