18-Oct-2021

Clinical Study Protocol

HARMONY Brazil: Prospective, Multi-site, Study to Evaluate Subject Satisfaction with Facial Appearance Overall and the Aesthetic and Psychosocial Impact of Combined Facial Treatment

CMO-MA-FAS-0580

Version 2

Drug Development Phase:	Phase 4, Post marketing
Investigational Products:	BOTOX®, JUVÉDERM® VOLITE® [redacted], JUVÉDERM® VOLBELLA® with Lidocaine, JUVÉDERM® VOLIFT® with Lidocaine, JUVÉDERM® VOLUMA® with Lidocaine, JUVÉDERM® VOLUX® with Lidocaine; HArmonyCa™ Lidocaine
Indications:	Hyperkinetic Facial Lines, Deep Skin Depressions, Face Contouring, Volume Restoration, Superficial Cutaneous Depressions, Improvement of Skin Hydration and Elasticity, Facial Soft Tissue Augmentation
Sponsor:	AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064 USA
Version and Date	Version 2, 18-Oct-2021

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

CONFIDENTIAL INFORMATION

Protocol Approval Signature Page

Sponsor: AbbVie Inc.

I have read and understand the contents of this clinical protocol for Study No. CMO-MA-FAS-0580 dated 18-Oct-2021 and agree to meet all obligations of the Sponsor as detailed in all applicable regulations and guidelines. In addition, I will inform the Principal Investigator and all other investigators of all relevant information that becomes available during the conduct of this study.

Approved By:

[redacted] October 18, 2021

Signature **Date**

[redacted]
Global Aesthetic Medical Affairs

Principal Investigator's Agreement

I have read and understand the contents of this clinical protocol for Study No. CMO-MA-FAS-0580 dated 18-Oct-2021 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 (the Sponsor has certified GCP training completed) and all applicable laws and regulations.
- Maintain all information supplied by the Sponsor in confidence and, when this information is submitted to a Research Ethics Board (REB) 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:	
Clinic:	
Address:	

Protocol Synopsis

Sponsor:	**Investigational Products:**	**Developmental Phase:**
AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064 USA	BOTOX, JUVÉDERM® VOLITE® [redacted], JUVÉDERM® VOLBELLA® with Lidocaine, JUVÉDERM® VOLIFT® with Lidocaine, JUVÉDERM® VOLUMA® with Lidocaine, JUVÉDERM® VOLUX® with Lidocaine, HArmonyCA™ Lidocaine	Phase 4, Post-marketing

Title of Study: HARMONY Brazil: Prospective, Multi-site Study to Evaluate Subject Satisfaction with Facial Appearance Overall and the Aesthetic and Psychosocial Impact of Combined Facial Treatment

Protocol Number: CMO-MA-FAS-0580

Protocol Version: 2

Number of Subjects and Study Centers: 60 subjects at 7 study centers in Brazil

Indication:

BOTOX is indicated for the treatment of hyperkinetic facial lines.

JUVÉDERM VOLBELLA with Lidocaine is indicated for treatment of any fine lines and medium-sized skin depressions due to conditions such as premature aging. JUVEDERM VOLBELLA with Lidocaine can also be used for enhancement and pouting of the lips to correct structural defects such as asymmetry, contour deformities, and volume loss.

JUVÉDERM VOLIFT with Lidocaine is indicated for treatment of any deep skin depressions due to conditions such as premature aging. Face contouring and volume restoration to correct facial structural defects such as asymmetry, contour deformities, volume loss in the lips, cheeks, chin, lower face.

JUVÉDERM VOLUMA with Lidocaine is indicated for treatment to restore the volume of the face.

JUVÉDERM VOLITE [redacted] is indicated for treatment, by filling, of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity.

JUVEDERM VOLUX with Lidocaine is an injectable implant intended to restore and generate facial volume in chin and mandible areas.

HArmonyCa Lidocaine injectable gel is a dermal filler intended for facial soft tissue augmentation.

Primary Study Objective:

To quantify the psychological and emotional impact of comprehensive aesthetic treatment with a portfolio of the Sponsor's products by measuring the change from baseline in the Rasch-transformed score of the FACE-Q Satisfaction with Facial Appearance Scale to the final study visit (V7).

