NCT03425253

Study ID: CMO-MA-FAS-0513

Title: A Prospective, Open-label Study to Evaluate Sequential Treatment with BELKYRA® and Juvéderm® VOLUMA™ with Lidocaine for Overall Improvement in Jawline Contour

Protocol Date: 21Mar2018

Clinical Study Protocol

A Prospective, Open-label Study to Evaluate Sequential Treatment with BELKYRA® and Juvéderm® VOLUMA™ with Lidocaine for Overall Improvement in Jawline Contour

Protocol Number:	CMO-MA-FAS-0513
Drug Development Phase:	Phase IV, Post-marketing
Investigational Product:	BELKYRA® / Juvéderm® VOLUMA™ with Lidocaine
Sponsor:	Allergan Pharmaceuticals International Limited Clonshaugh Industrial Estate Coolock, Dublin 17, Ireland
Version and Date	Version 2.0 21-March-2018
Serious Adverse Event Reporting Information - Drug: BELKYRA®	[redacted]
Serious Adverse Event Reporting Information - Device: JUVÉDERM® VOLUMA™	[redacted]
Allergan Medical Safety Physician Contact Information	[redacted]

Conduct: In accordance with the ethical principles that originate from the Declaration of Helsinki and that are consistent with International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP) and regulatory requirements as applicable.

PRINCIPAL INVESTIGATOR'S AGREEMENT

I have read and understand the contents of this clinical protocol for Study No. CMO-MA-FAS-0513 Version 2.0, 21-March-2018 and will adhere to the study requirements as presented, including all statements regarding confidentiality.

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices (Sponsor has certified GCP training completed) and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to an Institutional Review Board (IRB), Independent Ethics Committee (IEC) or another group, it will be submitted with a designation that the material is confidential.

I have read this protocol in its entirety and I agree to all aspects.

Signature	**Date**

Name of Principal Investigator:

<Enter Name and Title>

PROTOCOL SUMMARY

Sponsor:	**Investigational Products:**	**Developmental Phase:**
Allergan Pharmaceuticals International Limited, Clonshaugh Industrial Estate, Coolock, Dublin 17, Ireland	BELKYRA® / Juvéderm® VOLUMA™ with Lidocaine	Phase IV, Post-marketing

Title of Study: A Prospective, Open-label Study to Evaluate Sequential Treatment with BELKYRA® and Juvéderm® VOLUMA™ with Lidocaine for Overall Improvement in Jawline Contour

Protocol Number: CMO-MA-FAS-0513

Number of Subjects: Approximately 50 subjects in main study, approximately 10 subjects in the Biopsy Sub-study.

Indication: Reduction of submental fat and restoration of facial volume for overall improvement in the contour of the jawline.

Primary Study Objective:

To evaluate the combined effectiveness of sequential BELKYRA® treatments of convexity or fullness associated with submental fat and Juvéderm® VOLUMA™ with Lidocaine (hereafter referred to as VOLUMA™) to restore volume along the mandible in enhancing the overall contour of the jawline.

Secondary Study Objectives:

- To evaluate the Investigator's and subject's assessment of aesthetic improvement of the lower face and jawline.
- To evaluate histological changes from baseline to after BELKYRA® treatment(s).

Methodology:

This Phase IV trial is a prospective, open-label, multi-center, interventional, drug and medical device, post-marketing study. Each subject will act as his/her own control. All subjects will sign an informed consent form at the Screening Visit (Visit 1). Eligible subjects will undergo treatment with BELKYRA® injected into subcutaneous pre-platysmal fat tissue in the submental area (Visit 2.1/Day 0). Seven days after the initial BELKYRA® treatment (Visit 3.1), the subject will return to the clinic for a safety evaluation. Eight weeks after BELKYRA® treatment, the submental profile will be evaluated by the Investigator and subject. If the Investigator and subject agree that no further intervention is required to achieve the desired result, subjects may receive VOLUMA™ treatment (Visit 4). If further intervention is required to achieve the desired result, subjects may receive up to 5 optional BELKYRA® treatments (Visits 2.2 to 2.6). Optional BELKYRA® treatments will be administered at least 8 weeks apart, for a maximum of 6 treatments (including initial BELKYRA® treatment at Visit 2.1/Day 0). Subjects who receive optional BELKYRA® treatments will be contacted by telephone

7 days after treatment for safety evaluation (Visits 3.2 to 3.6). Eight weeks after each BELKYRA® treatment, the submental profile will be assessed as described above and a decision made whether further BELKYRA® treatments are desired. When it is determined that further BELKYRA® intervention is not required or the maximum number (6) of BELKYRA® treatments have been administered, the subject receives VOLUMA™ treatment (Visit 4). Fourteen days after VOLUMA™ treatment, subjects will return to the clinic and the Investigator will assess whether a VOLUMA™ Touch-up treatment is to be performed (Visit 5). All subjects will attend a final exit-visit 4 weeks after the last VOLUMA™ treatment (Visit 6).

Subjects will have the option of participating in a Biopsy Sub-study. Participation in the sub-study is voluntary and will not affect the subject's eligibility to participate in the main study. Biopsy samples will be collected from the submental region at Visit B1 and B2. Samples will be collected at 2 timepoints: Visit B1 will occur at least 4 weeks before the first BELKYRA® treatment (at Visit 2.1); Visit B2 will occur 8 weeks after the last BELKYRA® treatment and at least 4 weeks prior to VOLUMA™ treatment (at Visit 4). The initial BELKYRA® treatment (Visit 2.1) will not occur until the initial biopsy site has healed (at least 4 weeks after biopsy); if not healed by 4 weeks, BELKYRA® treatment will be postponed until healed. The VOLUMA™ treatment (Visit 4) will not occur until the second biopsy site has healed (at least 4 weeks after biopsy); if not healed by 4 weeks, VOLUMA™ treatment will be postponed until healed. Histological changes from baseline to after BELKYRA® treatment(s) will be evaluated.

Data will be collected at each clinic visit for all relevant parameters per the *Schedule of Visits and Procedures* (*Table 1.1*).

[redacted]

All adverse events (AEs) will be collected from the signing of the informed consent form (Visit 1) through to the last study visit (Visit 6). Serious adverse events (SAEs) will be reported directly to Allergan within the specified time, format, and procedure described in *Section 9: Adverse Events*. Injection site reactions (ISRs) recorded during the VOLUMA™ treatment period will be collected in an ISR Diary as described in *Section 7.1.8: Injection Site Reaction (ISR) Diary.*

Criteria for Evaluation:

Primary Endpoint

The primary endpoint will be the responder rate for jawline improvement on the Allergan Loss of Jawline Definition Scale (ALJDS), which is defined as the proportion of subjects who show ≥ 1-point improvement from baseline on the ALJDS at the final study visit (after last VOLUMA™ treatment received), as assessed by the Investigator.

Secondary Endpoints

- Change from baseline to last BELKYRA® treatment for ALJDS
- Change from baseline to final study visit for FACE-Q™ Satisfaction with lower face and jawline score
- Change from baseline to final study visit for FACE-Q™ Appraisal of Neck
- Change from baseline to final study visit for FACE-Q™ Appraisal of Area under Chin
- Change from baseline to final study visit for CR (Clinician-Reported) and PR (Patient-reported) Submental Fat Rating Scale (SMFRS) scores
- Change from baseline to final study visit for Submental Skin Laxity Grade (SMSLG) score
- Change from baseline to final study visit in jawline definition based on Independent Reviewer assessment using the ALJDS and photographic images

[redacted]

Key Criteria for Inclusion:

1. Male and females 18 to 65 years of age inclusive on the day of initial BELKYRA® treatment
2. Sign the Independent Ethics Committee (IEC)/Institutional Review Board (IRB)-approved informed consent form (ICF) prior to any study-related procedures being performed
3. Grade 2 or above on the ALJDS [redacted]
4. Submental fat graded by the Investigator as 2 or 3 using the CR-SMFRS [redacted]
5. [redacted]
9. Accept the obligation to forego any treatment or behavior (e.g., unshaven facial hair; significant changes to dietary or exercise habits) during the subject's participation in the study that may affect the assessments of the submental area

[redacted].

Key Criteria for Exclusion:

1. [redacted]
2. A grade of 4 on the SMSLG [redacted]
3. Grade 4 on the Allergan Jowl Fat Rating Scale (AJFRS) (See Appendix 13: Allergan Jowl Fat Rating Scale)
4. Body mass index (BMI) > 35 kg/m2 as determined at Screening
5. [redacted]
6. History of, or current symptoms of dysphagia.
7. [redacted]
8. History of temporary, semi-permanent or permanent facial or neck dermal filler injections ([redacted] below the medial canthi at any time prior to treatment, or within 52 weeks before Screening for treatment above the medial canthi, o[redacted]
9. History of facial and/or neck plastic surgery, tissue grafting or permanent facial implants [redacted]) anywhere in the face or neck, [redacted]
10. History of any intervention (e.g., liposuction, surgery, or lipolytic agents) to treat submental fat (SMF)
11. Evidence of any cause of enlargement in the submental area (e.g., thyroid enlargement, cervical adenopathy, ptotic submandibular gland) other than localized SMF
12. History of mesotherapy or ablative procedures to the face and/or neck 52 weeks before Screening
13. History of skin resurfacing [redacted] in the neck or submental area within 26 weeks before Screening
14. Treatment with botulinum toxin injections in the neck or submental area within 26 weeks before Screening
15. Subjects on prescription topical retinoid therapy and/or topical hormone cream applied to the face, who have not been on a consistent dose regimen for at least 26 weeks before Screening and who are unable to maintain regimen for the study
16. Systemic retinoid therapy within 52 weeks before Screening
17. Current use of oral corticosteroids

18. Is on a regimen of anticoagulation therapy (eg, warfarin, clopidogrel)

[redacted]

20. Has current injection site inflammatory or infectious processes, abscess, an unhealed wound, or a known cancerous or precancerous lesion in chin, masseter, or submental region

[redacted]

22. Planned oral surgery or other dental procedures (e.g., tooth extraction, orthodontia, or implantation) within 2 weeks prior to and after VOLUMA™ treatment

[redacted]

Products, Dose, and Mode of Administration:

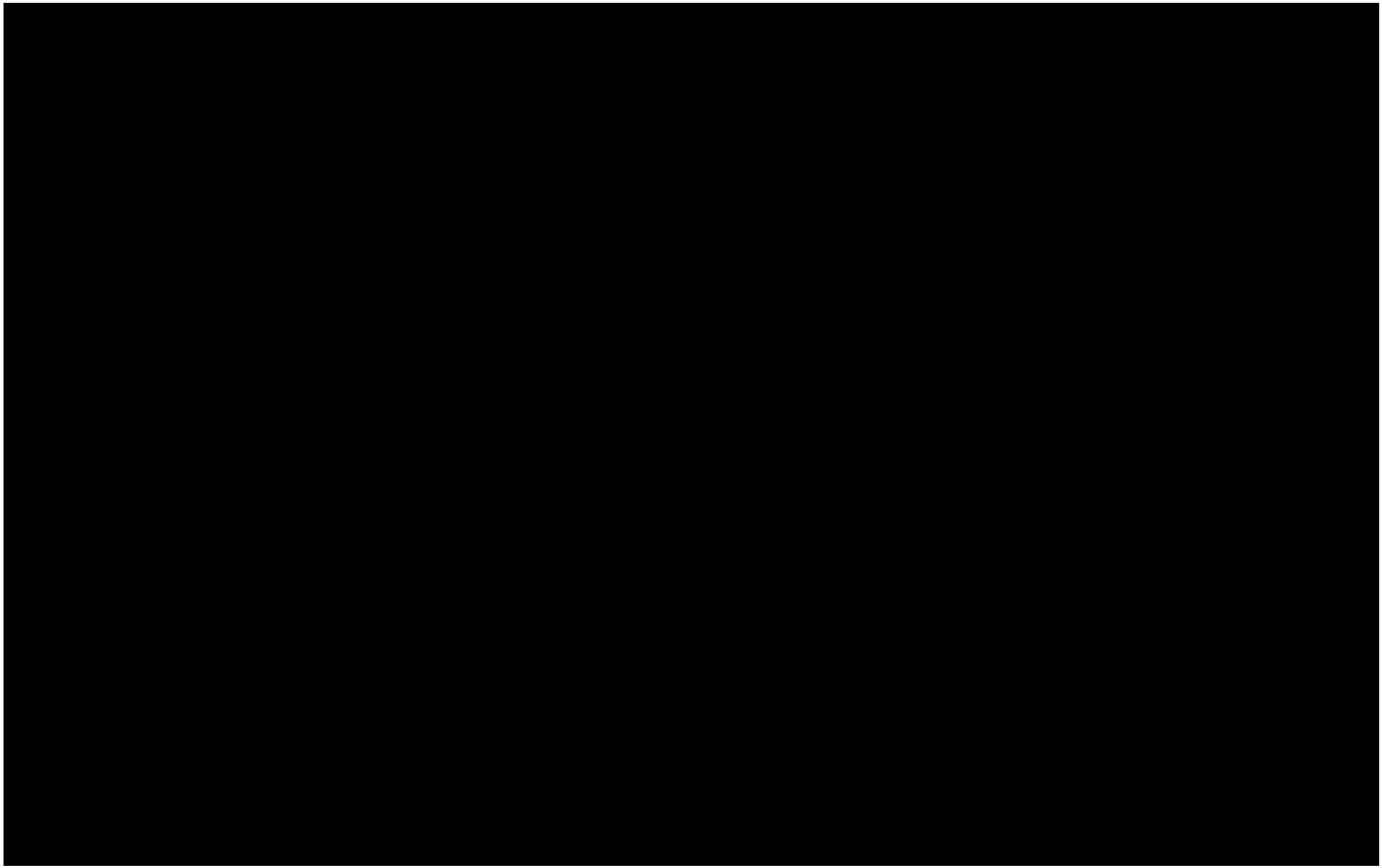
BELKYRA® (deoxycholic acid) is a clear, colorless, sterile solution supplied in 2 mL vials intended for single subject use. Each milliliter of the solution contains 10 mg of deoxycholic acid.

BELKYRA® is injected into subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm^2.

- A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), and injected 1 cm apart
- Up to 6 single treatments may be administered at intervals no less than 8 weeks apart

VOLUMA™ injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of cross-linked HA produced by

Streptococcus species of bacteria, formulated to a concentration of 20 mg/mL, and 0.3% lidocaine in a physiological buffer. It is supplied in prefilled syringes containing 1 mL of product at a concentration of 20mg/mL. The Investigator will determine the appropriate volume of VOLUMA™ to be injected for restoring volume along the mandibular border and enhancement of the overall contour of the jawline. The maximum total volume allowed for an individual subject for the initial and touch-up treatments combined is 6.0 mL, 3 mL per side.
Concomitant Medications: Throughout the study, Investigators can prescribe any concomitant medications or treatments deemed necessary, with the exception of investigational drugs.
Study Duration: Duration of subject participation will be a minimum of 12 weeks and up to approximately 64 weeks, depending on the number of BELKYRA® injections needed and participation in the Biopsy Sub-study.
Statistical Methods: Two analysis populations will be used for analysis of efficacy: the Full Analysis Set (FAS) population, defined as all subjects enrolled and who have at least treatment and one post-treatment efficacy assessment - this population will be used for analysis of all endpoints; and Evaluable Set (ES) population, defined as subjects who received both study treatments (i.e., both BELKYRA® and VOLUMA™) and one post-treatment efficacy assessment – this population will be used for analysis of the primary endpoint. The Safety Analysis Set (SAS), defined as all subjects who consented to participation - this population will be used for safety analyses. The primary efficacy endpoint is the responder rate for jawline improvement on the ALJDS, which is defined as the proportion of subjects who show ≥ 1-point improvement from baseline on the ALJDS at the final study visit (after last VOLUMA™ treatment received), as assessed by the Investigator. Descriptive statistics will be used to summarize the responder rate and 95% confidence intervals will be provided. Details of the analyses for all other efficacy endpoints will be documented in the Statistical Analysis Plan (SAP).



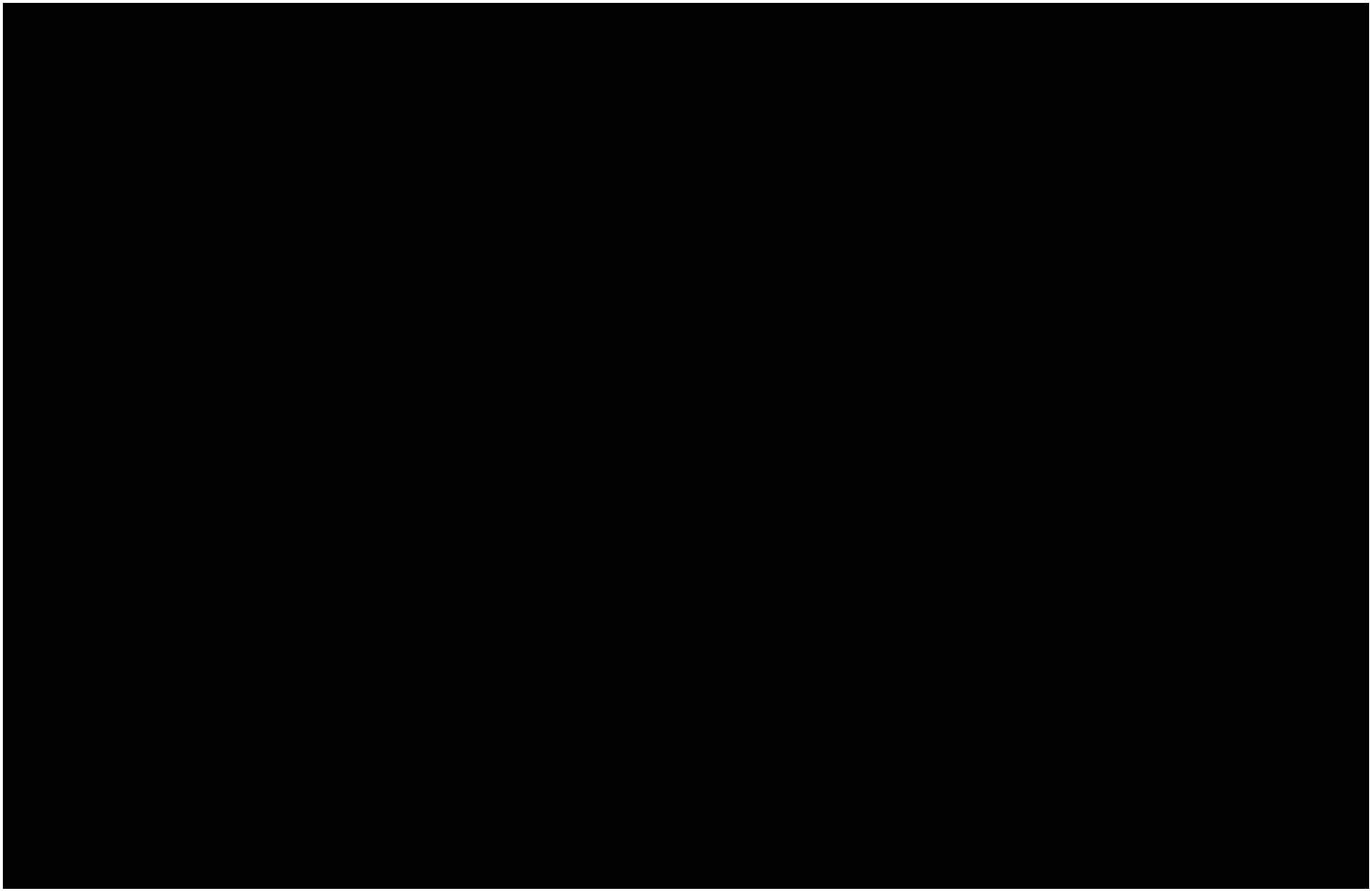


TABLE OF CONTENTS

[redacted]

[redacted]

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALJDS	Allergan Loss of Jawline Definition Scale
BMI	body mass index
CFR	Code of Federal Regulations
CR-SMFRS	Clinician-Rated Submental Fat Rating Scale
eCRF	electronic case report form
ES	Evaluable Set
FAS	Full Analysis Set
FDA	Food and Drug Administration
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	hyaluronic acid
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
ISR	injection site reaction
NSAIDs	non-steroidal anti-inflammatory drugs
PR-SMFRS	Patient-Rated Submental Fat Rating Scale
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SMF	submental fat
SMSLG	Submental Skin Laxity Grade
UADE	unanticipated adverse device effect
US	United States
VOLUMA™	Juvéderm® VOLUMA™ with Lidocaine

1 INTRODUCTION

1.1 BACKGROUND

The defining feature of the lower face is the jawline, or mandible (Shire, 2008). Its shape affects the mouth, chin, and neck. Factors affecting jawline definition are jowling, the development of the prejowl notch or sulcus, and marionette lines (Shire, 2008). The chin is also important to overall facial appearance. If the chin is of less than ideal size, it will cause other areas of the face to appear too large or too small. If the chin projection or width is inadequate, the adjacent neck and jowl soft tissues appear prematurely aged (Sykes and Fitzgerald, 2016). As in other areas of the face, changes in the jawline are products of soft tissue and bony changes (Bass, 2015).

Submental fullness associated with the accumulation of submental fat (SMF) can lead to an unappealing submental profile/convexity and may blunt the definition of the jawline. Further, it negatively affects the satisfaction and well-being of a substantial proportion of the population (Schlessinger et al, 2013; Rohrich et al, 2006). Current treatment options for SMF reduction include traditional aesthetic surgical procedures performed under general anesthesia, or targeted liposuction which may be performed under general or local anesthesia. However, not all patients are suitable candidates for, or willing to undergo, these invasive procedures and the potential complications (Patel, 2006; Koehler, 2009; Kamer and Minoli, 1993; Wong et al, 2012; Pelosi and Pelosi, 2010; Mejia et al, 2009). Because the jawline and chin play a strong role in the facial profile, there has been an increasing desire for safe and effective tools that can contour the area nonsurgically. The use of energy-based devices for lipolysis has been investigated as a less invasive approach (Coleman et al, 2009) but may still require accompanying surgery in more severely affected cases (Leclère et al, 2014) and safety concerns remain (Ersek, 2011).

Recently, BELKYRA® (deoxycholic acid solution for injection) was approved for the treatment of moderate to severe convexity or fullness associated with SMF in adults ([*Appendix 1: BELKYRA® Product Information*). When injected into subcutaneous fat tissue, BELKYRA® physically disrupts the cell membrane of adipocytes and causes adipocytolysis, the destruction of fat cells. Notably, the activity of BELKYRA® is attenuated by protein, making protein-poor tissues such as subcutaneous fat more sensitive to its cytolytic effects. As a result, when injected into fat tissue, nearby protein-rich tissues such as skin and muscle are largely unaffected (Thuangtong et al, 2010).

While treatment with BELKYRA® has been shown to be safe and effective in reducing SMF in patients who desire a minimally invasive treatment for their condition (Humphrey et al, 2016; Jones et al, 2016), it may only address one aspect of the overall contour of the jawline. Further definition may be gained by subsequent treatment with a dermal filler such as a hyaluronic acid (HA) injectable gel placed along the jawline. HA fillers have become a primary treatment for facial rejuvenation, with an established record of safety and effectiveness (Jones and Flynn, 2010). Juvéderm® VOLUMA™ with Lidocaine (hereafter referred to as VOLUMA™) is a member of the Juvéderm® family of HA-based dermal fillers that has been specifically developed for volumizing by injection into deeper tissue, e.g., to augment facial volume for aesthetic improvement. It is currently approved for restoring volume of the face by deep (subcutaneous and/or supraperiosteal) injection and has been

increasingly utilized for structural support of the chin and for the angle of the jaw and jawline (and other areas) in the aging patient (Goodman, 2015).

1.2 RATIONALE FOR THE STUDY

This study has been designed to evaluate the safety and effectiveness of sequential treatment with BELKYRA® (for the treatment of convexity and fullness associated with submental fat) and VOLUMA™ (to restore volume along the mandibular border) to enhance the overall contour of the jawline. While each of these treatments may individually produce improvements in the definition of the jawline, a comprehensive treatment approach may be required to more fully address a patient's aesthetic concerns.

In addition, a subset of patients will participate in a Biopsy Sub-study that will investigate changes in histopathology of tissue taken from the submental area, including collagen formation, between baseline (pre-treatment) and after the last BELKYRA® treatment (post-treatment).

2 STUDY OBJECTIVES AND CLINICAL HYPOTHESIS

2.1 STUDY OBJECTIVES

2.1.1 Primary Study Objective

To evaluate the combined effectiveness of sequential BELKYRA® treatments of convexity or fullness associated with submental fat and VOLUMA™ to restore volume along the mandible in enhancing the overall contour of the jawline.

2.1.2 Secondary Study Objectives

- To evaluate the Investigator's and subject's assessment of aesthetic improvement of the lower face and jawline.
- To evaluate histological changes from baseline to after BELKYRA® treatment(s).

2.2 CLINICAL HYPOTHESIS

The clinical hypothesis of this study is that a significant proportion of subjects sequentially treated with BELKYRA® and VOLUMA™ will achieve at least a 1-point improvement in the Allergan Loss of Jawline Definition Scale (ALJDS) following completion of the BELKYRA® and VOLUMA™ sequence at study exit, as compared to baseline.

3 STUDY DESIGN

This Phase IV trial is a prospective, open-label, multi-center, interventional, drug and medical device, post-marketing study. Each subject will act as his/her own control. Subjects will attend a minimum of 6 and maximum of 18 visits (see *Figure 3.1*)

Approximately 50 subjects will be enrolled. Approximately 10 subjects are expected to participate in the Biopsy Sub-study.

3.1 BIOPSY SUB-STUDY

Eligible subjects will have the option of participating in a Biopsy Sub-study. Participation in the sub-study is voluntary and will not affect the subject's eligibility to participate in the main study. The Biopsy Sub-study will evaluate changes in tissue samples taken from the submental area. Samples will be collected at least 4 weeks before BELKYRA® treatment (Visit B1) and again (at Visit B2) 8 weeks following the final BELKYRA® treatment and at least 4 weeks prior to VOLUMA™ treatment (at Visit 4). *See Section 6.2.2: Biopsy - Visit B1, Section 6.2.7 Biopsy – visit B2, Section 7.1.7: Biopsy,* and *Figure 3.1*.

3.2 BELKYRA® TREATMENT

Subjects will undergo treatment with BELKYRA® injected into subcutaneous fat tissue in the submental area (Visit 2.1/Day 0) (note: Screening and Visit 2.1/Day 0 may occur the same day if all eligibility criteria are confirmed prior to treatment and the subject is not participating in the Biopsy Sub-study). Seven days after the initial BELKYRA® treatment (Visit 3.1), the subject will return to the clinic for a safety evaluation. Eight weeks after BELKYRA® treatment, the submental profile will be evaluated by the Investigator and subject. If the Investigator and subject agree that no further intervention is required to achieve the desired result, subjects may receive VOLUMA™ treatment (Visit 4). If further intervention is required to achieve the desired result, subjects may receive up to 5 optional BELKYRA® treatments (Visits 2.2 to 2.6). Optional BELKYRA® treatments will be

administered at least 8 weeks apart, for a maximum of 6 treatments (including initial BELKYRA® treatment at Visit 2.1/Day 0). Subjects who receive optional BELKYRA® treatments will be contacted by telephone 7 days after each treatment for safety evaluation (Visits 3.2 to 3.6). Eight weeks after each BELKYRA® treatment, the submental profile will be assessed, as described above, and a decision made whether further BELKYRA® treatments are desired. When it is determined that further BELKYRA® intervention is not required or the maximum number (6) of BELKYRA® treatments have been administered, the subject receives VOLUMA™ treatment (Visit 4).

NOTE: Subjects participating in the Biopsy Sub-study will have an additional visit (Visit B2) between the final BELKYRA® treatment and the first VOLUMA™ treatment. See *Figure 3.1* and *Section 3.1: Biopsy Sub-Study*.

3.3 VOLUMA™ TREATMENT

The initial VOLUMA™ treatment will occur at Visit 4, either 8 weeks after the final BELKYRA® treatment or, if the subject is participating in the Biopsy Sub-study, after the biopsy site has healed. Fourteen days after initial VOLUMA™ treatment, subjects will return to the clinic and the Investigator and subject will assess whether a VOLUMA™ Touch-up treatment is to be performed (Visit 5). The optional Touch-up treatment will occur at Visit 5. All subjects will attend a final Exit Visit 4 weeks after the last VOLUMA™ treatment (Visit 6).

NOTE: If the Investigator and the subject agree that following BELKYRA® treatment, VOLUMA™ treatment is no longer desired or necessary, the subject may exit the study at this time. The subject will be considered as an early discontinuation, and procedures for Visit 6 (Exit Visit) will be performed instead of Visit 4 procedures.

4 STUDY POPULATION AND ENTRY CRITERIA

4.1 NUMBER OF SUBJECTS

Approximately 50 subjects will be treated in this study. Approximately 10 subjects will participate in the Biopsy Sub-study. Subjects who discontinue after receiving treatment on Day 0 will not be replaced.

4.2 INCLUSION CRITERIA

The following are requirements for entry into the study.

1. Male and females 18 to 65 years of age inclusive on the day of initial BELKYRA® treatment
2. Sign the Independent Ethics Committee (IEC)/Institutional Review Board (IRB)-approved informed consent form (ICF) prior to any study-related procedures being performed
3. Grade 2 or above on the ALJDS [redacted]

4. Submental fat graded by the Investigator as 2 or 3 using the Clinician-Rated Submental Fat Rating Scale (CR-SMFRS) [redacted]

[redacted]

4.3 EXCLUSION CRITERIA

[redacted]

2. A grade of 4 on the Submental Skin Laxity Grade (SMSLG) [redacted]
3. Grade 4 on the Allergan Jowl Fat Rating Scale (AJFRS) *(See Appendix 13: Allergan Jowl Fat Rating Scale)*
4. Body mass index (BMI) > 35 kg/m^2 as determined at Screening

[redacted]

6. History of, or current symptoms of dysphagia

[redacted]

8. History of temporary, semi-permanent or permanent facial or neck dermal filler injections [redacted]) below the medial canthi at any time prior to treatment, or within 52 weeks before Screening for treatment above the medial canthi, [redacted]
9. History of facial and/or neck plastic surgery, tissue grafting or permanent facial implants [redacted]) anywhere in the face [redacted]
10. History of any intervention (e.g., liposuction, surgery, or lipolytic agents) to treat SMF

11. Evidence of any cause of enlargement in the submental area (e.g., thyroid enlargement, cervical adenopathy, ptotic submandibular gland) other than localized SMF
12. History of mesotherapy or ablative procedures to the face and/or neck 52 weeks before Screening
13. History of skin resurfacing [redacted] in the neck or submental area within 26 weeks before Screening
14. Treatment with botulinum toxin injections in the neck or submental area within 26 weeks before Screening
15. Subjects on prescription topical retinoid therapy and/or topical hormone cream applied to the face, who have not been on a consistent dose regimen for at least 26 weeks before Screening and who are unable to maintain regimen for the study
16. Systemic retinoid therapy within 52 weeks before Screening
17. Current use of oral corticosteroids
18. Is on a regimen of anticoagulation therapy (eg, warfarin, clopidogrel)
- [redacted]
20. Has current injection site inflammatory or infectious processes, abscess, an unhealed wound, or a known cancerous or precancerous lesion in chin, masseter, or submental region
- [redacted]
22. Planned oral surgery or other dental procedures (e.g., tooth extraction, orthodontia, or implantation) within 2 weeks prior to and after VOLUMA™ treatment
- [redacted]

4.4 PERMISSIBLE AND PROHIBITED MEDICATIONS/TREATMENTS

4.4.1 Permissible Medications and/or Treatments

Therapy considered necessary for the subject's welfare may be given at the discretion of the Investigator, including but not limited to medications for other conditions (i.e., hypertension, diabetes, etc.), and treatment of adverse events (AEs). Medications should be taken consistently throughout the study and at the Investigator's discretion. All therapies administered, prescription or over-the-counter, will be recorded at each visit along with the reason the medication is taken.

4.4.1.1 Anesthesia

Oral analgesics or non-steroidal anti-inflammatory drugs (NSAIDs), topical and/or injectable local anaesthesia (e.g., lidocaine), and/or cooling using cool packs may be applied to the area of injection (for treatment or biopsy) at the discretion of the Investigator/Injector. The type of anesthesia (topical, local injectable, etc), anesthesia medication used and dose of anesthesia during the treatment is at the clinical judgment of the Investigator/Injector. Use of injectable anesthesia during the treatment will be limited to the area of injection only. Anesthesia use elsewhere is prohibited.

The type, drug, dose and administration method of anesthesia shall be recorded. Anesthesia is to be administered according to local site practice. It must be confirmed that the subject is not allergic to the anesthetic drug to be used prior to administration.

4.4.1.2 Rescue Medications

Although it has been reported that hyaluronidase is effective in reversing the effects of misplaced or excess HA-based dermal fillers, no product has been approved for this indication. Administration of hyaluronidase is considered to be "off-label" and has not been provided as a part of the study regimen. If in the Investigator's judgment it is deemed to be necessary to inject hyaluronidase for the safety of the subject, then the Investigator may inject at his/her discretion, capturing this information as a concomitant medication. Note that the use of hyaluronidase for aesthetic purposes (e.g., to reverse overcorrection) is not permitted.

4.4.1.3 Acceptable Contraceptive Methods

Women of childbearing potential are required to practice a reliable method of contraception throughout the study. The following methods of contraception, if properly used, are generally considered reliable: oral contraceptives, patch contraceptives, injection contraceptives, male condom with intra-vaginal spermicide, diaphragm or cervical cap with spermicide, vaginal contraceptive ring, intrauterine device, surgical sterilization (bilateral tubal ligation), vasectomized partner, or sexual abstinence.

Men, whose sexual partners are women of childbearing potential are required to practice a reliable method of contraception throughout the study. The following methods of contraception, if properly used, are generally considered reliable: male condom with intra-vaginal spermicide, vasectomy or sexual abstinence.

The Investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study. The method of contraception will be recorded for all female participants of childbearing potential.

4.4.2 Prohibited Medications/Treatments

The decision to administer a prohibited medication/treatment will be made with the safety of the study participant as the primary consideration. When possible, the Sponsor or Sponsor's representative should be notified before a prohibited medication/treatment is administered.

Subjects must not be enrolled in another study and may not receive another investigational product during the course of this study.

Prior to attending study visits, subjects must not apply facial cosmetics.

For information regarding medications/treatments requiring washout prior to treatment, see *Section 6.1.3: Washout of Prohibited Medications/Treatments*.

4.4.2.1 Anticoagulant Medications

Subjects on a regimen of anticoagulation therapy (eg, warfarin, clopidogrel) should not be enrolled in this study. NSAID use is permitted to improve patient comfort during BELKYRA® treatment.

Subjects who receive VOLUMA™ and who are taking NSAIDs must be warned of the potential increased risk of bleeding and hematomas during injection.

Use, discontinuation and resumption, as applicable, of anticoagulant medication will be recorded as concomitant medication.

4.4.2.2 Facial Procedures/Treatments

During the study, subjects must not:

- Receive permanent facial implants (eg, polymethylmethacrylate, silicone, polytetrafluoroethylene) anywhere in the face or neck
- Undergo fat injections in the malar, chin, or jawline area
- Undergo any piercing or tattooing procedures below the subnasale
- Undergo semi-permanent dermal fillers (eg, calcium hydroxylapatite, L-polylactic acid) below the subnasale
- Undergo mesotherapy or cosmetic treatment (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, moderate or greater depth chemical peel, liposuction, lipolysis, or other ablative procedures) anywhere in the face or neck
- Receive botulinum toxin injections in the chin, masseter, periorial area, or platysmal bands

4.4.2.3 Special Diet or Activities

Within the first 24 hours after filler treatment with VOLUMA™, at Visit 4, and if a Touch-up treatment is performed at Visit 5, subjects should avoid strenuous exercise, extensive sun or heat exposure and alcoholic beverages. Exposure to any of the above may cause temporary redness, swelling, and/or itching at the injection sites.

4.4.2.4 Weight Loss Medications

Subject should not be prescribed medication with the purpose of inducing weight loss during the course of the study. Additionally, subjects should not be prescribed other medications for which significant weight loss is a known common side effect without consulting with the Sponsor.

5 TREATMENT

5.1 INVESTIGATIONAL PRODUCT

Commercial grade product will be provided by Allergan for use in this study. The product will be labeled as investigational and shall be used only for subjects enrolled in this trial, at no cost to the subject, in accordance with the conditions specified in the protocol. Commercial grade product obtained by any other method shall not be used for subjects in this study. Allergan will provide each study site with sufficient study treatment/devices for all study subjects.

5.1.1 BELKYRA®

BELKYRA® is a clear, colorless, sterile solution supplied in 2 mL vials, 4 vials in each kit. The vials are intended for single subject use. Each milliliter of the solution contains 10 mg of deoxycholic acid.

BELKYRA® is injected into subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm^2.

- A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), and injected 1 cm apart.
- Up to 6 single treatments may be administered at intervals no less than 8 weeks apart.

BELKYRA® should be administered by a licensed healthcare professional.

5.1.2 VOLUMA™

VOLUMA™ injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of cross-linked HA produced by *Streptococcus* species of bacteria, formulated to a concentration of 20 mg/mL, and 0.3% lidocaine in a physiological buffer. VOLUMA™ injectable gel is supplied in 1 mL syringes, 2 syringes per kit. The maximum total volume allowed for an individual subject for the initial and touch-up treatments combined during the study is 6 mL (3 mL per side).

5.1.3 Blinding and Randomization

This is an open-label, single-arm study. Thus, blinding and randomization methods will not be implemented.

5.1.4 Treatment Assignment

Sequentially numbered investigational product (IP) will be provided to each investigative site. IP will be assigned sequentially to eligible subjects beginning with the lowest numbered unassigned IP at the site. Each kit will be assigned to one subject. Unopened vials/syringes in an assigned kit may be used for subsequent treatments for the assigned subject. Kits shall not be shared between subjects.

The assigned IP will be labelled with the subject's initials, subject's study number and date of assignment. The IP number(s) assigned to a specific subject will be recorded in that subject's source document and on the site's inventory list as described in *Section 5.2.1: Storage*.

BELKYRA® will be provided in kits containing 4 vials, each vial containing 2 mL of product. Each kit will be labeled as investigational product and will be sequentially numbered. A maximum of 5 vials (10 mL) may be used per treatment. Partially used vials/kits shall not be shared between individuals.

VOLUMA™ will be provided in kits containing 2 syringes, each syringe containing 1 mL of product. Each kit will be labeled as investigational product and will be sequentially numbered. The maximum of 3 kits (total volume 6 mL) is allowed per subject for the initial and touch-up treatments combined. Partially used syringes/kits shall not be shared between individuals.

5.2 STORAGE, HANDLING AND DESTRUCTION

5.2.1 Storage

All study drug/devices must be stored in a locked, secure area accessible only to study personnel. The study site shall keep an inventory of all kits received, used and not used. The disposition of each vial/syringe contained in the kit will also be inventoried.

5.2.1.1 BELKYRA®

The vials of BELKYRA® should be stored at room temperature in a locked, limited-access storage area.

5.2.1.2 VOLUMA™

VOLUMA™ is to be stored at room temperature in a locked, limited-access storage area.

5.2.2 Handling

5.2.2.1 BELKYRA®

BELKYRA® is clear, colorless and free of particulate matter. BELKYRA® vials should be visually inspected for particulate matter and/or discoloration. If the solution is discolored

and/or contains particulate matter, the vial is to be labeled as "DAMAGED" and a new vial obtained for the subject. Document the reason the original vial was considered damaged. Record the vial number for the damaged vial and the vial number for the replacement vial that was used. Used, partially used or damaged vials should be handled per *Section 5.2.3 Destruction.*

Detailed instructions for BELKYRA® handling are in the *BELKYRA® Summary of Product Characteristics*.

5.2.2.2 VOLUMA™

VOLUMA™ is an injectable gel with a clear appearance. If a syringe contains material that is not clear, do not use the syringe. If either one or both syringes in a kit is defective (e.g., gel is not clear, plunger does not work, etc.), the entire kit is considered damaged. Label the kit as "DAMAGED" and obtain a new kit for the subject. Document the reason the original kit was considered damaged. Record the kit number for the damaged kit and the kit number for the replacement kit that was used. All syringes (unused, partially-used or used) should be returned to the kit. Used, partially used or damaged kits should be handled per *Section 5.2.3 Destruction.*

Detailed instructions for VOLUMA™ handling are provided in the *JUVÉDERM® VOLUMA™ WITH LIDOCAINE Directions for Use* (*Appendix 2*).

5.2.3 Destruction

All vials/kits shall be retained in a secure location for audit by the Sponsor. Partially-used and unused kits will be shipped for destruction by the site monitor. Used kits shall be destroyed at the site following local site practices and regulations after the kit has been audited by the site monitor.

5.3 TREATMENT ADMINISTRATION

5.3.1 BELKYRA®

The safe and effective use of BELKYRA® depends on the use of the correct number and locations for injections, proper needle placement, and administration techniques. A brief summary of the method of use is provided below; full details of treatment administration will be provided in *Appendix 1: BELKYRA® Product Information*.

BELKYRA® is injected into subcutaneous fat tissue in the submental area using an area-adjusted dose of 2 mg/cm^2. The Investigator will determine the appropriate area of submental tissue to be treated.

- A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), and injected 1 cm apart.
- Up to 6 single treatments may be administered at intervals no less than 8 weeks apart.

The planned treatment area should be outlined with a surgical pen and a 1 cm injection grid applied to mark the injection sites. Injections near the area of the marginal mandibular nerve

should be avoided. Similarly, injection into the platysma should also be avoided. BELKYRA® should not be injected outside the defined parameters.

- Using a large bore needle, draw 1 mL of BELKYRA® into a sterile 1 mL syringe and expel any air bubbles in the syringe barrel.
- Have the subject tense the platysma. Pinch the submental fat and, using a 30 gauge (or smaller) 0.5-inch needle, inject 0.2 mL of BELKYRA® into the pre-platysmal fat next to each of the marked injection sites by advancing the needle perpendicular to the skin.
- Injections that are too superficial (into the dermis) may result in skin ulceration. Do not withdraw the needle from the subcutaneous fat during injection as this could increase the risk of intradermal exposure and potential skin ulceration.
- Avoid injecting into the post-platysmal fat by injecting BELKYRA® into fat tissue at the depth of approximately mid-way into the subcutaneous fat layer.
- If at any time resistance is met as the needle is inserted, indicating the possibility of contact with fascial or nonfat tissue, the needle must be withdrawn to an appropriate depth before the injection is administered.
- Avoid injecting into other tissues such as the muscle, salivary glands and lymph nodes.
- Upon needle withdrawal, pressure may be applied to each injection site as necessary to minimize bleeding; an adhesive dressing may be applied.