Secondary Study Objectives:

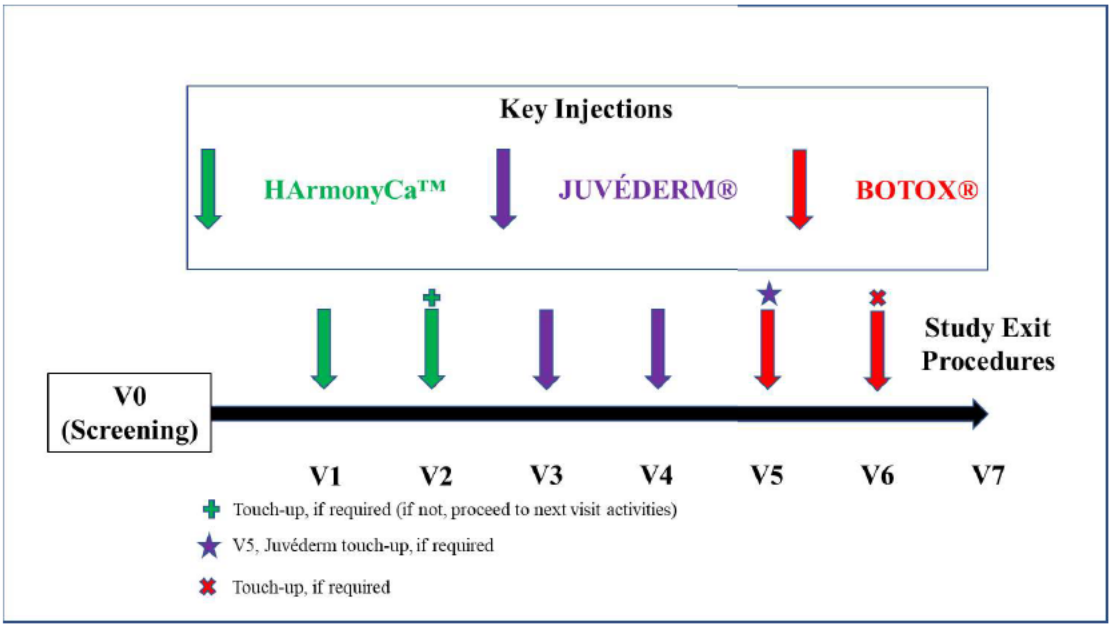
- To determine the subject's self-appraisal of age-related facial appearance, psychological function, and overall satisfaction with skin modules.
- To quantify the investigator's and subject's assessment of aesthetic improvement.

Methodology:

This Phase 4 study is a prospective, interventional, multicenter, combination filler medical device and drug post marketing study. Each subject will be in the study for up to approximately 5 months and act as his/her own control. All products will be used as per their license only. The investigators will perform all treatments and evaluations.

The study is planned to enroll 60 subjects consecutively at approximately 7 study sites in Brazil. Recruitment will also target men, who are typically under-represented in aesthetic studies.

Overall Study Design



All subjects will sign an informed consent form (ICF) and begin the study at the screening visit (V0). Subjects following screening (V0) will enter the study at V1 to begin treatment with HArmonyCa Lidocaine, Juvéderm fillers at Visit 3, and BOTOX at V5 as indicated in the study design diagram above. If the decision is made to not treat with HArmonyCa Lidocaine, the subject may begin with Juvéderm fillers at V1. As indicated in the diagram, touch-ups of HArmonyCa (V2), Juvéderm (V5), and BOTOX (V6) are optional. If a touch-up of HArmonyCa (V2) is not performed, the subject may advance in the study timeline to the next study visit procedures. If a touch-up of BOTOX (V6) is not performed, the subject will return

on schedule for V7. A subject not receiving Juvéderm (V5) touch-up would continue with BOTOX treatment (and all study procedures) outlined for V5.

To reduce the number of subject visits, V0 can be combined with the initial treatment visit (V1), if judged by the investigator to be appropriate and acceptable for the subject. Identical study procedures will not be repeated where the visits are combined.

All adverse events (AEs) and injection site reactions (ISRs) will be collected from when the ICF is signed through to the last study visit. Serious adverse events (SAEs) will be reported directly to the Sponsor within 24 hours.

Criteria for Evaluation:

Primary Endpoint

The primary endpoint is the change from baseline in the overall Rasch-transformed score of the FACE-Q Satisfaction with Facial Appearance Scale to the final study visit (V7).