For information on use of local anesthesia and use of rescue medications, refer to *Section 4.4.1.1: Anesthesia* and *Section 4.4.1.2: Rescue Medications*, respectively. For information on prohibited medications/treatments refer to *Section 4.4.2: Prohibited Medications/Treatments*.

5.3.2 VOLUMA™

The Investigator will determine the appropriate volume of VOLUMA™ to be injected for restoring volume along the mandibular border and enhancement of the overall contour of the jawline. Two weeks following the initial VOLUMA™ treatment (Visit 4), touch up treatment may be administered at Visit 5. The maximum total volume allowed for an individual subject for the initial and touch-up treatments combined is 6 mL (3 mL per side).

A brief summary of the method of use is provided below; full details for the injection of VOLUMA™ will be provided in *Appendix 2: Juvéderm® VOLUMA™ with Lidocaine Directions For Use*.

Use of needle or cannula for the procedure is per investigator judgement. If the Investigator opts to use a cannula for the procedure, the specific cannula to be used will be per Allergan guidance.

- Prior to the injection, the area to be treated should be disinfected thoroughly.
- Confirm that the product flows out of the needle or cannula upon depressing the plunger rod.

- After needle or cannula insertion and before injection, it is recommended to slightly withdraw the plunger to aspirate and verify the needle or cannula is not intravascular.
- The product should be injected slowly, applying the least amount of pressure necessary.
- If the needle or cannula becomes blocked, pressure on the plunger rod should not be increased; instead, the injection should be stopped and the needle or cannula replaced.
- If immediate blanching occurs at any time during the injection, the injection should be stopped and appropriate action taken such as massaging the area until its return to a normal color.
- After the injection, it is important to massage the area treated in order to ensure that the substance has been uniformly distributed.

For information on use of local anesthesia and use of rescue medications, refer to *Section 4.4.1.1: Anesthesia* and *Section 4.4.1.2: Rescue Medications*, respectively. For information on prohibited medications/treatments refer to *Section 4.4.2: Prohibited Medications/Treatments.*

6 STUDY VISIT SCHEDULE AND PROCEDURES

6.1 SUBJECT ENTRY PROCEDURES

Prospective subjects as defined by the criteria in *Section 4.2: Inclusion Criteria* and *Section 4.3: Exclusion Criteria* will be considered for entry into this study.

6.1.1 Informed Consent

The study will be discussed with the subject. The subject must give written informed consent prior to the performance of any study-related procedures, inclusive of screening procedures, or change(s) in treatment, e.g. washout of medications. The subject must give patient privacy authorization in accordance with relevant country and applicable local privacy requirements.

The Biopsy Sub-study is optional for all eligible subjects. Subjects will indicate on the written informed consent whether or not they agree to participate in the sub-study. Participation in the core study will not be contingent on participating in the sub-study.

See *Section 11.6: Informed Consent* for additional information and requirements regarding informed consent.

6.1.2 Subject Number

All subjects who provide informed consent will be assigned a subject number that will be used as the subject identifier on all study documentation throughout the study.

[redacted]

[redacted]

6.1.4 Subject Enrollment

An individual who provides written informed will be assigned a subject number and will undergo screening for participation. Subjects who meet eligibility criteria (See Section 4.2 and 4.3) will receive BELKYRA® treatment. Subjects who meet eligibility criteria and consent to participate in the Biopsy Sub-study will have a biopsy sample collected prior to the treatment with BELKYRA®.

Eligible subjects who withdraw after undergoing biopsy and before receiving BELKYRA® treatment may be replaced by another suitable subject in order that 50 subjects are treated with BELKYRA® and are included in the Full Analysis Set for analysis (see Section 10.1.1). The subject number will not be reassigned to a different subject. Subjects who have received BELKYRA® treatment will not be replaced.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.3 POST-TREATMENT INSTRUCTIONS FOR SUBJECTS

Prior to leaving the study site, the subject's next study visit should be scheduled and a reminder card provided to the subject. The subject's contact information should be verified to enable reminder phone call, text and/or email(s).

6.3.1 BELKYRA® Treatment Period

During the BELKYRA® treatment period, subjects will be instructed prior to leaving the site to:

- Contact the study site (or have a family member or friend contact the study site) to report any hospitalizations.
- Report any adverse events to the Investigator at the next study visit
- Maintain the dose of any concomitant medication. If there are any changes to medications, dosages, or frequency, the changes must be reported to the Investigator at the next study visit.
- Maintain the frequency of any concomitant procedure. If there are any changes to concomitant procedures, the changes must be reported to the Investigator at the next study visit.
- Contact the study site as soon as possible if the subject cannot make the next scheduled study visit in order to reschedule.

6.3.2 Biopsy Sub-Study

For subjects who consent to participate in the Biopsy Sub-study, instructions on care of the biopsy lesion will be provided.

6.3.3 VOLUMA™ Treatment Period

During the VOLUMA™ treatment period (Visits 4 to 6), subjects will additionally be instructed to:

- Within the first 24 hours after study treatment, avoid strenuous exercise, extensive sun or heat exposure, and alcoholic beverages.
- Complete the ISR Diary: every day, one page per day, around the same time of the day as the treatment.
- Bring the ISR Diary to the next study visit.

7 METHODS OF ASSESSMENT AND ENDPOINTS

7.1 STUDY PROCEDURES

7.1.1 Demographic Data

Subject demographic data will be collected at the Screening Visit.

These data include date of birth, age, gender, race, and ethnicity. Height and weight measurements will also be collected for use in calculating BMI.

7.1.2 Medical History

Medical history will be obtained from each subject at the Screening Visit.

Medical history includes pertinent surgical history and a detailed history of prior facial aesthetic procedures with start and stop dates, if applicable, as well as any discontinuations due to intolerability or toxicity.

7.1.3 Concomitant Medications/Procedures

Concomitant medication/procedure status shall be collected at all visits. Concomitant medications include prescription medications, dietary supplements, over-the-counter medications, and oral herbal preparations.

A list of concomitant medications/procedures will be collected at the Screening visit. Data collected shall be medication/treatment name, dose, frequency, start date, stop date (if applicable). All medications or treatments received within 4 weeks before the Screening visit shall be recorded. Medications/procedures received more than 4 weeks before Screening and in the Investigator's judgment is pertinent to this study, should also be recorded.

Following treatment at Day 0, subjects will be asked at each subsequent study visit whether any new medication/procedures have been administered or if any changes in dosage or frequency, have occurred since the previous visit. All concomitant medications and procedures will be recorded on eCRFs.

7.1.4 Fitzpatrick Skin Type

The subject's Fitzpatrick skin type will be determined at the Screening visit using the parameters listed in *Appendix 12.*

7.1.5 Urine Pregnancy Test

The urine pregnancy test will be performed at the Screening visit and prior to administration of any study treatment. The urine pregnancy test will be performed only for women of childbearing potential. The woman's childbearing status must be clearly reported in the source documentation.

The pregnancy test will be performed by urine dipstick. Positive pregnancy test results must be repeated to confirm the result. Women of childbearing potential must have a negative pregnancy test before any study treatments are given.

7.1.6 Photographic Imaging

Standardized facial photographic images will be captured prior to each study treatment and within 60 minutes of VOLUMA treatment. Equipment and training for the capturing of images will be provided by a vendor selected by Allergan. Captured images will be transferred to the imaging vendor for archiving. Instructions for image capture, transmission and central assessment will be contained in the procedure manual.

7.1.7 Biopsy

Subjects who consent to participate in the optional Biopsy Sub-study will have a biopsy sample collected at least 4 weeks prior to the first BELKYRA® treatment at Visit B1. Biopsy sample collection may occur on the same day as Screening (Visit 1) if all eligibility criteria are confirmed prior to performing the biopsy. A second biopsy sample will be collected 8 weeks following the last BELKYRA® treatment at Visit B2. When the second biopsy lesion is healed (at least 4 weeks), VOLUMA™ treatment may occur (see Figure 3.1).

Biopsy samples, approximately 2 mm, will be excised from the submental area approximately 1.5 cm left and right of midline (baseline and post-treatment, respectively). Biopsy samples will be transferred to 10% neutral buffered formalin and shipped to a central laboratory for histopathology.

Additional details on biopsy logistics (e.g. sample collection, fixative, shipping) will be available in the Biopsy Manual.

7.1.8 Injection Site Reaction (ISR) Diary

The ISR Diary will be completed by the subject beginning on the day of treatment with VOLUMA™ and for daily for 4weeks.

If Touch-up treatment is received at Visit 5, the initial ISR Diary provided at Visit 4 will be collected. A new ISR Diary will be dispensed and started at touch-up treatment. Four weeks of ISR will be collected after the last VOLUMA™ treatment. An example of the ISR Diary is available in *Appendix 11.*

7.2 EFFICACY MEASURES

7.2.1 Allergan Loss of Jawline Definition Scale

The ALJDS is an Investigator assessment of jawline contour measured by a 5-point scale (see *Appendix 3*). The Investigator will use the ALJDS to perform a live assessment of the subject at the visits specified in *Table 1.1: Schedule of Visits and Procedures*. Photographic images will be collected to capture the subject status at the time of the live assessments.

A third party Independent Reviewer (IR) will use the photographic images collected during the subject visits to evaluate jawline definition using the ALJDS.

7.2.2 Clinician-Reported Submental Fat Rating Scale (CR-SMFRS)

The CR-SMFRS is an Investigator assessment measured on a 5-point scale (see *Appendix 4*). The Investigator will use the CR-SMFRS to perform a live assessment of the subject at the visits specified in *Table 1.1: Schedule of Visits and Procedures*. Photographic images will be collected to capture the subject status at the time of the live assessments.

7.2.3 Patient-Reported Submental Fat Rating Scale (PR-SMFRS)

The PR-SMFRS is a subject assessment measured on a 5-point scale (see *Appendix 5*). The subject is instructed to position his or her head as described for the CR-SMFRS assessment and is asked to complete a questionnaire about the area under their chin using a mirror to help them. The subject completes a live assessment at the visits specified in *Table 1.1: Schedule of Visits and Procedures*. Photographic images will be collected to capture the subject status at the time of the live assessments.

7.2.4 Submental Skin Laxity Grade (SMSLG)

The SMSLG is based on the Investigator's clinical evaluation of the subject, including palpation of the chin and neck area, oblique and profile views of the chin and neck, as well as observation of the pronation, supination, and lateral movement of the head (see *Appendix 6*). The Investigator will use the SMSLG to perform a live assessment of the subject at the visits specified in *Table 1.1: Schedule of Visits and Procedures*. Photographic images will be collected to capture the subject status at the time of the live assessments.

7.2.5 FACE-Q™ Questionnaires

The FACE-Q™ modules were designed to assess the impact of treatment from the subject's perspective, specifically the impact of treatment from the subject's appraisal of the area under their chin (see *Appendix 7*), neck (see *Appendix 8*), and satisfaction with lower face and jawline (see *Appendix 9*).

7.2.5.1 Appraisal of Area Under Chin

The subject will assess satisfaction using the 5 items on the Appraisal of Area Under Chin module of the FACE-Q™ questionnaire. The responses to the 5 items are combined to create a scale score that ranges from 0 (worst) to 100 (best).

7.2.5.2 Appraisal of Neck

The subject will assess satisfaction using the 10items on the Neck module of the FACE-Q™ questionnaire. The responses to the 10 items are combined to create a scale score that ranges from 0 (worst) to 100 (best).

7.2.5.3 Satisfaction of Lower Face and Jawline

The subject will assess satisfaction using the 5 items on the Satisfaction of Lower Face and Jawline module of the FACE-Q™ questionnaire. The responses to the 5 items are combined to create a scale score that ranges from 0 (worst) to 100 (best).

7.2.6 Global Aesthetic Improvement Scale (GAIS) Questionnaires

7.2.6.1 GAIS Investigator

Investigator's assessment of global facial aesthetic improvement as measured by the 5-point GAIS (see *Appendix 10*).

7.2.6.2 GAIS Subject

Subject's assessment of global facial aesthetic improvement as measured by the 5-point GAIS (see *Appendix 10*).

[redacted]

8 DISCONTINUATION CRITERIA

8.1 DISCONTINUATION OF THE STUDY

The Investigator or Allergan, may terminate the Investigator's participation in this study after submission of a written notice. Allergan may terminate the study at any time for any reason.

8.2 DISCONTINUATION OF SUBJECTS

A subject may voluntarily withdraw or the Investigator may withdraw the subject at any time without prejudice to the subject's future medical care by the Investigator or institution. It is the responsibility of the site Investigator to discontinue a subject's participation when the subject's health or wellbeing is threatened by continuation in the study.

For any subjects who withdraw from the study, the date and reason for withdrawal will be recorded on the eCRF. If an AE or ISR is ongoing at the time of the withdrawal, the Investigator will attempt to follow the subject until the AE or ISR has resolved or stabilized.

8.2.1 Withdrawal Criteria

The following circumstances shall result in a subject's discontinuation from the study:

- If a subject becomes pregnant,
- Subject is lost to follow-up. Subjects may be withdrawn if they do not return for follow-up visits. If a subject fails to return for one or more scheduled study visits, the Investigator will attempt to contact the subject to determine and document the reason the subject has failed to return and to encourage compliance with the study visit schedule.

The following circumstances may result in a subject's discontinuation from the study. Investigator should contact Allergan prior to withdrawal of the subject.

- AEs or serious adverse events (SAEs) that render the subject unable to continue study participation
- Protocol violation
- Non-compliance with study requirements
- During the study, the subject meets any of the Exclusion Criteria listed in section 4.3
- Progressive injury (at the discretion of the Investigator)
- There are changes in the subject's condition that render the subject unacceptable for further participation in the judgment of the Investigator
- A subject is unable to physically or mentally tolerate the use of the test treatment
- Discretion of Investigator

The reason for withdrawal shall be documented in the source documents and in the eCRF.

9 ADVERSE EVENTS

Throughout the course of the study (from the date of informed consent), all AEs will be monitored and recorded in source documents and on the AE eCRF. If an AE occurs, the first concern will be the safety of the study participant. All AEs related to study treatments or procedures will be followed until resolved or stabilized based on the Investigator's clinical judgment or until follow-up is no longer possible.

9.1 DEFINITIONS

9.1.1 Adverse Events (AE)

9.1.1.1 Drug

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs will be assessed and documented, as appropriate, throughout the study (i.e., after informed consent has been obtained). At each visit, the Investigator will begin by querying for adverse events by asking each subject a general, non-directed question such as "How have you been feeling since the last visit?" Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented on the AE eCRF.

9.1.1.2 Medical Device

An AE is defined as any undesirable physical, psychological or behavioral effect experienced by a subject during his/her participation in a study, in conjunction with the use of the device, whether or not it is considered related to the procedure or the product. AEs may include, but are not limited to, subjective or objective symptoms spontaneously offered by the subject, solicited via subject interviews, uncovered by review of concomitant medications, therapies, and treatments and/or observed by the Investigator. The Investigator will record the description (sign, symptom and diagnosis), location, onset, resolution, seriousness, severity, cause, and action taken for any event on the AE eCRF. To maintain study blind, the Evaluating Investigator must not be present during the safety evaluations.

Disease signs and symptoms that existed prior to the study injections are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition or the condition worsens in intensity or frequency during the study.

9.1.1.3 Injection Site Reaction (ISR)

ISRs following treatment with dermal fillers include redness, pain after injection, tenderness to touch, firmness, swelling, lumps/bumps, bruising, itching, discoloration, and other specified events. Subjects will maintain a diary record of the presence, location, frequency, severity, and duration of any ISR for 4 weeks after treatment with VOLUMA™ (initial treatment at Visit 4 and Touch-up at Visit 5, if applicable). (See *Section 7.1.8: Injection Site Reaction (ISR) Diary* for further details).

Subjects will indicate the occurrence of an ISR and severity (none, mild, moderate, severe) of the event. ISRs that persist longer than 4 weeks (i.e., ongoing at the end of the diary period) will be reported as AEs and followed as described in *Section 9.2: Procedure for Reporting Adverse Events*. If an ISR is ongoing or appears 4 weeks after the subject's last study visit, it will be followed up by Allergan Product Surveillance separate from this study protocol.

9.1.2 Serious Adverse Events (SAE)

An SAE is any AE occurring at any dose that results in any of the following outcomes: death, a life-threatening AE, subject hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (See *Section 9.3: Procedures for Reporting an SAE*).

Note: Allergan considers all cancer AEs as SAEs. In addition, Allergan considers any abortion (spontaneous or not spontaneous) as an SAE.

9.1.3 Unanticipated Adverse Device Effects (UADE)

An Unanticipated Adverse Device Effect (UADE) is any device-related SAE that meets one or more of the following criteria:

- Is not identified in nature, severity, or frequency in current literature on the product
- Is life-threatening, even if temporary in nature
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

Also considered an UADE is any device malfunction that would be likely to cause or contribute to a death or serious injury if the malfunction were to recur. The Investigator will notify the Allergan Medical Affairs Department within 24 hours of any device malfunction and the Clinical Research representative will provide instruction for the return of any faulty syringe for evaluation.

As required by United States (US) Code of Federal Regulation (CFR) 21 §812.46(b)(2), if the Sponsor determines that an UADE presents an unreasonable risk to study subjects, the Sponsor will terminate the investigation within 5 working days of the unreasonable risk determination.

9.1.4 Severity

Definitions for classification of severity appear below in Table 9.1. The Investigator will review these definitions with the subject for use when completing the subject diary. For events reported on the AE eCRF, e.g., ISRs that persist beyond the diary period and other AEs, the Investigator will determine the severity classification based on these definitions, his/her experience in the use of dermal fillers, and/or the subject's description of the event.

Note: A "severe" AE is not the same as an "SAE", which is defined above. Seriousness of AEs is defined in *Section 9.1.2: Serious Adverse Events (SAE)*.

Table 9.1 Classification of Adverse Events by Severity

Mild:	Symptoms are barely noticeable or do not make the subject uncomfortable. The AE/ISR does not interfere with performance or functioning. Prescription drugs are not ordinarily needed for relief of symptoms.
Moderate:	Symptom are of sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs/therapies may be needed.
Severe:	Symptoms are of such sufficient severity to cause the subject severe discomfort. Performance of daily activities is compromised. Treatment of symptom(s) with prescription drugs/therapies may be needed.
Not applicable:	In some cases, an AE/ISR may be an "all or nothing" finding that cannot be graded.

9.1.5 Relationship to Study Medication or Study Device

A determination will be made, by the Investigator, of the relationship (if any) between an AE and the study drug, anesthesia employed, the study device, or the injection procedure, as applicable. A causal relationship is present if a determination is made that there is a reasonable possibility that the AE may have been caused by the drug, device, or study procedure.

9.2 PROCEDURE FOR REPORTING ADVERSE EVENTS

All AEs must be recorded in source documents and on the appropriate eCRF. All AEs that are drug-related and unexpected (not listed as treatment-related in the current Package Insert or Directions for Use) must be reported to the governing IRB as required by the IRB, local regulations, and the governing health authorities. Any adverse event that is marked "ongoing" at the Exit Visit must be followed-up as appropriate.

9.3 PROCEDURES FOR REPORTING AN SAE

Any SAE occurring during the study period (beginning with informed consent) and through 30 days after study exit must be immediately reported on 2 SAE forms. Both drug and device SAE fax forms must be recorded and faxed to the appropriate numbers on the front page of the protocol. All subjects with an SAE must be followed up and the outcomes reported. The Principal Investigator must supply the Sponsor and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy reports and terminal medical reports) if required. The Sponsor shall evaluate all SAEs for both drug and device. Device SAEs will be documented in writing as to whether they meet the definition of an UADE. These shall be reported to all participating Investigators, the regulatory authorities, and the IRB.

In the event of a serious adverse event, the Investigator must:

1. Notify Allergan immediately (within 24 hours) using the SAE reporting forms (for information see page 1 of the protocol). Emergency phone numbers and relevant Allergan personnel contacts are also on the front page of protocol.

2. Obtain and maintain in his/her files all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.

3. Provide Allergan with a complete, written case history (SAE report form) including copies of supporting reports (e.g., progress notes, laboratory reports) and a statement from the Investigator as to whether the event was or was not related to the use of the investigational drug or device.

4. Promptly inform the governing IRB/IEC of the SAE, if it is device-related, as required by the IEC/IRB, local regulations, and the governing health authorities.

9.4 PROCEDURES FOR REPORTING PREGNANCY

If a female of childbearing potential becomes pregnant during the study, the Investigator will notify the Sponsor immediately by completing the Pregnancy Surveillance Form after the pregnancy is confirmed. The subject will be withdrawn from the study per *Section 8.2.1: Withdrawal Criteria*. The Investigator shall (1) notify the subject's physician that the subject was being treated with BELKYRA® or BELKYRA® plus VOLUMA™, as appropriate, and (2) follow the progress of the pregnancy. The Investigator must document the outcome of the pregnancy and provide a copy of the documentation to Allergan.

Pregnancy by itself will not be considered an AE or SAE. Hospitalization for a normal delivery does not constitute an SAE. However, the occurrence of an adverse pregnancy outcome for the mother or child may constitute an AE or SAE, and these should be reported as described in *Section 9.2: Procedure for Reporting Adverse Events*. Allergan considers any abortion (spontaneous or not spontaneous) as an SAE and should be reported as described in *Section 9.3: Procedures for Reporting an SAE.*

10 STATISTICAL METHODS

10.1 GENERAL STATISTICAL CONSIDERATIONS

General statistical analysis methods are provided below; full details will be provided in a separate Statistical Analysis Plan (SAP), which will be finalized prior to database lock.

Data will be summarized using descriptive statistics (number of observations (n), mean, standard deviation, median, minimum, and maximum for continuous variables; and n and percent for categorical variables). Confidence intervals (95%) will be provided for the efficacy endpoints.

Three critical time points, baseline (Visit 2.1/Day 0), Visit 4 (end of BELKYRA® treatment, prior to VOLUMA™ treatment), and end of study (Exit/Visit 6; end of VOLUMA™ treatment), will be referenced in most of statistical analyses for this study.

Baseline is defined as the latest assessment prior to any study treatments for each subject. End of study is the last clinical visit an enrolled subject has in this study. For subjects who complete this study, the end of study visit will be their Visit 6 visit; for subjects who drop out

early, they will be asked to come back for the last clinical visit for end of study data collection.

10.1.1 Analysis Populations

The following analysis populations will be used:

- Full Analysis Set (FAS) – Consists of all subjects who received BELKYRA®
- Evaluable Set (ES) – Consists of subjects in the Full Analysis Set who received BELKYRA® and VOLUMA™ and a post-treatment efficacy assessment at Visit 6 (Exit Visit).
- Safety Analysis Set (SAS) – Consists of all subjects who consented to participation. Includes subjects who are defined as Full Analysis Set as well as subjects who were biopsied but did not receive BELKYRA®

The FAS population will be used for summary of subject disposition, demographics, baseline characteristics and efficacy analyses of endpoints assessed up to end of BELKYRA® treatment; the ES population will be used for the efficacy analyses of endpoints assessed at the final study visit, and the SAS population will be used for safety analyses.

10.1.2 Subgroups

As males and females may have differing expectations / perceptions of aesthetic improvement, data will be analyzed by gender separately.

Additional subgroup analysis will be discussed in the study SAP.

10.2 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Subject disposition, demographics and baseline characteristics will be summarized using descriptive statistics.

10.3 EXPOSURE AND CONCOMITANT THERAPIES

Subject study treatment exposure and compliance will be summarized using descriptive statistics.

The latest version of the World Health Organization Drug Dictionary will be used to classify prior and concomitant medications and therapies by therapeutic class and drug/device name. Prior medication/therapy is defined as those started by enrolled subjects before the date of first study treatment. Concomitant medication/therapy is defined as those taken on or after the date of first treatment. Prior and concomitant medications/therapies will be summarized using descriptive statistics.

10.4 STUDY ENDPOINTS

10.4.1 Primary Endpoint

The primary endpoint will be the responder rate for jawline improvement on the ALJDS, which is defined as the proportion of subjects who show ≥ 1-point improvement from baseline on the ALJDS at the final study visit (after last VOLUMA™ treatment received), as assessed by the Investigator.

10.4.2 Secondary Endpoints

10.4.2.1 Allergan Loss of Jawline Definition Scale (ALJDS)

- Change from baseline to last BELKYRA® treatment on ALJDS
- Change from baseline to final study visit in jawline definition based on Independent Reviewer assessment using the ALJDS and photographic images

10.4.2.2 FACE-Q Questionnaires

- Change from baseline to final study visit on the FACE-Q™ Satisfaction with Lower Face and Jawline module at the final study visit.
- Change from baseline to final study visit on the FACE-Q™ Appraisal of Neck
- Change from baseline to final study visit on the FACE-Q™ Appraisal of Area Under Chin

10.4.2.3 Clinician-Reported and Patient-Reported Submental Fat Rating Scale (CR-SMFRS and PR-SMFRS)

Change from baseline to final study visit for CR-SMFRS and PR-SMFRS scores.

10.4.2.4 Submental Skin Laxity Grade (SMSLG) Score

[redacted]

[redacted].

10.5 EFFICACY ANALYSES

Unless stated otherwise, all efficacy analyses will compare post-treatment assessment values to the subject's corresponding baseline assessment value.

10.5.1 Primary Efficacy Analysis

Responder rate for jawline severity, which is defined as the proportion of subjects who show ≥ 1-point improvement from baseline on the ALJDS compared to baseline assessment at the final study visit (after last VOLUMA™ treatment received) will be summarized by the number and percentage of subjects and exact 95% confidence interval will be provided.

10.5.2 Secondary Efficacy Analysis

The secondary efficacy endpoints will be analyzed similar to the primary efficacy endpoint.

The change from baseline to the exit visit in each of the FACE-Q™ modules overall Rasch-transformed scores will be analyzed using paired t-test (or Wilcoxon signed-rank test if normality assumptions are not met).

[redacted]

10.5.4 Missing Data

Missing data strategy will be documented in the study SAP.

10.5.5 Adverse Events

AEs will be coded using MedDRA version 17.0 or higher, and presented by system organ class and preferred term. Treatment-emergent AEs will also be summarized by SAEs, AE severity, AE leading to treatment or study early termination, and relationship to study drugs/devices. Summary tables will be presented by the study treatment drug.

10.6 INTERIM ANALYSES AND DATA MONITORING

No interim analysis is planned.

10.7 DETERMINATION OF SAMPLE SIZE

In the 2 US pivotal trials for BELKYRA® (ATX-101-11-22 and ATX-101-11-23), 79.1% and 77.9% of subjects, respectively, demonstrated a ≥ 1 grade improvement in the CR-SMFRS 12 weeks following the final treatment. In the VOLUMA-002 study, the responder rate defined as the percentage of subjects whose overall mid-face volume deficit improved (i.e., decreased) by ≥ 1 point from baseline based on the average of the 2 blinded Evaluating Investigators'

assessments at Month 6 using the 6-point Mid-Face Volume Deficit Scale, was 85.6% at Month 6.

In this study, as BELKYRA® and VOLUMA™ will be administered sequentially, the estimated responder rate for the jawline severity is set lower at 78.0%.

The sample size will provide reasonable precision of the estimations of the parameters of interests. With 40 subjects, the half-width of the 95% confidence interval for the proportion of subjects who show ≥ 1-point improvement from baseline on the ALJDS compared to baseline assessment at the final study visit (after last VOLUMA™ treatment received) is 14.0% assuming the improvement rate is 78%. To account for 20% study drop-out rate and/or subjects who may not continue for the VOLUMA™ treatment, 50 subjects will be enrolled.

The sample size calculation was performed using the PASS 2008 software for one single proportion.

10.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSIS

Any changes to the conduct or planned analyses will be handled via protocol or SAP amendment, respectively.

11 REGULATORY, ETHICAL, AND LEGAL OBLIGATIONS

11.1 DECLARATION OF HELSINKI

The Investigator will ensure that this study is conducted in accordance with the most recent revision of the Declaration of Helsinki.

11.2 GOOD CLINICAL PRACTICE

The study will be conducted according to the study protocol and to Standard Operating Procedures that meet the guidelines provided by the International Conference on Harmonization (ICH) for Good Clinical Practice in clinical studies.

11.3 INDEPENDENT ETHICS COMMITTEES

Before implementing this study, the protocol, the proposed subject informed consent forms, and other information for the subjects must be reviewed by a properly constituted committee or committees responsible for approving clinical studies. The IEC/IRB written, signed approval letter/form must contain approval of the designated Investigator, the protocol (identifying protocol title, date and version number), the subject informed consent form (date, version), and any other subject facing documents.

11.4 REGULATORY AUTHORITY APPROVAL

The study is utilizing all products as per their licensed usage and indications. No regulatory approval will be required.

11.5 PROTOCOL COMPLIANCE

The Investigator is responsible for compliance with the protocol at the investigational site. The Investigator is also responsible for reporting all issues of protocol non-compliance to the respective IEC/IRB and to the Sponsor. A representative of the Sponsor will make frequent contact with the Investigator and his/her research staff and will conduct regular monitoring visits at the site to review subject and study device accountability records for compliance with the protocol, e.g., subject eligibility criteria, volume of product injected, procedures performed, and follow-up visit schedule.

11.6 INFORMED CONSENT

Written informed consent is to be obtained from the subject prior to any study-related procedures or change in treatment. Privacy-related documentation will also be obtained from each subject prior to enrollment into the study, in accordance with relevant country and applicable local privacy requirements.

All subjects will be required to participate in the consent process. During the consent process, the person obtaining consent will inform the subject of all elements of informed consent. The Investigator must ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the clinical trial. Subjects must also be notified that they are free to withdraw from the clinical trial at any time without prejudice to future care. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

If the ICF is revised for any reason (e.g., protocol amendment or new safety data), the revised ICF must be reviewed and approved by the IEC/IRB. The revised ICF is not considered effective until approved by the IEC/IRB. All subjects currently enrolled in the clinical trial must sign the revised ICF. Subjects enrolled in the clinical trial after the revised ICF has been approved by the IEC/IRB will sign the revised version.

11.7 SUBJECT CONFIDENTIALITY AND DISCLOSURE

A report of the results of this study may be published or sent to the appropriate health authorities in any country in which the study drug may ultimately be marketed, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the Sponsor of the study, Allergan, or the governing health authorities or the US Food and Drug Administration (FDA) if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

In accordance with Health Insurance Portability and Accountability Act requirements, additional purposes of this study include the following: to publish anonymous subject data from the study and to create and maintain a data repository.

11.8 SPONSOR MONITORING OF STUDY DOCUMENTATION

A representative of the Sponsor will monitor the study on a periodic basis. The determination of the extent and nature of monitoring will be based on considerations such as

the objective, purpose, design, complexity, size, and endpoints of the study. This will be detailed in the Study Monitoring Plan.

Authorized representatives of Allergan or regulatory authority representatives will conduct on-site visits to review, audit and copy study-related documents. These representatives will meet with the Investigator(s) and appropriate staff at mutually convenient times to discuss study-related data and questions.

11.9 STUDY DOCUMENTS

The Investigator must maintain source documents for each subject in the study, including all demographic and medical information etc., and keep a copy of the signed and dated informed consent forms. All information on the eCRFs must be traceable to these source documents in the subject's file.

11.10 COLLECTION OF STUDY DATA

This study will be conducted in compliance with the US FDA Code of Federal Regulations (21 CFR Part 11). The Investigator is responsible for ensuring that study data are properly recorded on each subject's eCRFs and related documents. An Investigator who has signed the protocol signature page shall sign for the eCRFs to attest that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on an eCRF shall be dated, initialed and explained, if necessary, and shall not obscure the original entry (i.e., an audit trail shall be maintained); this applies to both written and electronic changes and corrections.

11.11 ARCHIVING OF STUDY DOCUMENTS

All study-related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of all investigational products, and copies of eCRFs should be maintained on file. Allergan-specific essential documents are to be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents are to be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by Allergan.

11.12 DISCLOSURE OF INFORMATION

This study will be registered and results posted on www.clinicaltrials.gov. Allergan, as the Sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study Investigators and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple

centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

12 REFERENCES

1. Bass LS. Injectable filler techniques for facial rejuvenation, volumization, and augmentation. *Facial Plast Surg Clin North Am* 2015;23:479-488.

2. Coleman KM, Coleman WP III, Benchetrit A. Non-invasive, external ultrasonic lipolysis. *Semin Cutan Med Surg* 2009;28:263–267.

3. Ersek RA. Evaluation of new ultrasound technologies should include assessments of peripheral nerve function. *Aesthet Surg* J 2011;31:837.

4. Goodman GJ. An interesting reaction to high- and low-molecular weight combination hyaluronic acid. *Dermatol Surg* 2015;41 Suppl 1;S164-S166.

5. Humphrey S, Sykes J, Kantor J, Bertucci V, Walker P, Lee DR et al. ATX-101 for reduction of submental fat: a phase III randomized controlled trial. *J Am Acad Dermatol* 2016;75(4):788-797.

6. Jones D, Flynn T. Hyaluronic acids: clinical applications. In: Jones D, editor. Injectable fillers: principles and practice. Oxford, UK: Wiley-Blackwell; 2010. p. 158-174.

7. Jones DH, Carruthers J, Joseph JH, Callender VD, Walker P, Lee DR et al. REFINE-1, a multicenter, randomized, double-blind, placebo-controlled, phase 3 trial with ATX-101, an injectable drug for submental fat reduction. *Dermatol Surg* 2016;42:38-49.

8. Kamer FM, Minoli JJ. Postoperative platysmal band deformity. A pitfall of submental liposuction. *Arch Otolaryngol Head Neck Surg* 1993;119:193–196.

9. Koehler J. Complications of neck liposuction and submentoplasty. *Oral Maxillofac Surg Clin N Am* 2009; 21:43–52, vi

10. Leclère FM, Moreno-Moraga J, Alcolea JM, Casoli V, Trelles MA. Laser Assisted Lipolysis for Neck and Submental Remodeling in Rohrich Type IV Patient: Fact or Fiction? *J Cosmet Laser Ther* 2014 Oct 6:1-20. [Epub ahead of print]

11. Mejia JD, Nahai FR, Nahai F, Momoh AO. Isolated management of the aging neck. Semin Plast Surg 2009;23:264–273.

12. Patel BCK. Aesthetic surgery of the aging neck: options and techniques. *Orbit* 2006;25:327–356

13. Pelosi MA III, Pelosi MA II. Liposuction. *Obstet Gynecol Clin North Am* 2010;37:507–519.

14. Rohrich RJ, Rios JL, Smith PD, Gutowski KA. Neck rejuvenation revisited. *Plast Reconstr Surg* 2006;118(5):1251-1263.

15. Schlessinger J, Weiss SR, Jewell M, et al. Perceptions and practices in submental fat treatment: a survey of physicians and patients. *Skinmed* 2013;11(1):27-31.

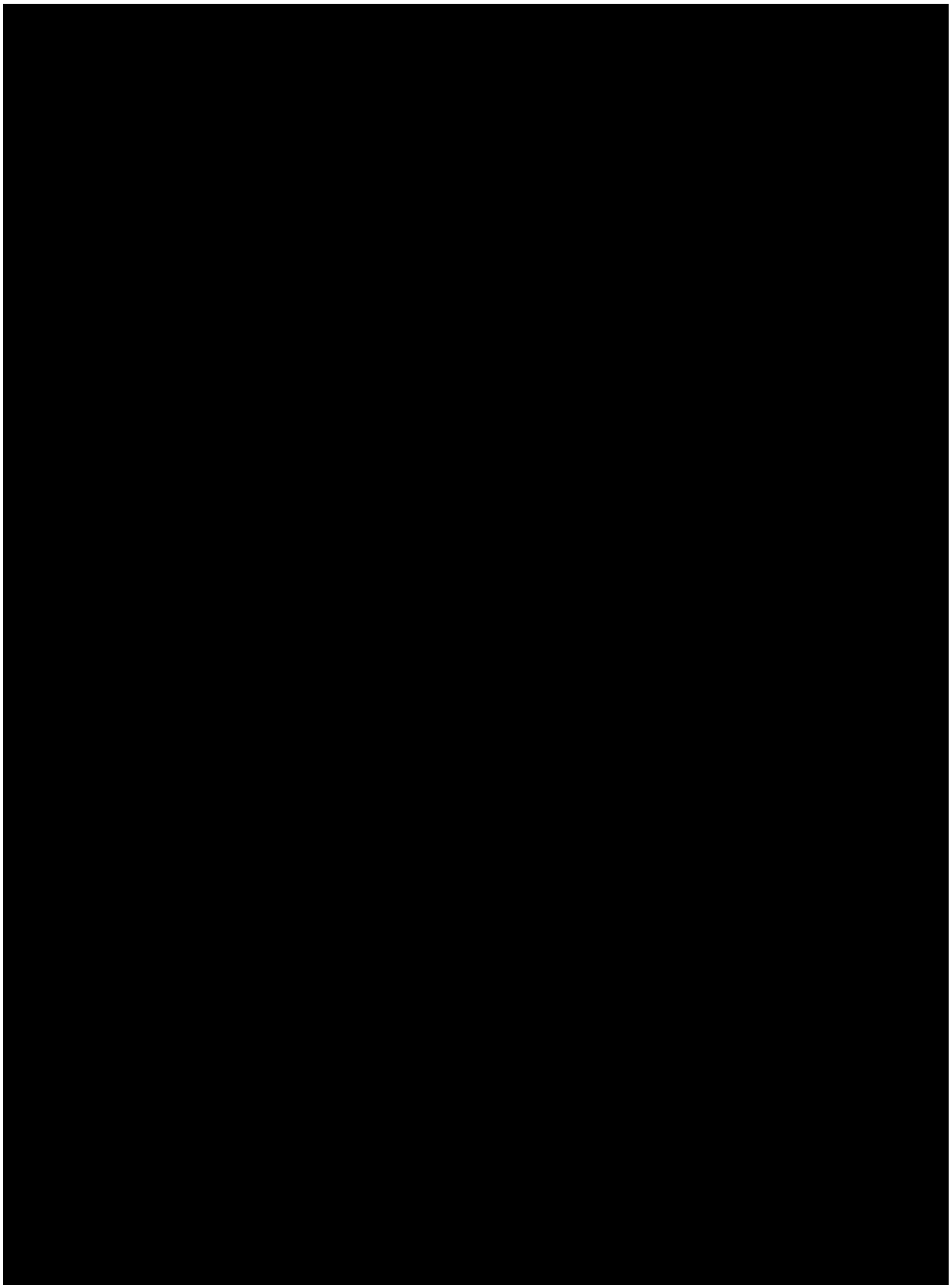
16. Shire JR. The importance of the prejowl notch in face lifting: the prejowl implant. Facial *Plast Surg Clin North Am* 2008;16:87-97.

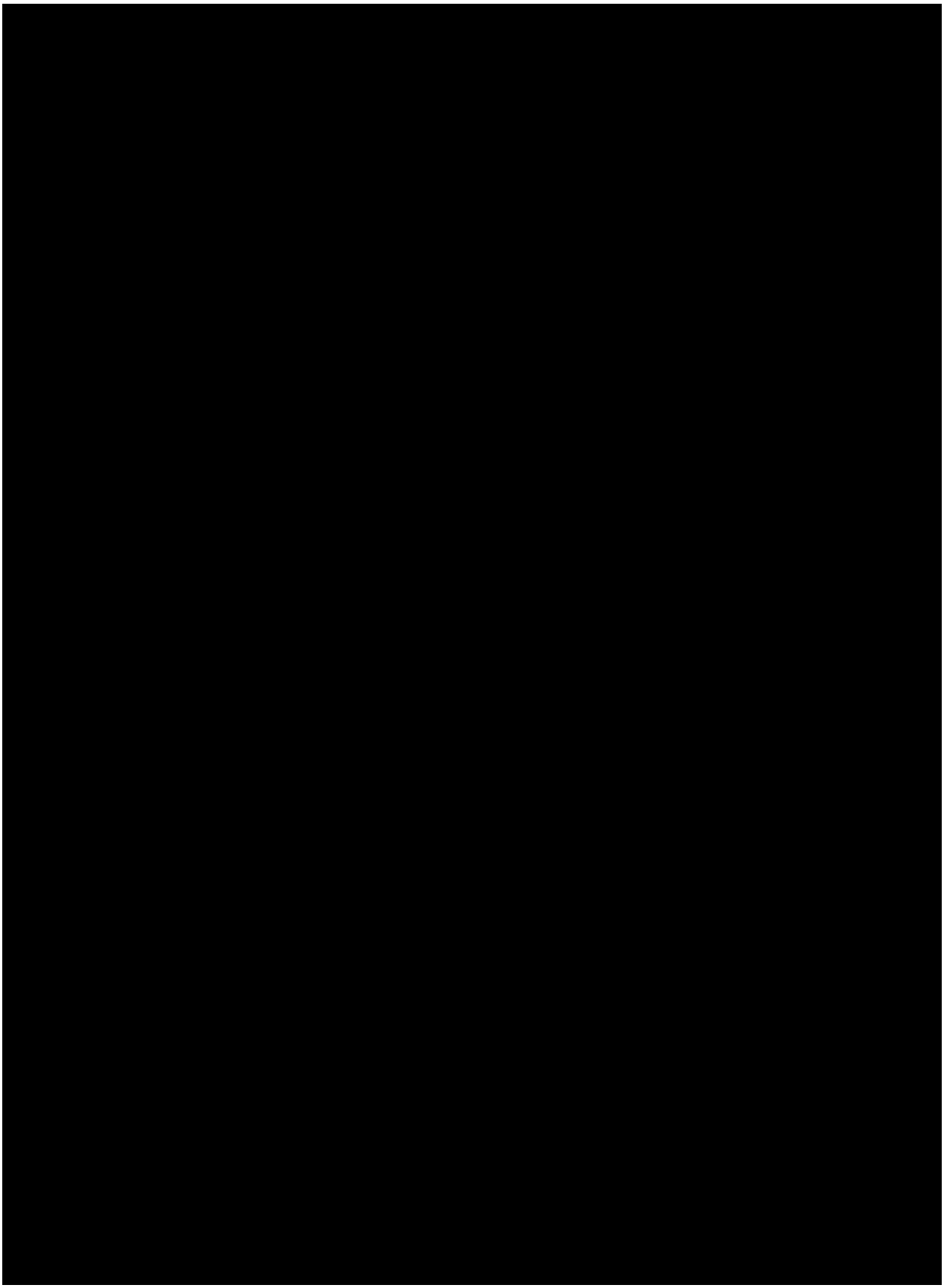
17. Sykes JM, Fitzgerald R. Choosing the best procedure to augment the chin: is anything better than an implant? *Facial Plast Surg* 2016;32:507-512.