Key Secondary Endpoints

- Subject's assessment of age-related facial appearance as measured by the change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Aging Appraisal to final study visit (V7)
- Subject's assessment of psychological well-being as measured by the change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Psychological Function Scale to final study visit (V7)
- Subject's assessment of social function as measured by the change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Social Function Scale to final study visit (V7)
- Subject's assessment of overall satisfaction with skin as measured by the change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Satisfaction with Skin to final study visit (V7)
- Subject's assessment of age-related facial appearance as measured by self-perception of age (SPA) at baseline before any treatment to final study visit (V7); responders are defined as having achieved a younger category.

Other Secondary Endpoints

- Investigator's assessment of global facial aesthetic improvement as measured by the 5-point global aesthetic improvement scale (GAIS) at final study visit (V7)
- Subject's assessment of global facial aesthetic improvement as measured by the 5-point GAIS at final study visit (V7)
- Change in subject's satisfaction with appearance of periorbital area as measured by the periorbital aesthetic appearance questionnaire (PAAQ) from baseline to final study visit (V7)

Key Inclusion Criteria:

1. 35 to 65 years of age, inclusive, at screening (male or female)
2. Accept the obligation not to receive any other facial procedures or treatments at any time during the study that are not related to the study
3. Women of childbearing potential must have a negative urine pregnancy test before each injectable treatment and practice a reliable method of contraception throughout the study.
4. Willing to avoid direct and prolonged sun exposure to the facial skin, which includes tanning beds, for the duration of the study
5. Must qualify to receive BOTOX in at least one area as per the approved Product Monograph including treatment of hyperkinetic lines for the glabellar, crow's feet, and forehead lines (GL, CFL, and FHL, respectively):
   - Glabellar injection: glabellar rhytides characterized as 2 (moderate) or 3 (severe) during maximum muscle contraction on the evaluation of the facial wrinkle scale (FWS)
   - CFLs characterized as 2 (moderate) or 3 (severe) during maximum smile on the evaluation of the FWS
   - FHLs of 2 (moderate) to 3 (severe) rating at maximum eyebrow elevation as assessed using the FWS
6. Must qualify to receive Juvéderm dermal filler treatments as per the approved Directions for Use and must use at least two different Juvéderm filler products in at least two different aesthetic subunits

Key Exclusion Criteria:

1. Body mass index (BMI) > 30 kg/m^2
2. Known allergy or sensitivity to any study products or their components
3. Pregnant, lactating, or planning to become pregnant at any time during the study
4. Received BOTOX or treatment with any other botulinum toxin product for any condition within 6 months before enrollment
5. Received (or is planning to receive) anti-coagulation, anti-platelet or thrombolytic medications (e.g., warfarin) or other substances known to increase coagulation time from 10 days prior to injection and up to 3 days post-injection
6. Undergone plastic surgery of the face and/or neck, tissue grafting, or tissue augmentation with silicone, fat, or other permanent dermal fillers, or be planning to undergo any of these procedures at any time during the study
7. Has undergone temporary or semi-permanent facial or neck dermal filler treatment (e.g., hyaluronic acid, calcium hydroxylapatite, poly-L-lactic acid) within 12 months before enrollment
8. Received mesotherapy, skin resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or non-ablative procedures) in the face or neck within 6 months prior to study enrollment

9. Marked facial asymmetry, brow or eyelid ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or an inability to substantially lessen the resting GLs and CFLs/facial rhytides by physically spreading them apart
10. Lip tattoos, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments
11. At any proposed injection site, presence of inflammation, infection at any injection site or systemic infection (study entry may be postponed until one week following recovery), noticeable acne scarring, cancerous or pre-cancerous lesion, or unhealed wound or have undergone radiation treatment in the area to be treated
12. Received any investigational product within 60 days prior to study enrollment or planning to participate in another investigation during the course of this study
13. An employee (or a relative of an employee) of the investigators, the Sponsor, or representative of the Sponsor
14. Condition or in a situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study
15. Current use of oral corticosteroids
16. Current use of nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen), from 10 days prior to injection up to 3 days post-injection
17. Prescription topical retinoid therapy and/or topical hormone cream applied to the face, for potential subjects who have not been on a consistent dose regimen for at least 6 months prior to enrollment and who are unable to maintain regimen for the study
18. Systemic retinoid therapy within one year prior to study enrollment
19. History or current symptoms of dysphagia
20. Medical condition that may increase the risk of exposure to botulinum toxin including diagnosed myasthenia gravis, Eaton-Lambert Syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function
21. Current use of aminoglycoside antibiotics, curare-like agents, or agents that might interfere with neuromuscular (skeletal) function
22. Profound atrophy/excessive weakness of muscles in target areas of injection
23. History of facial nerve palsy
24. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study treatment)
25. Very thin skin in the mid-facial region
26. Tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, i.e., significant convexity or projection from the infraorbital fat pads
27. Mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or human immunodeficiency virus–related disease