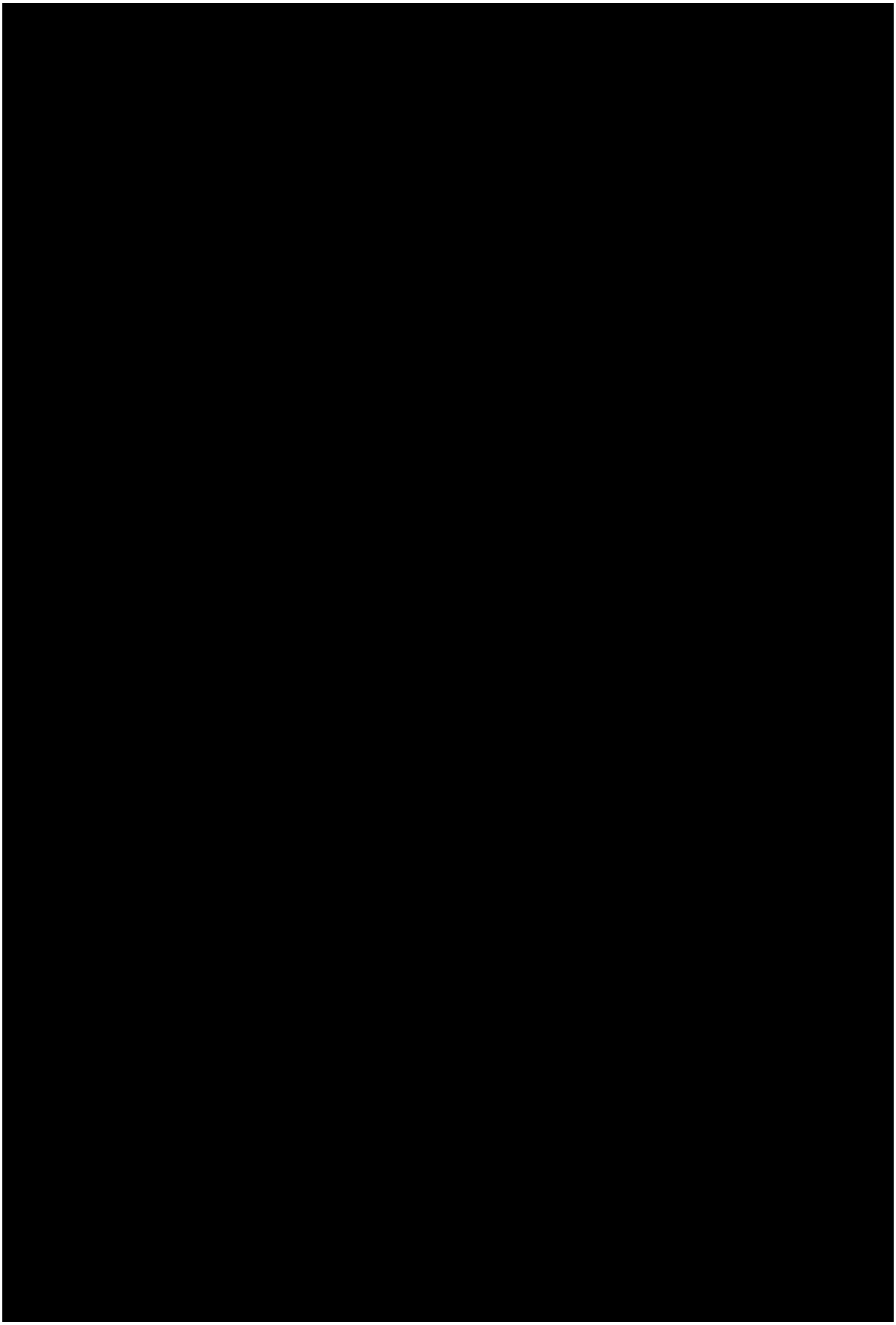
18. Thuangtong R, Bentow JJ, Knopp K, Mahmood NA, David NE, Kolodney MS. Tissue-selective effects of injected deoxycholate. *Dermatol Surg* 2010;36(6):899-908.

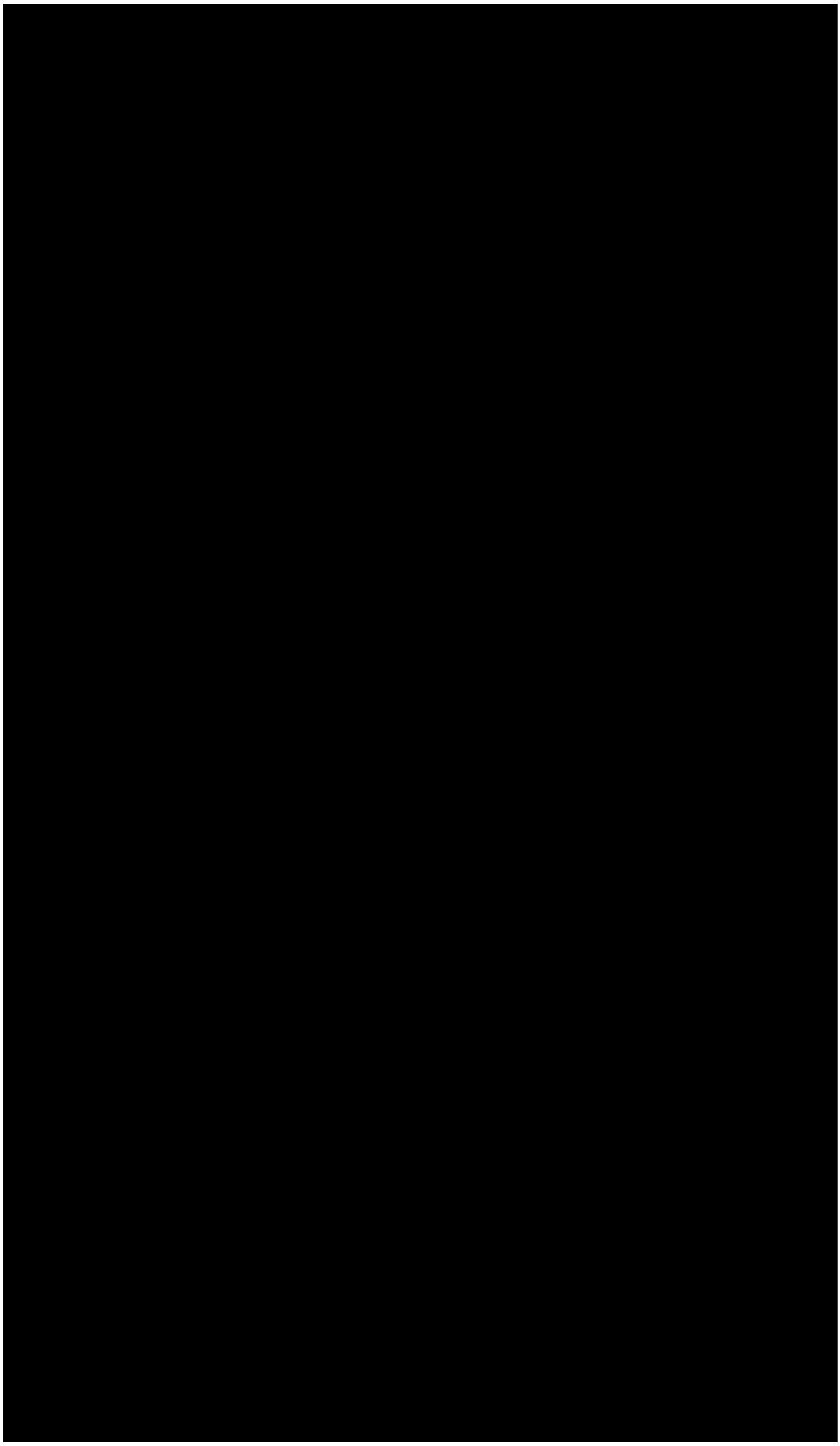
19. Wong SS, Wong SC, Yuen KY. Infections associated with body modification. *J Formos Med Assoc* 2012;111:667–681.

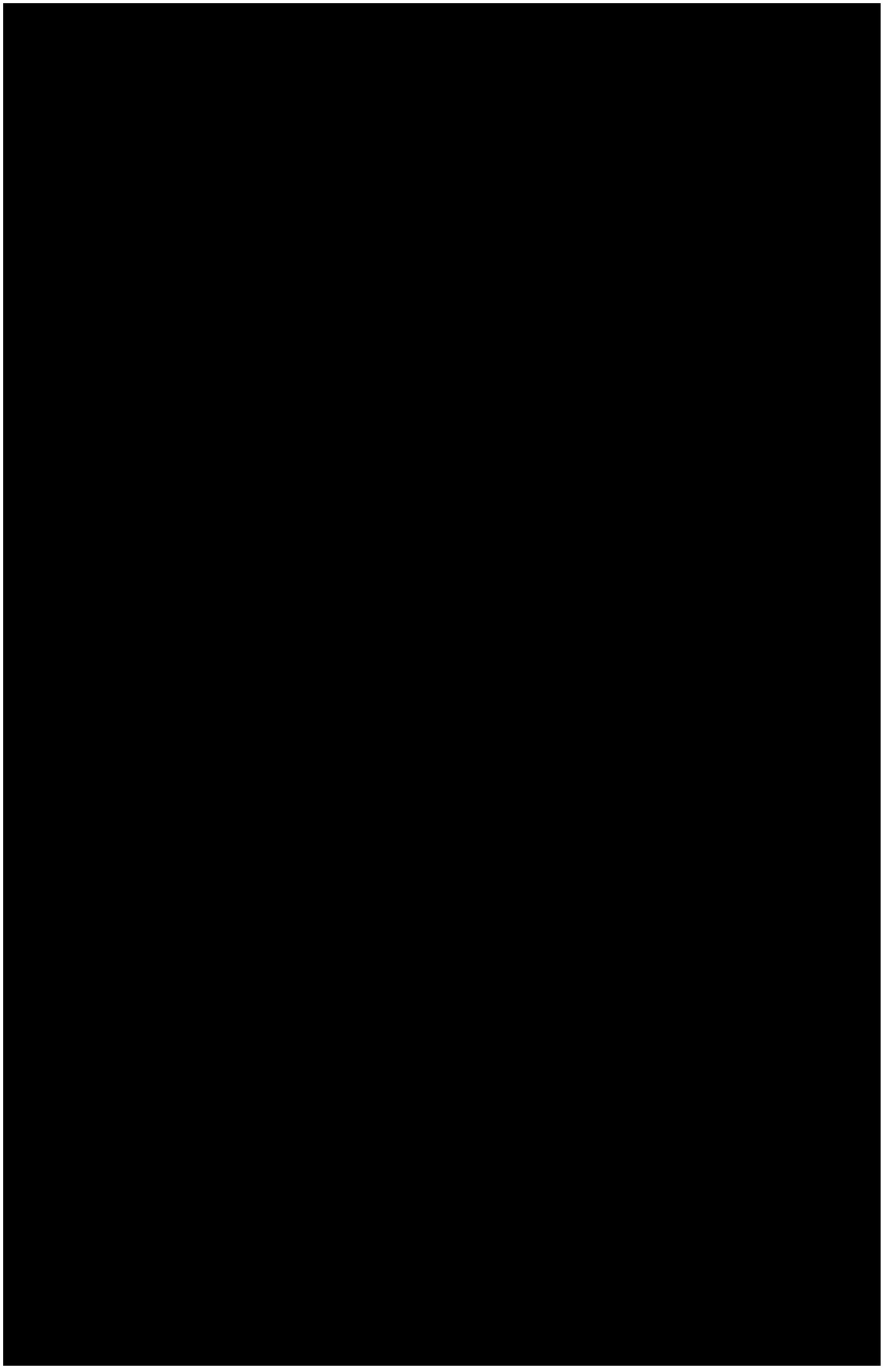
13 APPENDICES

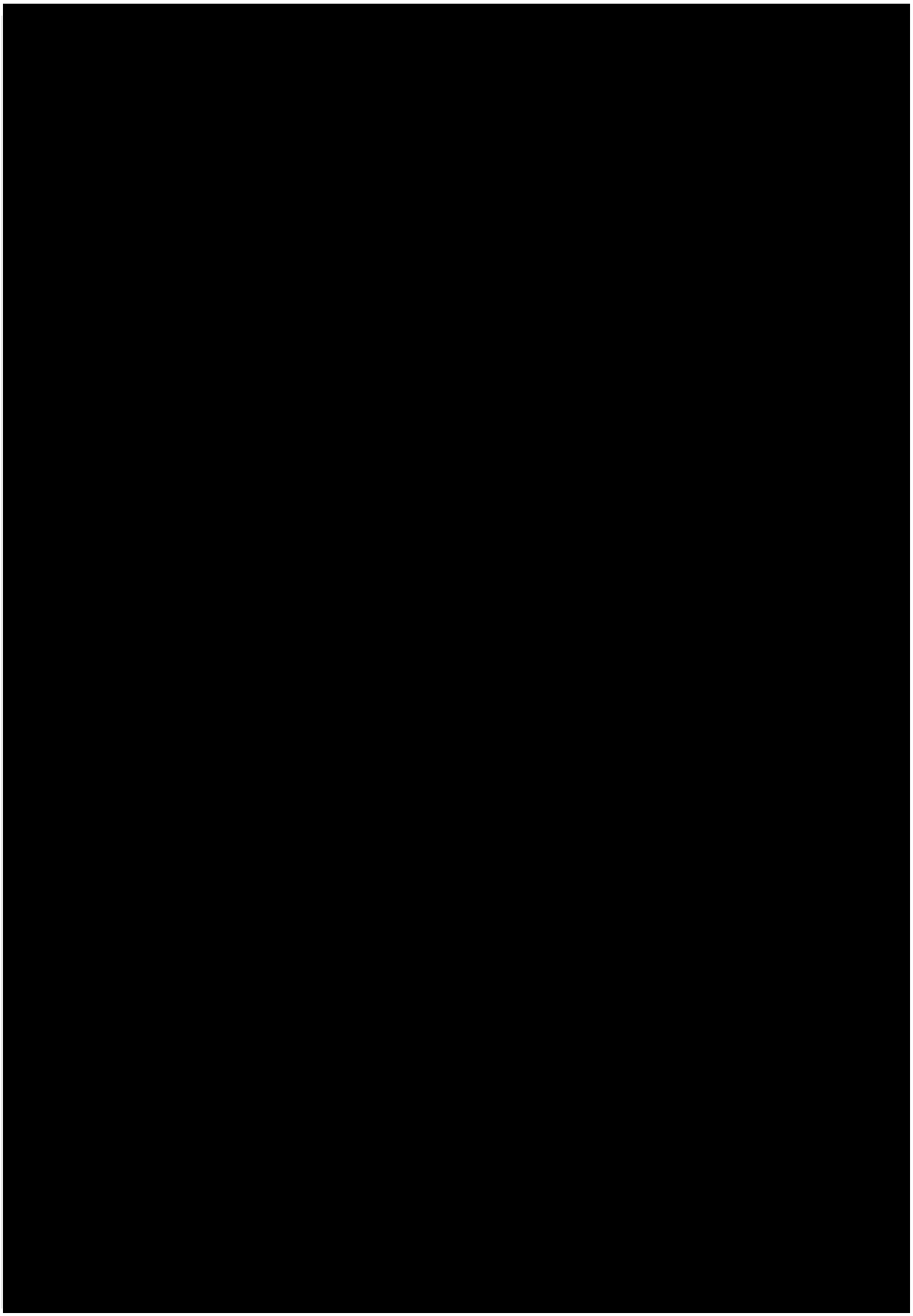


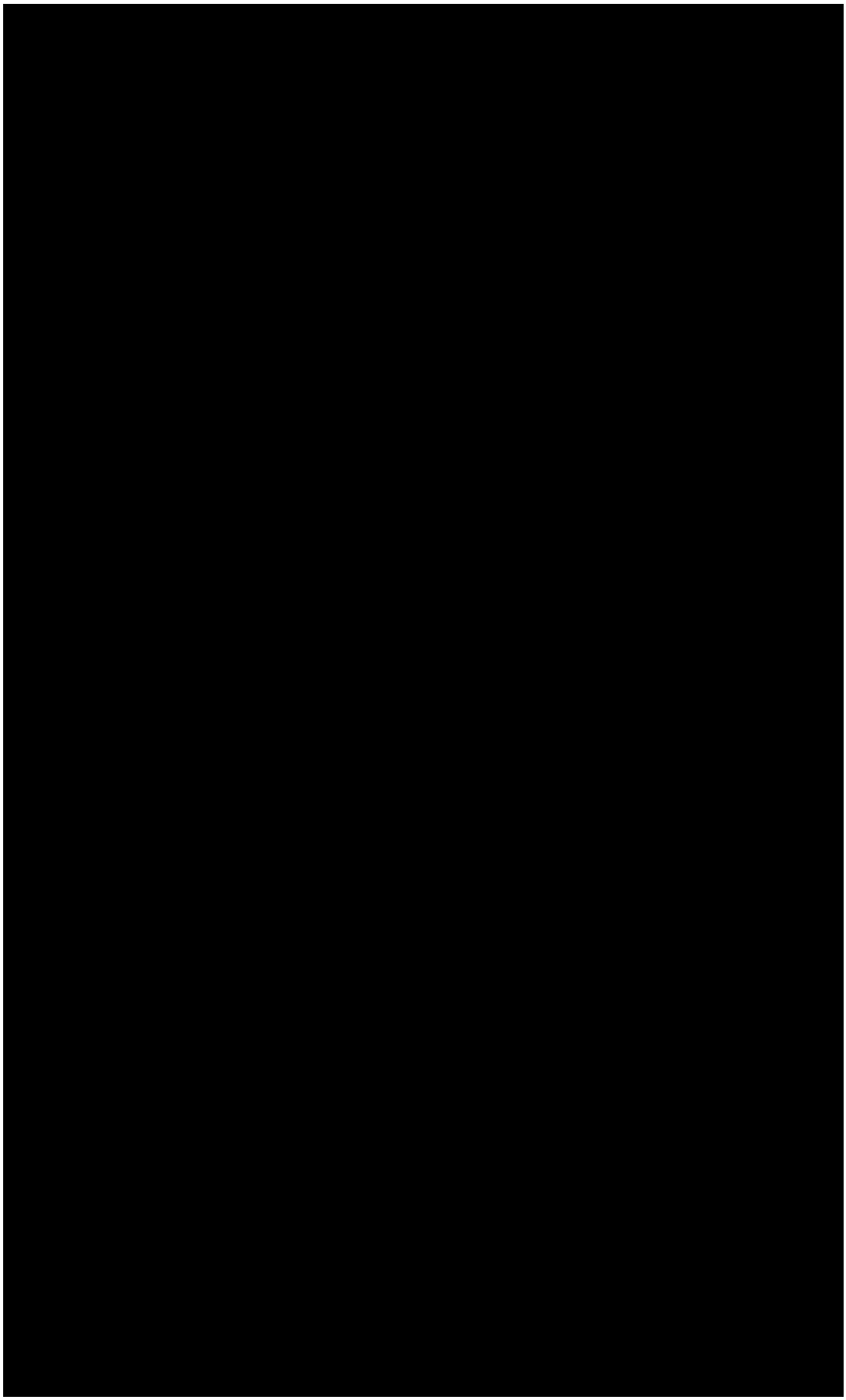


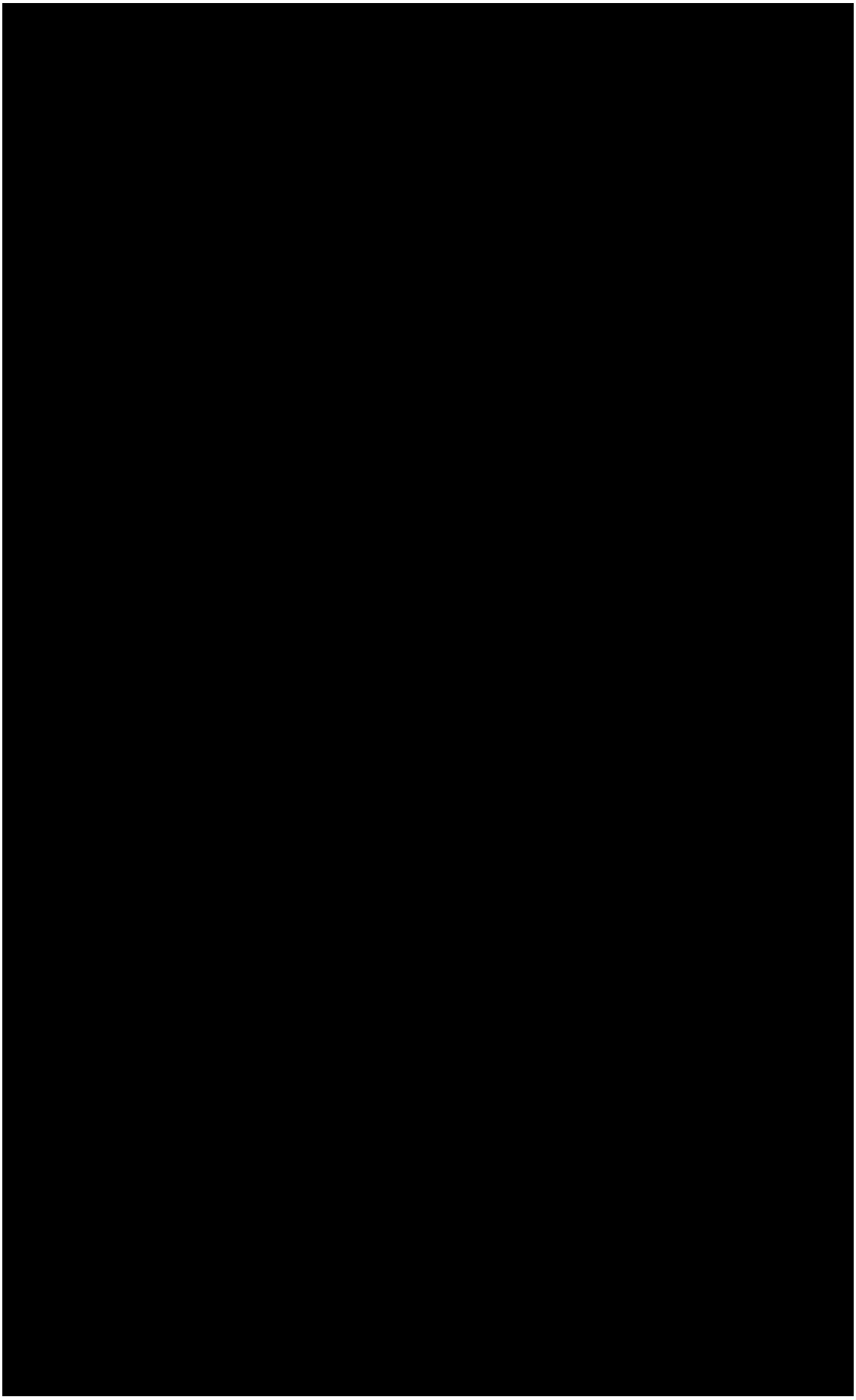


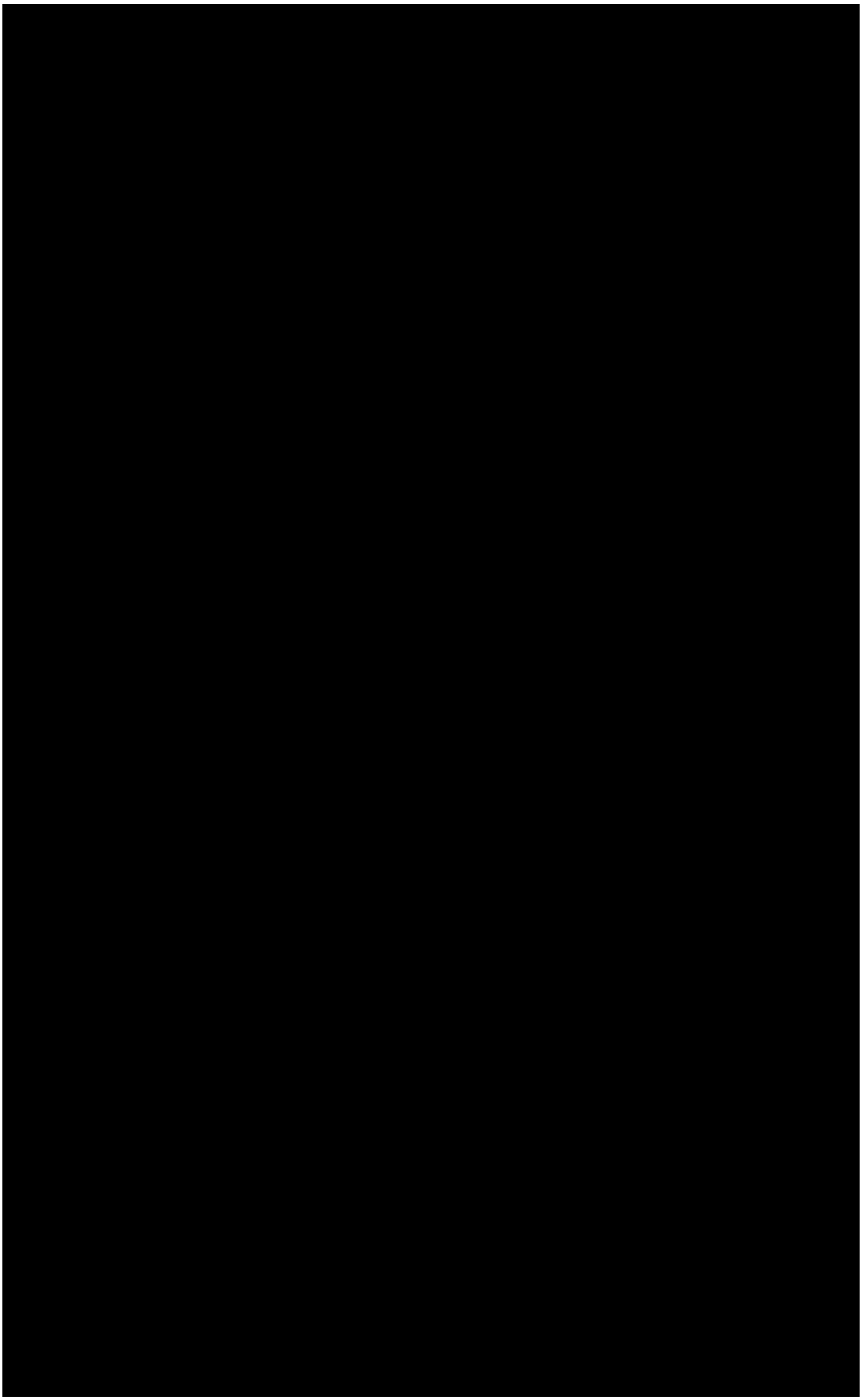


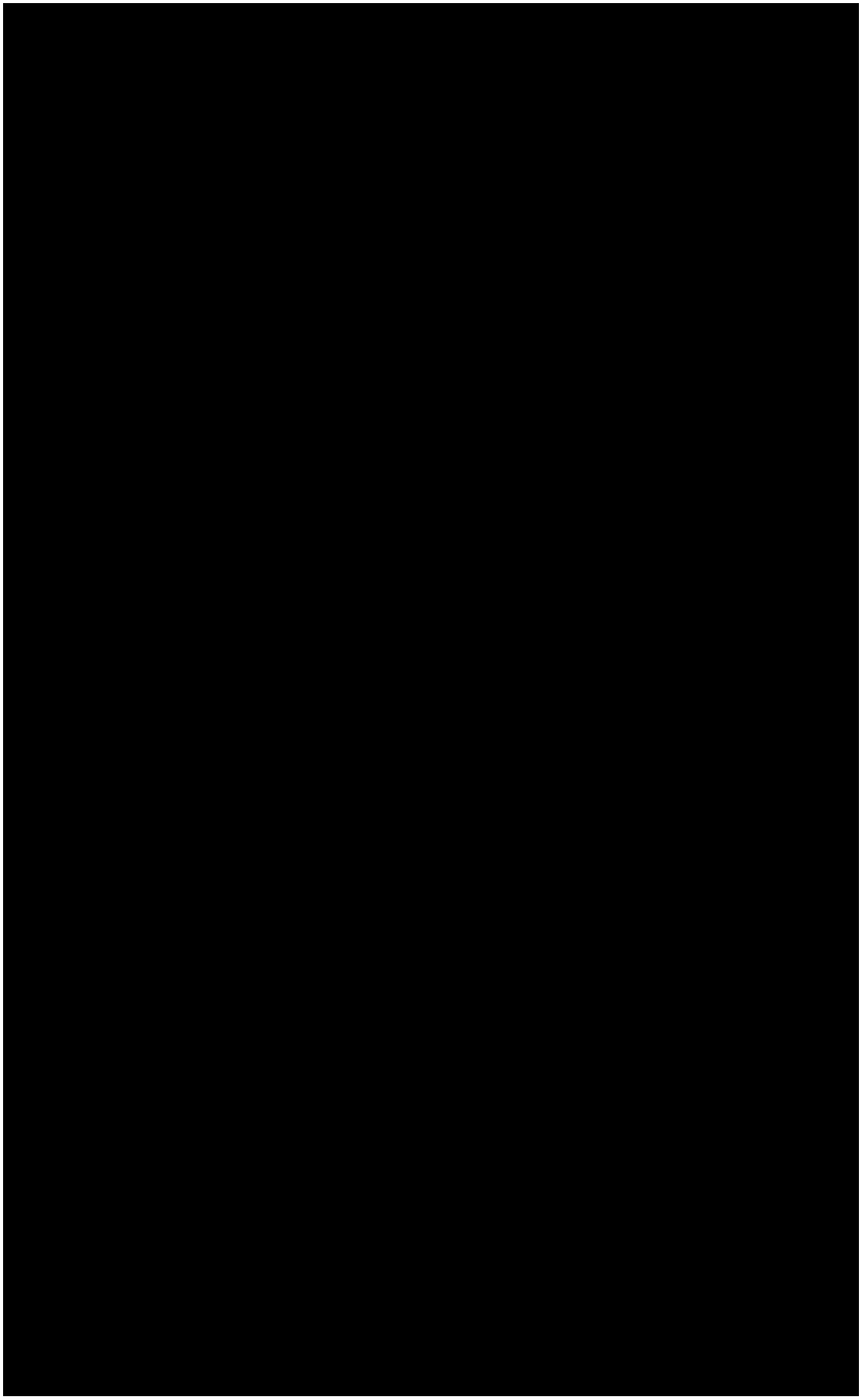


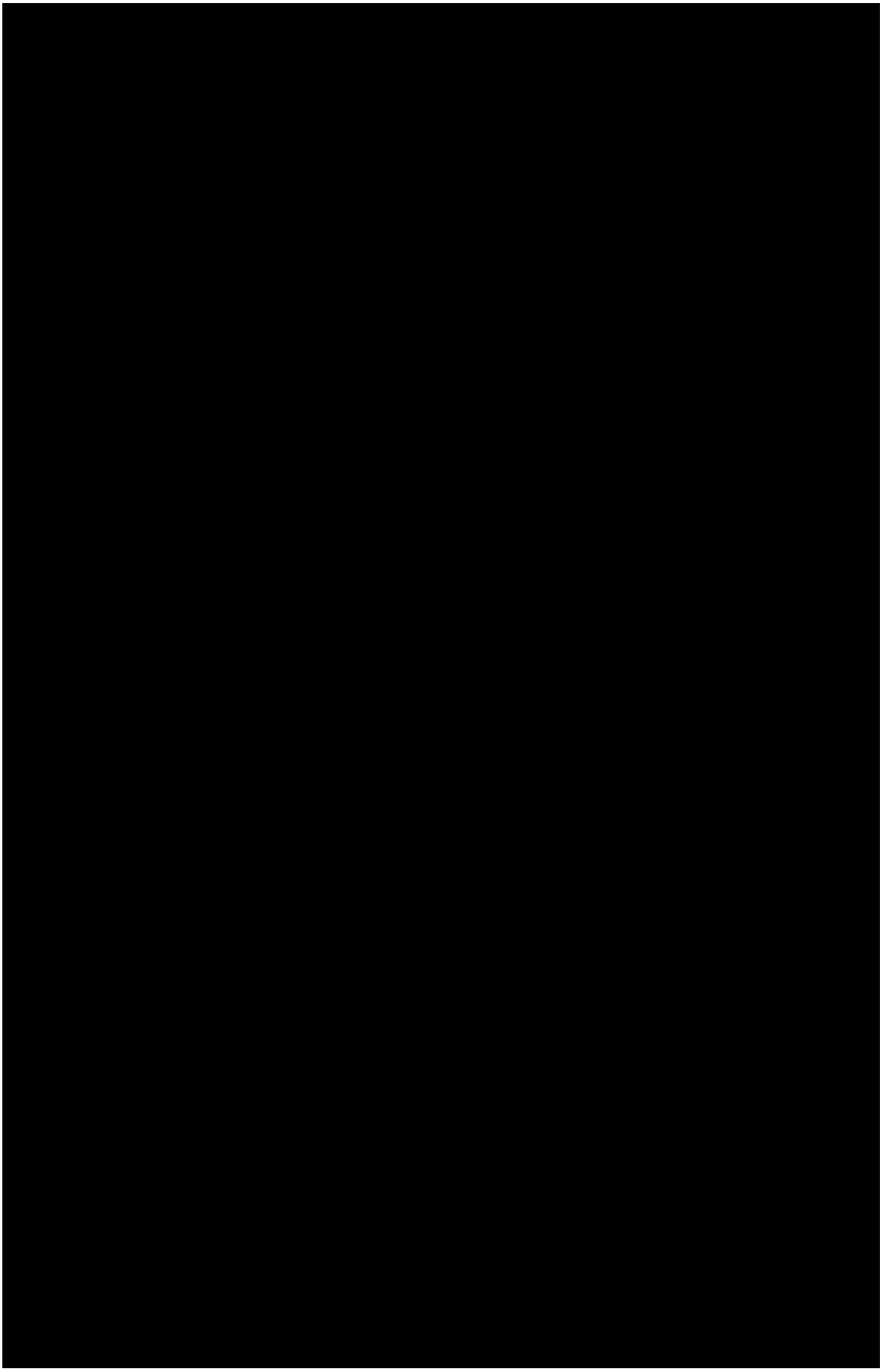


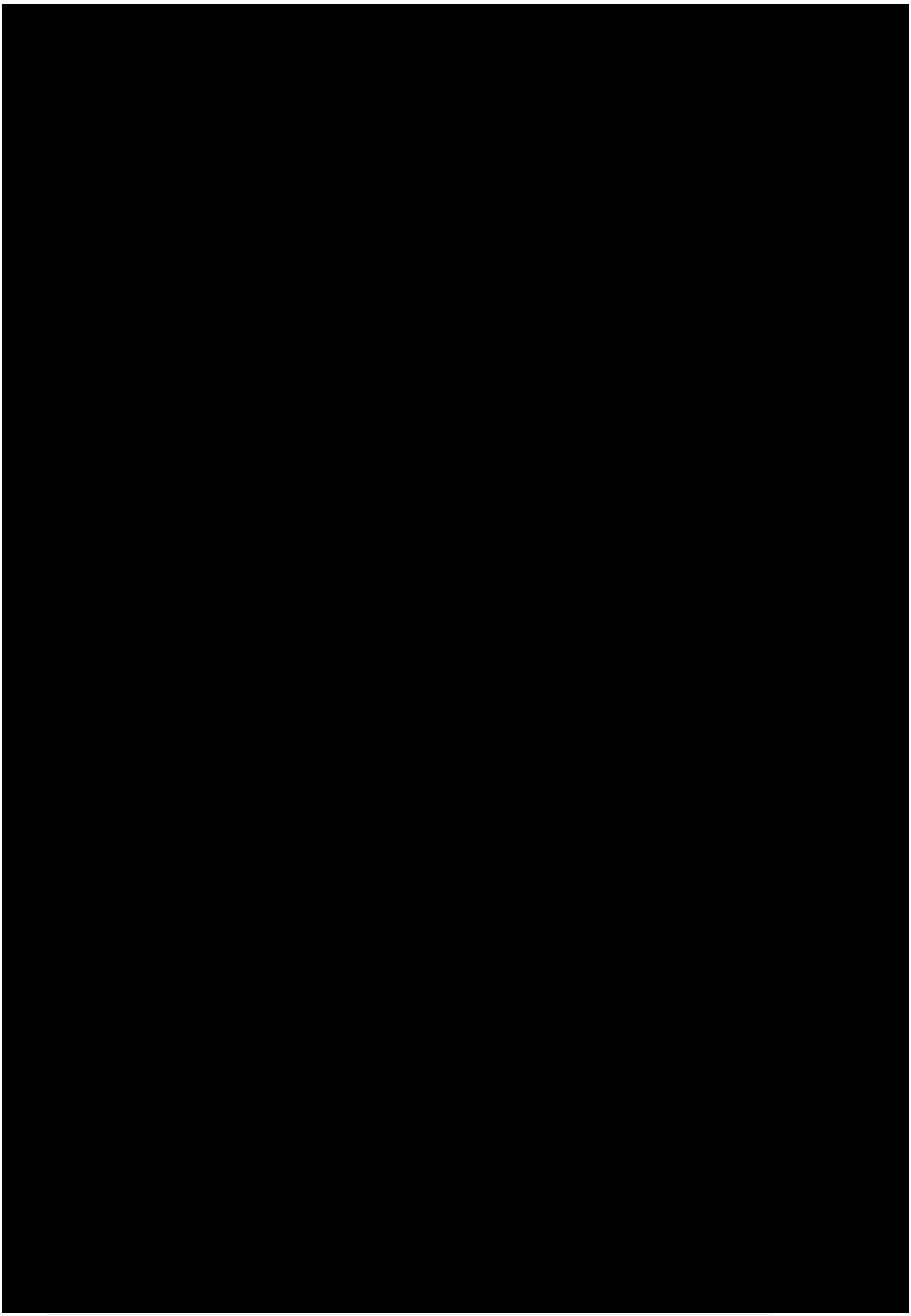


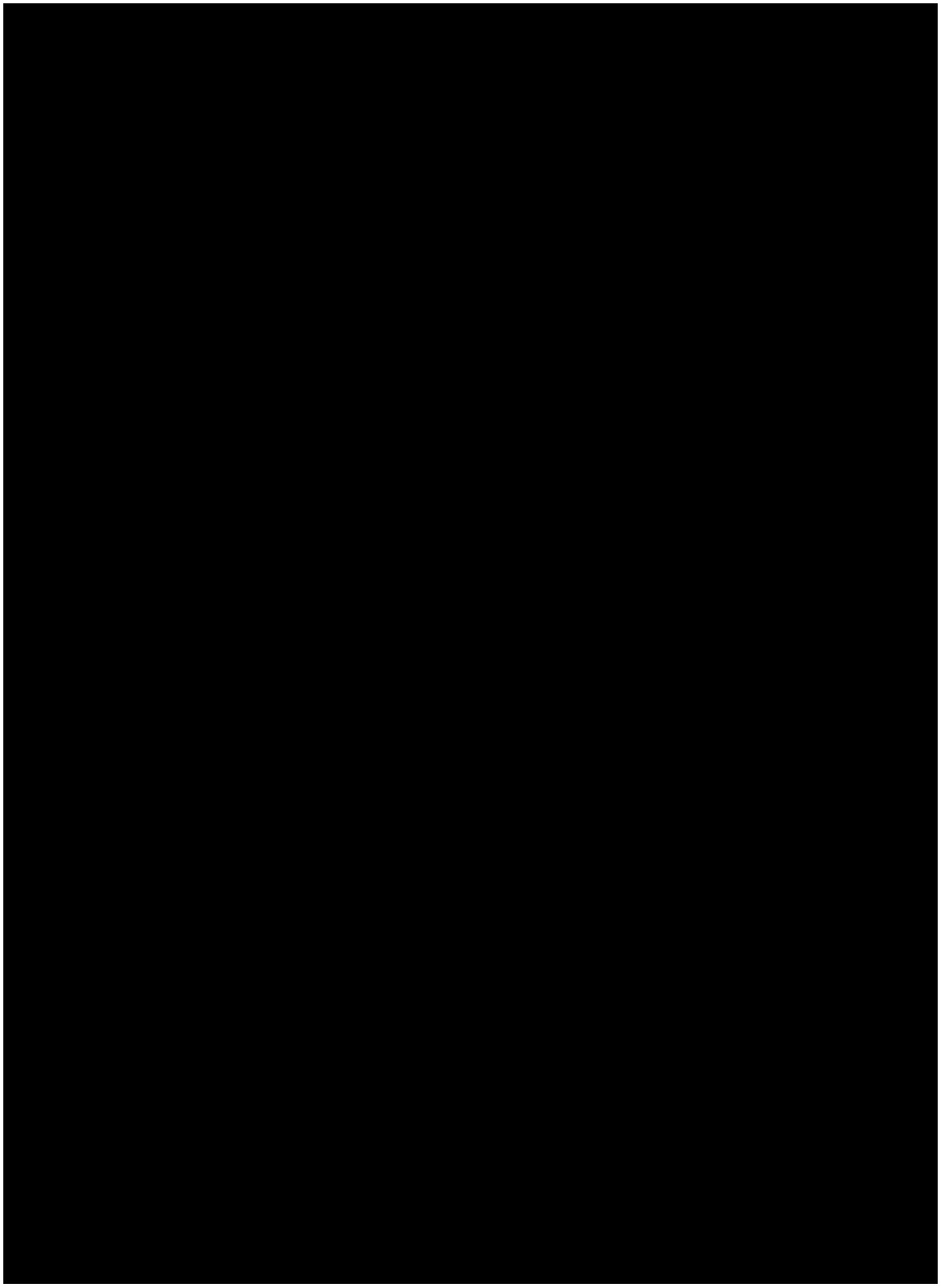


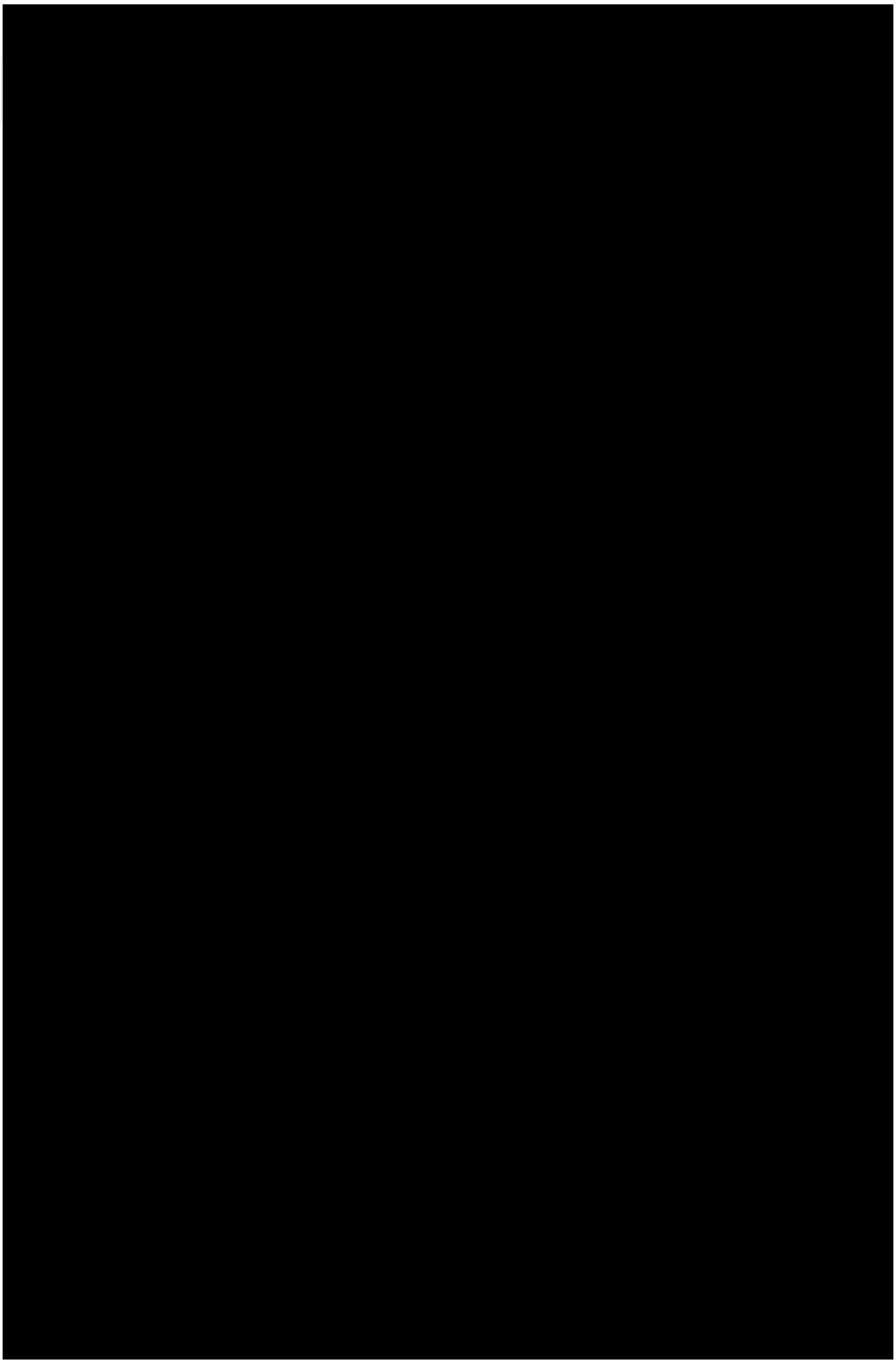


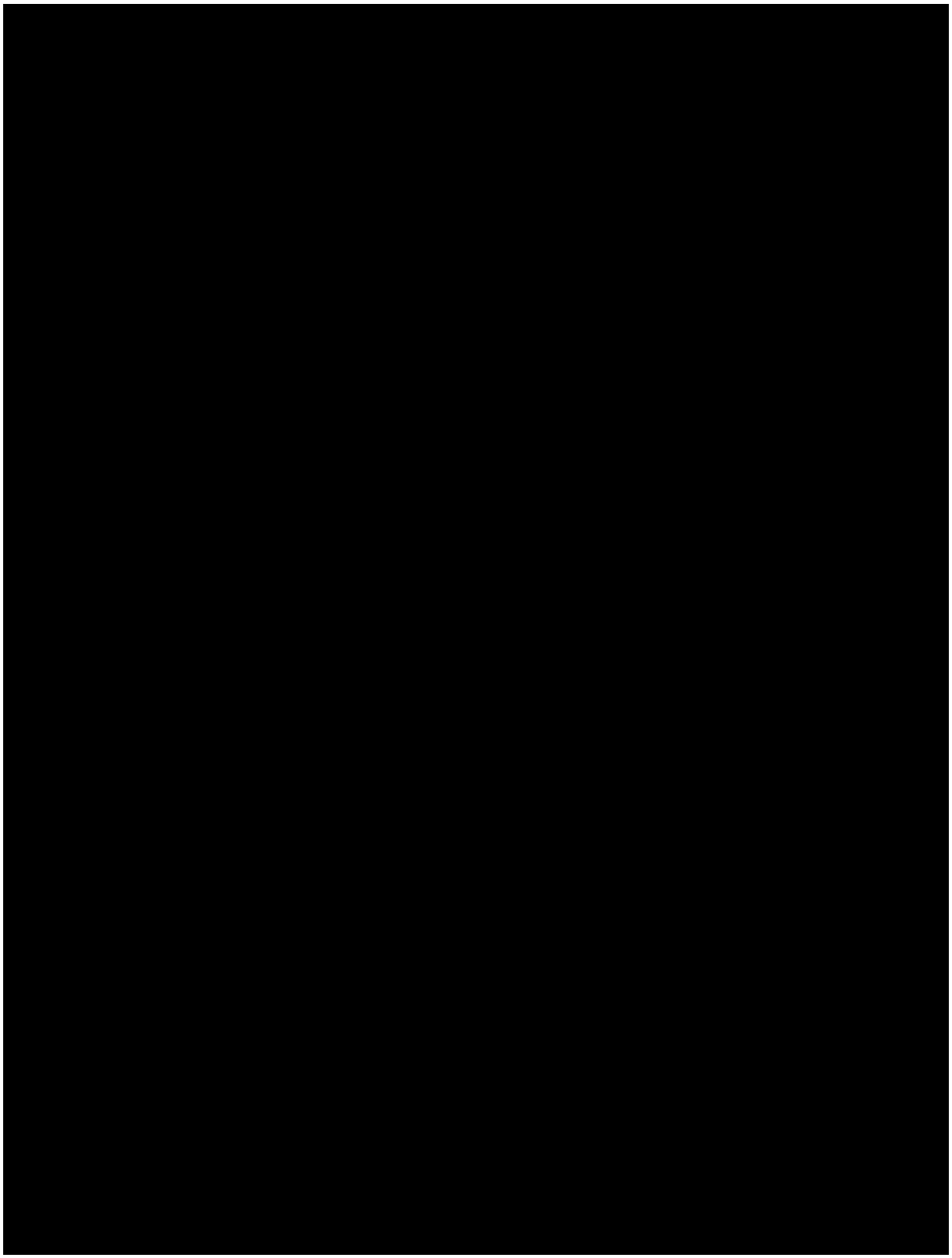


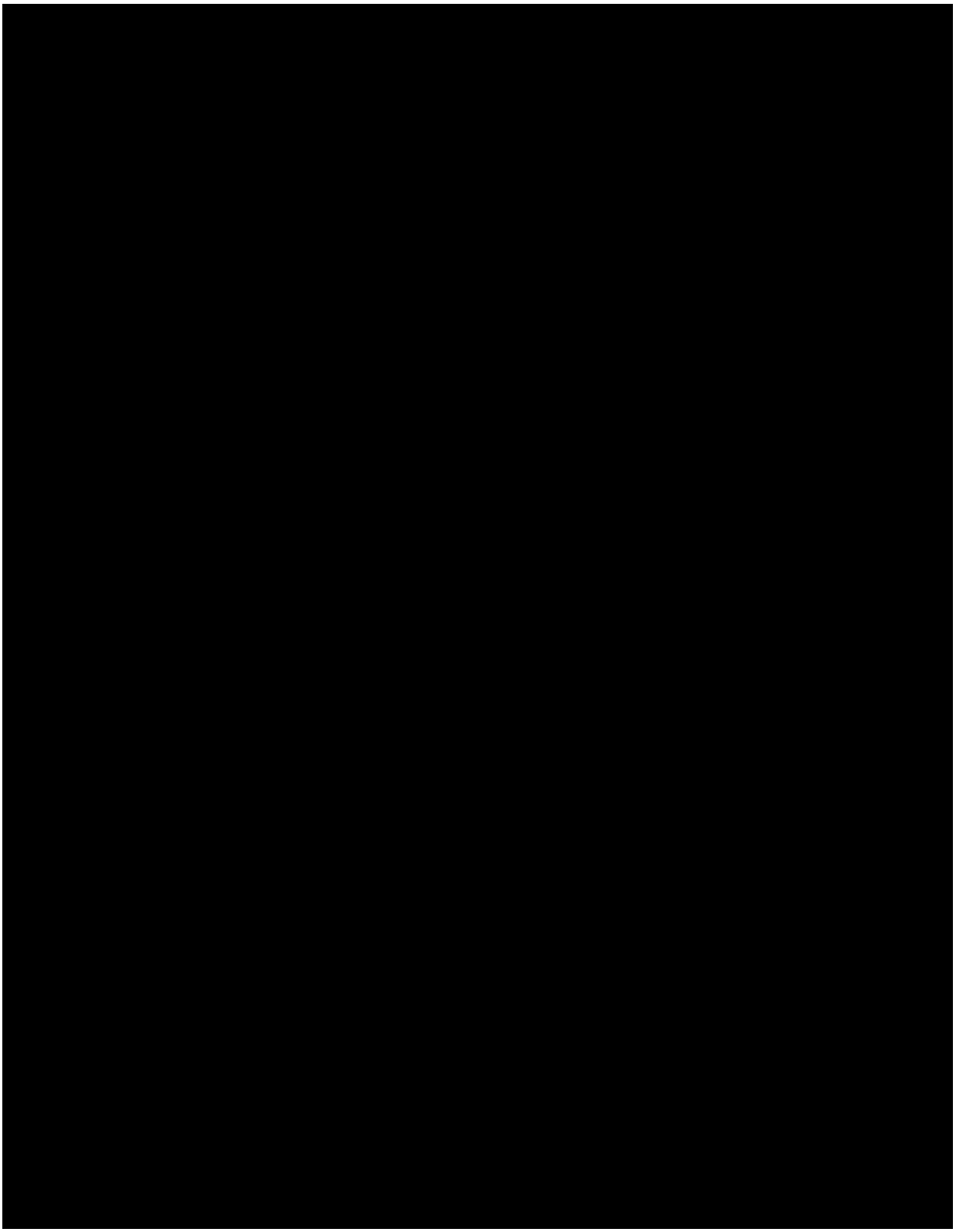


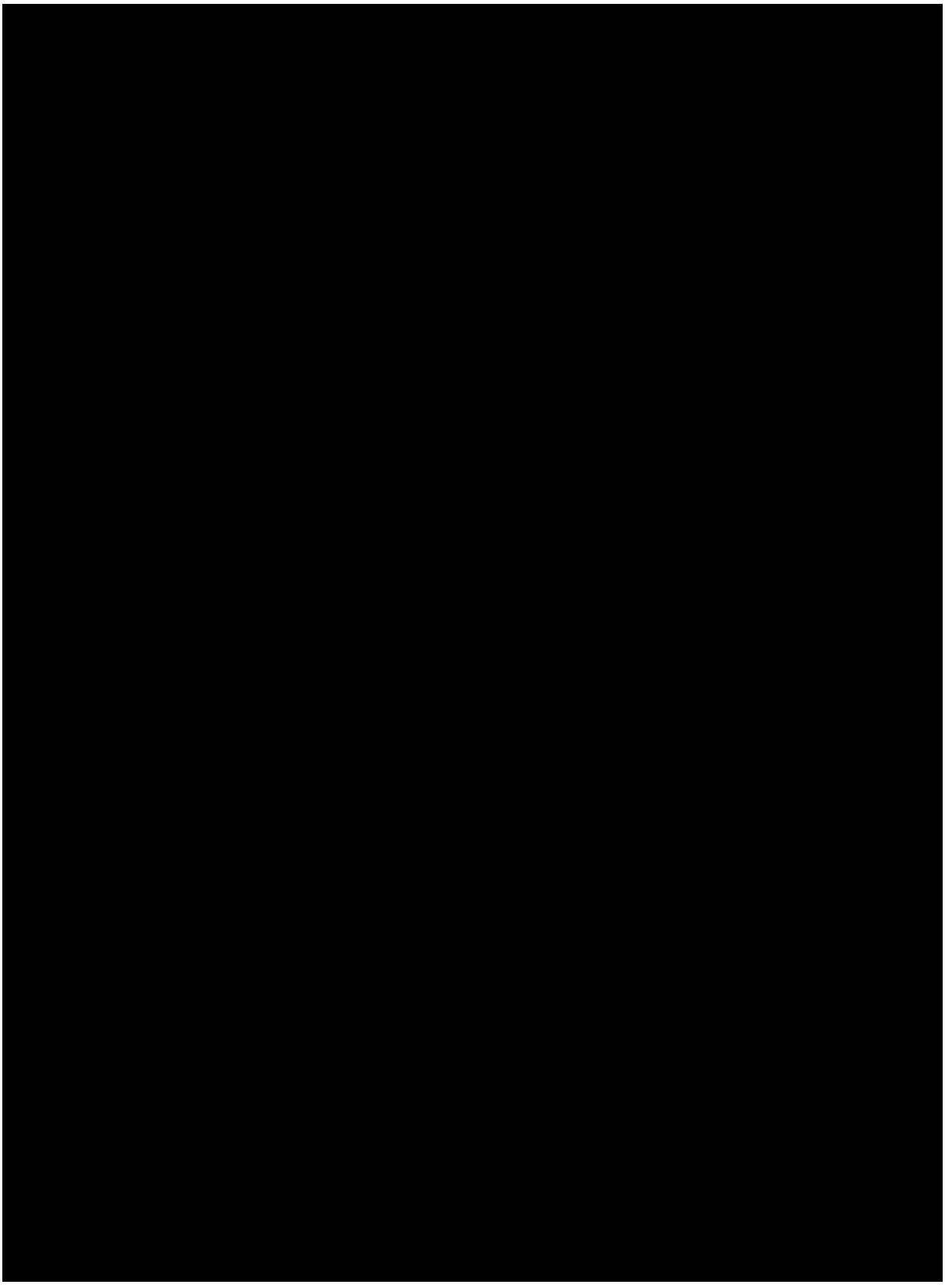


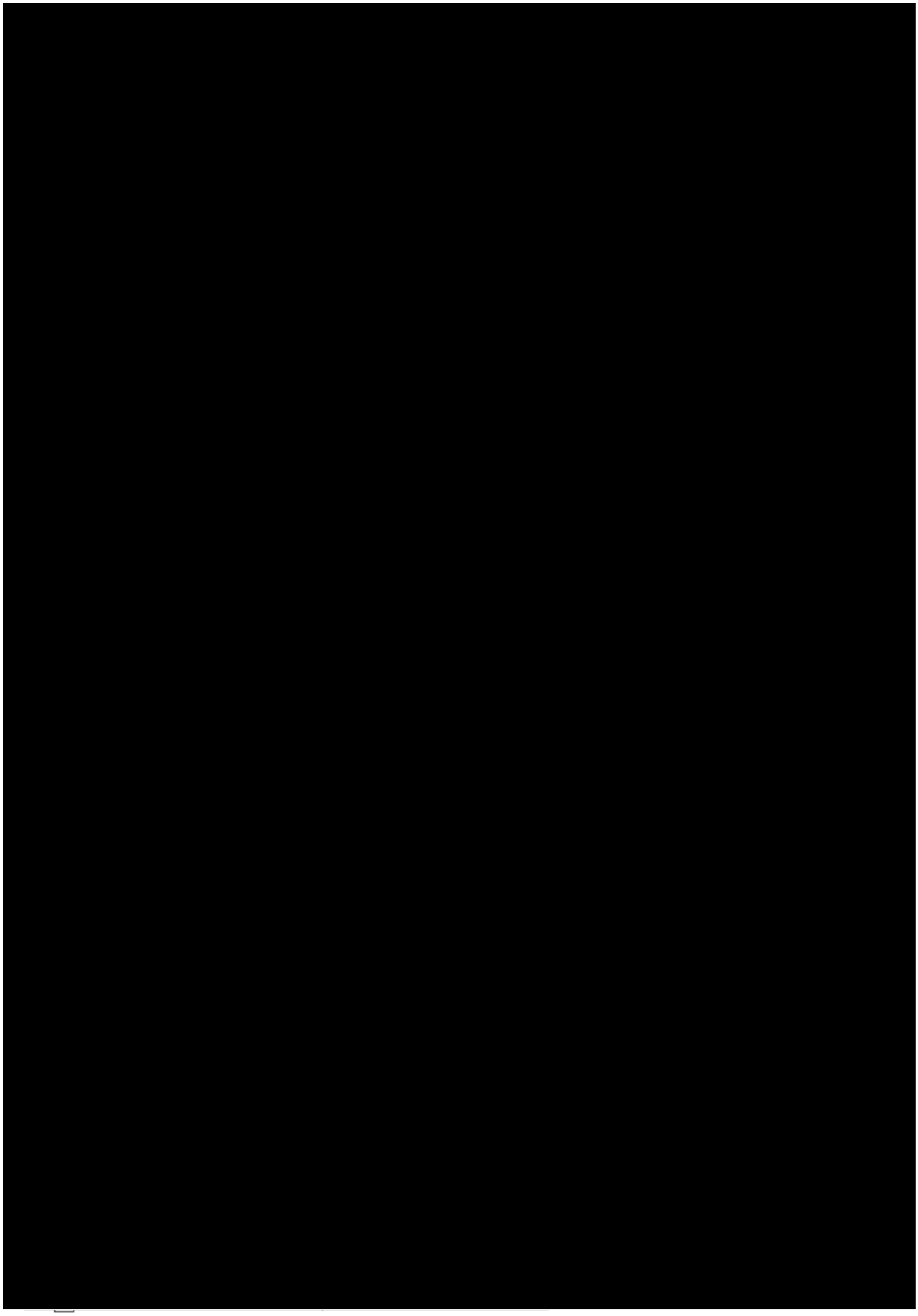


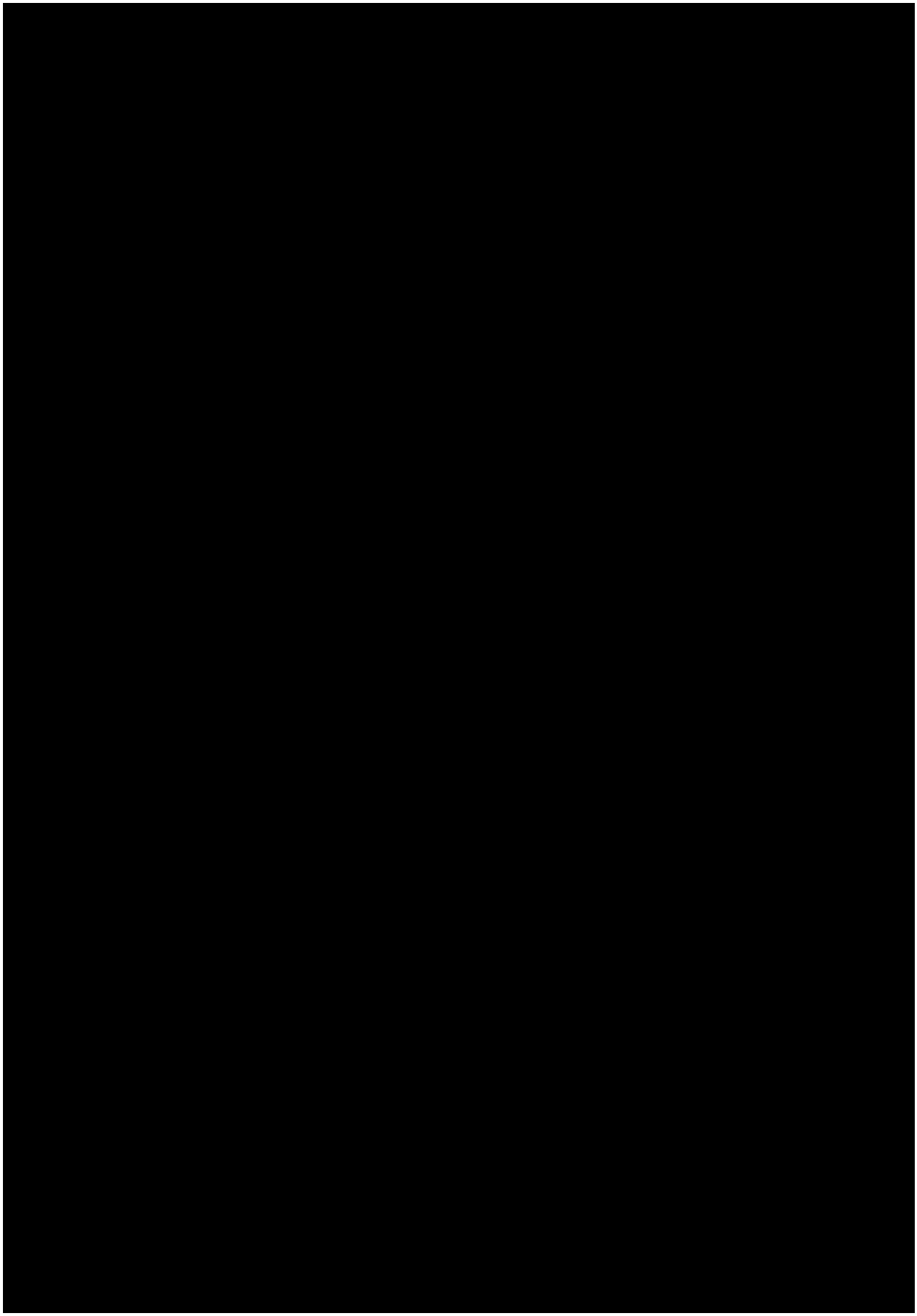


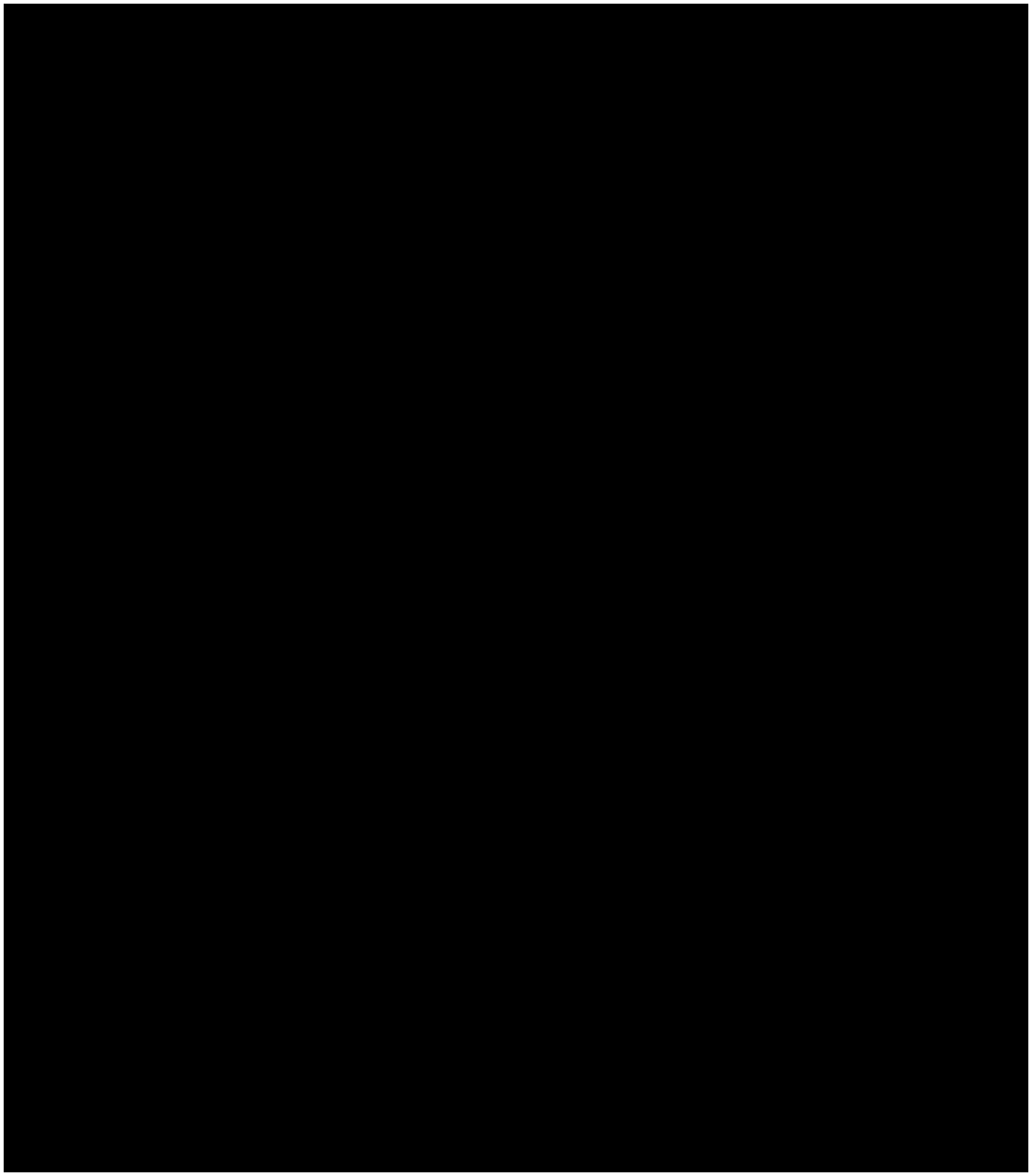


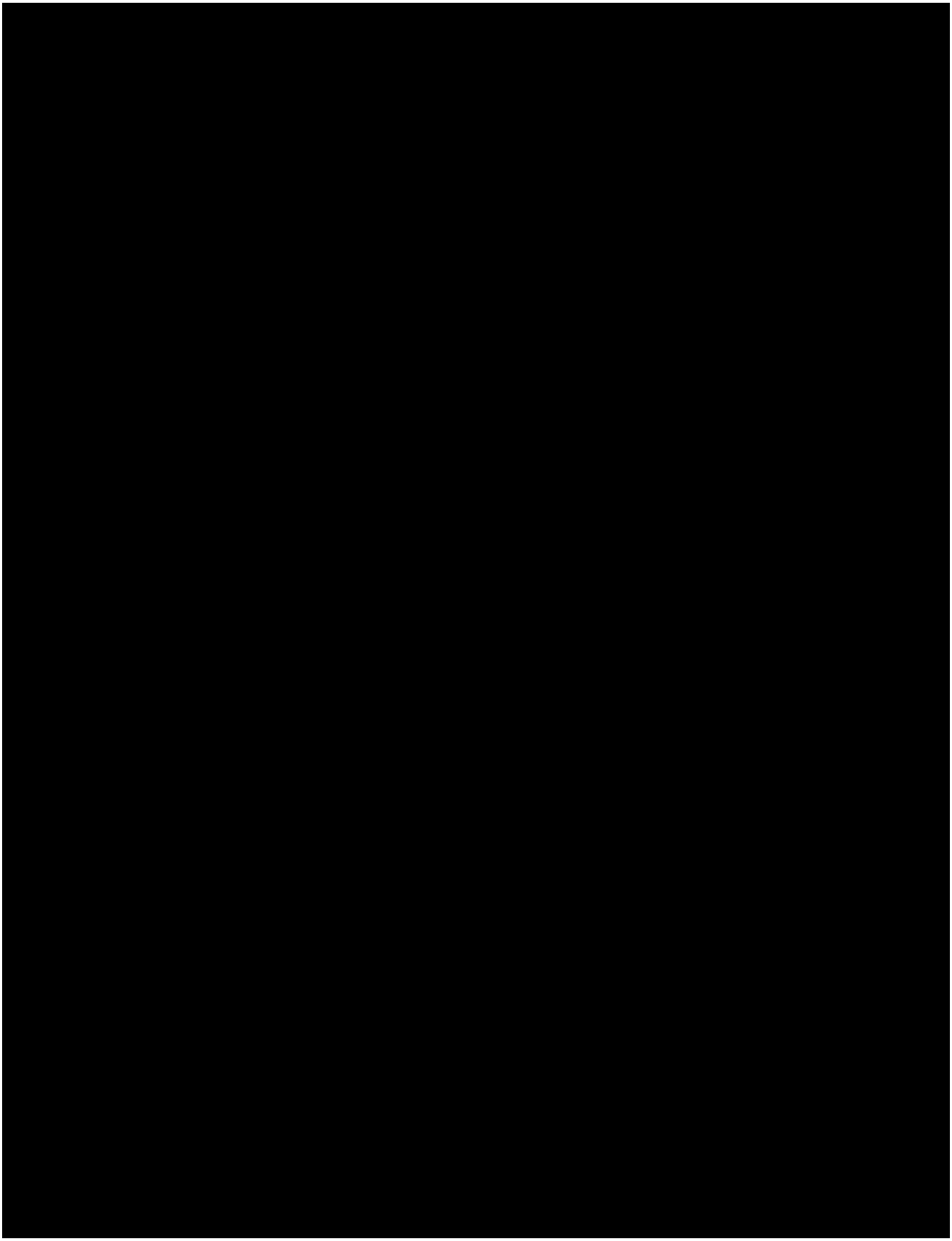


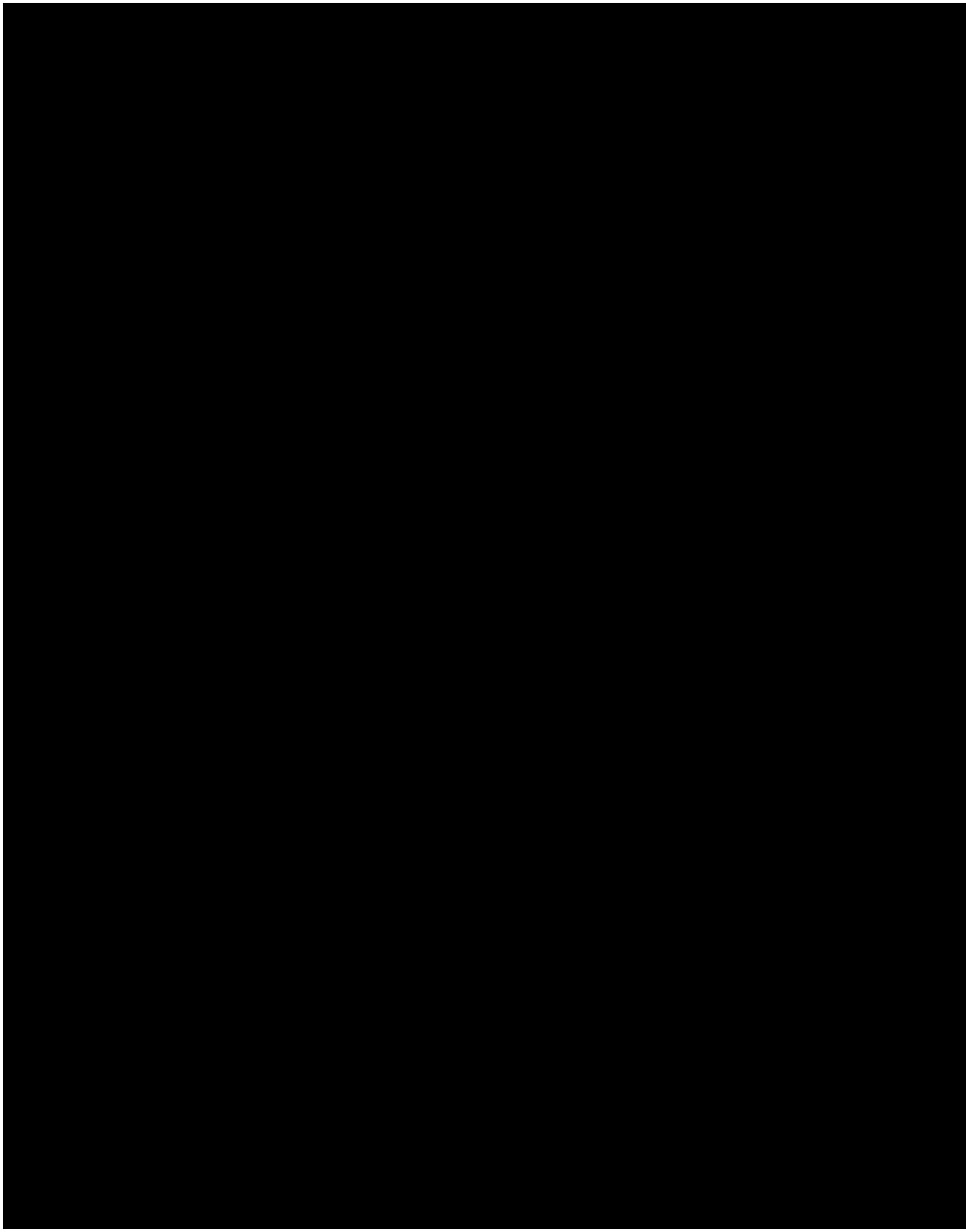


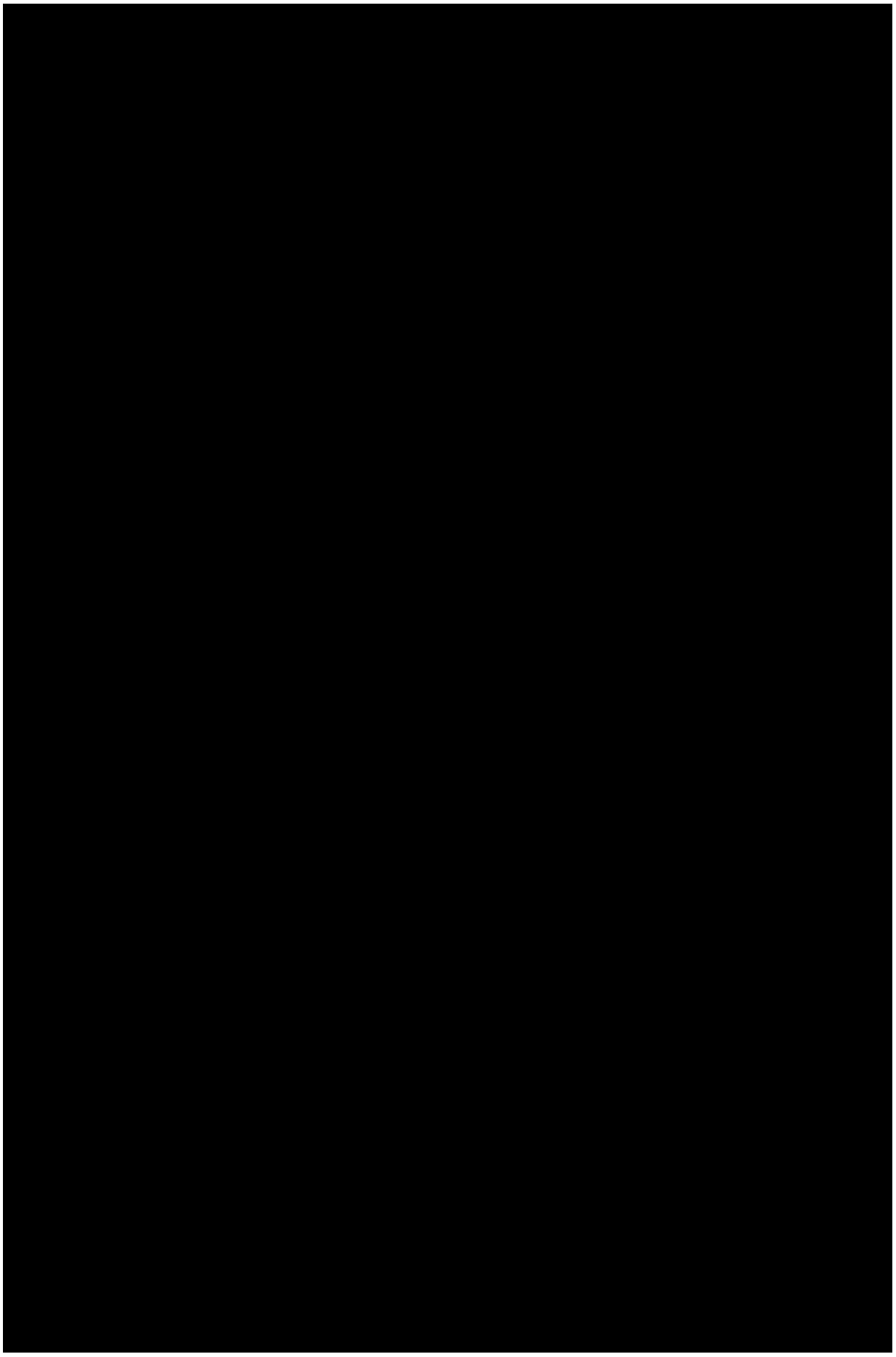


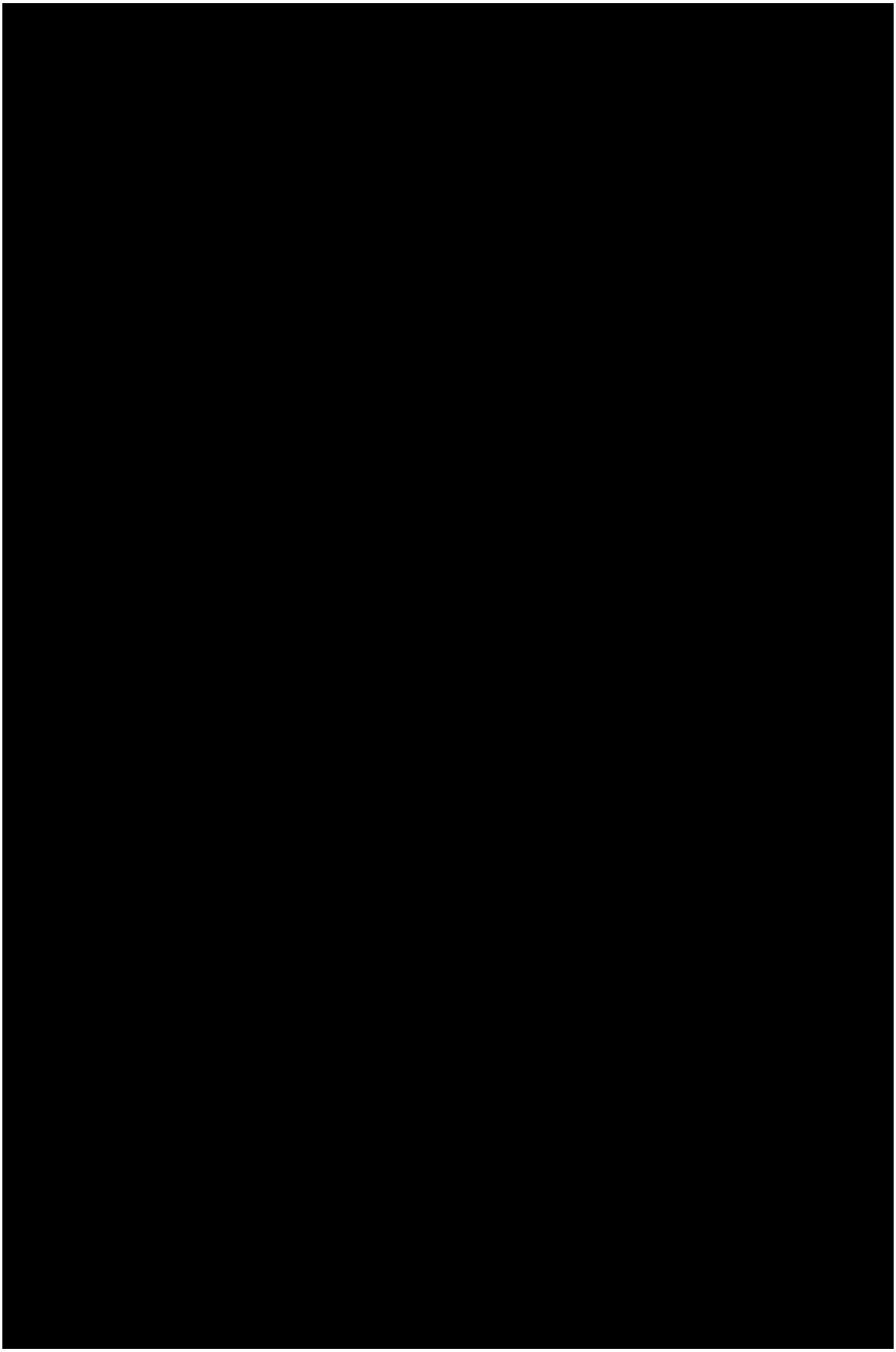