28. Undergone oral surgery or other dental procedures (e.g., tooth extraction, orthodontia, or implantation) within 30 days prior to enrollment or planning to undergo any of these procedures during the study
29. Subjects with neuromuscular disorders including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise
30. Subjects with a history of allergies or hypersensitivity to hyaluronic acid or lidocaine

Products, Dose, and Mode of Administration:

BOTOX

Subjects will receive BOTOX. The dose and the number of injection points may be adapted to the needs of the subject, based on their characteristics and location of the muscles to be treated. Subjects will receive at least one BOTOX treatment in the following areas: GLs, CFLs, and FHLs.

Facial Fillers

JUVÉDERM VOLBELLA with Lidocaine

The investigator will determine the appropriate volume of JUVÉDERM VOLBELLA to inject at initial and touch-up treatments based on his/her clinical experience and the subject's aesthetic goals. The maximum combined total volume allowed per subject for all facial areas treated for both the initial and touch-up treatments combined is 2 syringes (2 mL).

JUVÉDERM VOLIFT with Lidocaine

The investigator will determine the appropriate volume to be injected during initial and touch-up treatments based on his/her clinical experience. The maximum total volume of JUVÉDERM VOLIFT with Lidocaine allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).

JUVÉDERM VOLUMA with Lidocaine

The investigator will determine the appropriate volume to be injected during initial and touch-up treatments based on his/her clinical experience. The maximum total volume of JUVÉDERM VOLUMA with Lidocaine allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).

JUVÉDERM VOLITE [redacted]

The investigator will determine the appropriate volume to be injected during initial and touch-up treatments based on his/her clinical experience. The maximum total volume of JUVÉDERM VOLITE [redacted] allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).

JUVÉDERM VOLUX with Lidocaine

The investigator will determine the appropriate volume to be injected during initial and touch-up treatments based on his/her clinical experience. The maximum total volume of

JUVÉDERM VOLUX with Lidocaine allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).

HArmonyCa Lidocaine

The investigator will determine the appropriate volume to be injected during initial and touch-up treatments based on his/her clinical experience. The maximum total volume of HArmonyCa Lidocaine allowed per subject for the initial and touch-up treatment combined is 4 syringes (5 mL).

The investigator should not inject greater than 20 mL of filler (Juvéderm and HArmonyCa) per 60 kg (130 lbs.) body mass per year for a single subject.

Concomitant Medications:

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 (ie, hypertension, diabetes, etc.), treatment of AEs, estrogens, androgens, anti-androgenic agents, vitamins, iron supplements, folate, and herbal supplements. Medications should be taken consistently throughout the study and at the investigator's discretion.

All medications or treatments received by the subject within 30 days before the baseline visit and throughout the study, including the name of the drug or procedure, must be recorded in the study source documents and electronic case report form (eCRF) with end dates, if end dates are available.

Study Duration: Each subject will participate in the study for up to approximately 5 months.

Statistical Methods:

The analysis populations are defined in Section 11. Unless otherwise specified in the SAP, efficacy analyses will be based on the modified Intent-toTreat (mITT) and Evaluable Populations, safety analyses will be based on the Safety Analysis Population.

Primary Efficacy Analysis

The primary efficacy endpoint is change from baseline in the overall Rasch-transformed score of the FACE-Q Satisfaction with Facial Appearance Scale to the final study visit (V7). This will be analyzed using one sample t-test (or sign test if normality assumptions are not met).

Analysis of All Other Efficacy Endpoints

The same analysis procedures and methods used for the primary efficacy endpoint will be used for the other FACE-Q efficacy endpoints (FACE-Q Aging Appraisal, FACE-Q Psychological Function Scale, FACE-Q Social Function scale, FACE-Q Satisfaction with Skin). Details will be documented in the SAP.

Exploratory Analysis

Exploratory analysis may be performed on the collected video and photographs as part of this study only. The exact analysis will be detailed in the statistical analysis plan.