APPENDIX 14 VERSION HISTORY

Version Number	Version Date	Author	Changes Made
1.0	26Jul2017	[redacted]	Original version
1.1	17Aug2017	[redacted]	Non-substantial changes: [redacted] 2. Sections 5.1.1, BELKYRA – added statements regarding number of vials contained in kits 3. Sections 5.1.4, Treatment Assignments – added statements regarding partially used kits and unopened vials/syringes; added statements regarding number of vials contained in kits 4. Section 5.2.1 Storage – added instruction for inventory at vial and syringe level 5. Section 5.3.2 VOLUMA – specified that cannula used for VOLUMA treatment is per Allergan guidance.
1.2	26Sep2017	[redacted]	Non-substantial changes: [redacted]

1.3	21Nov2017	[redacted]	Non-substantial changes: 1. Protocol Summary (Secondary Endpoints) and Sections 7.2.1 and 10.4.2.1 Allergan Loss of Jawline Definition Scale– added Independent Reviewer assessment for the ALJDS 2. Section 4.4.1.1 Anesthesia – clarified "area of injection" such that anesthetic interventions apply to treatment or biopsy 3. Section 7.1.6 Photographic Imaging – specified imaging to also be completed "within 60 minutes after VOLUMA treatment" for consistency with Table 1.1 4. Section 7.1.7 Biopsy – changed biopsy sample size from "3-4mm" to "2mm". Changed location of biopsy excision site from "2cm" to "approximately 1.5cm" [redacted]
2.0	xxFeb2018	[redacted]	Substantial Changes: [redacted] 3. Section 6.1.4 Subject Enrollment – deleted subject status terms and definitions [redacted] 6. Section 10.1.1 Analysis Populations; Protocol Summary, Statistical Methods – modified analysis set titles and definitions to be consistent with non-randomized trials. Non-substantial Changes: [redacted]