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List of Abbreviations

Abbreviation	Definition
AR	adverse reaction
AE	adverse event
BMI	body mass index
CaHA	calcium hydroxyapatite
CFL	crow's feet lines (also known as lateral canthal lines in BOTOX product literature)
eCRF	electronic case report form
FHL	forehead lines
FWS	facial wrinkle scale
GAIS	global aesthetic improvement scale
GCP	Good Clinical Practice
GLs	glabellar lines
HA	hyaluronic acid
ICF	informed consent form
ICH	International Council for Harmonization
ISR	injection site reaction
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MITT	modified intent-to-treat
N/A	not applicable
NSAIDs	nonsteroidal anti-inflammatory drugs
PAAQ	periorbital aesthetic appearance questionnaire
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SPA	self-perception of age
USADE	unanticipated serious adverse device effect

1 Introduction

The negative psychosocial impact of facial aging has been well characterized from a variety of perspectives (Foos 2011, Zebrowski 2008, Sobanko 2015). Facial attractiveness is a factor perceived to be important in many social interactions. These concerns by the aging population have economic, legal, social, and psychological implications for achieving overall satisfaction with life in general. Therefore, the motivation for seeking minimally invasive cosmetic intervention is multi-faceted and potentially strong for those who are conscious of their appearance and have concerns about their perceived age.

The acceptance and use of minimally invasive procedures to reduce the visible signs of aging have increased in recent years (American Society of Plastic Surgeons 2012). Signs of aging can be observed in multiple regions of the face and affect all tissues. Reduced and disorganized collagen and elastin result in a loss of elasticity and thinning of the skin, which can manifest as dynamic and static facial rhytides and/or sagging, in addition to folds and wrinkles. Redistribution of subcutaneous fat may hollow some areas while increasing local fat deposits in others. Bony remodeling may alter the surface for support for all of the overlying soft tissues, which can accentuate sagging of the skin and other signs of aging (Farkas 2013, Kahn 2010, Yaar 2002).

Minimally invasive strategies to improve the signs of aging include the use of botulinum toxins to address the presence of dynamic wrinkles as well as dermal fillers to correct skin depressions or folds and to restore underlying structural or fat deficiencies. Botulinum toxins have been approved by the Brazilian Health Regulatory Agency (Anvisa) for the treatment of hyperkinetic facial lines (BOTOX® Product Monograph). Onabotulinumtoxin A (BOTOX) is widely used to treat undesirable static and dynamic facial lines (Binder 1998, Blitzer 1993, Carruthers 1994, Carruthers 2004b, Fagien 2003, Sommer 2003, Stotland 2007). Hyaluronic acid (HA)–based fillers are approved by the Brazilian Health Regulatory Agency (Anvisa) to restore volume of the face (Jones 2013, JUVÉDERM VOLUMA® with Lidocaine Directions for Use, Lupo 2008, Pinsky 2008). In addition, HArmonyCa Lidocaine contains a synthetic calcium hydroxyapatite (CaHA) active ingredient. CaHA has been used in the dermal filler market for more than 10 years. It acts via its osteoconductive potential and supports ingrowth of fibrous and vascular tissue (Berlin 2006). Based on the various compositions of each HA filler product and the approved indications, filler injections are targeted to fill wrinkles and folds in specific facial areas.

The Brazilian Health Regulatory Agency has approved the following filler products as indicated:

- JUVÉDERM VOLBELLA with Lidocaine is indicated for the treatment of any fine lines and medium-sized skin depressions due to conditions such as premature aging and for enhancement and pouting of the lips to correct structural defects such as asymmetry, contour deformities, and volume loss.
- JUVÉDERM VOLIFT with Lidocaine is indicated for the treatment of any deep skin depressions due to conditions such as premature aging and for face contouring and volume restoration to correct facial structural defects such as asymmetry, contour deformities, and volume loss in the lips, cheeks, chin, and lower face.
- JUVÉDERM VOLUMA with Lidocaine is indicated to restore volume of the face.

- JUVÉDERM VOLITE [redacted] is indicated for the treatment, by filling, of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity.
- JUVÉDERM VOLUX with Lidocaine is an injectable implant intended to restore and generate facial volume in chin and mandible areas.
- HArmonyCa Lidocaine injectable gel is a dermal filler intended for facial soft tissue augmentation.

In clinical trials, each Juvéderm product mentioned above has been demonstrated to be safe and effective for its approved indication (Carruthers 2004a, Jones 2013, Lupo 2008, Pinsky 2008). Studies of implants containing CaHA, both in vitro and in vivo, showed minimal or no inflammatory response, foreign body or giant cell granulomatous reaction, and no systemic toxicity (Lemperle 2003). Subject satisfaction or a psychological benefit has been reported following individual product treatments in several studies (Sommer 2003, Stotland 2007, Ogilvie 2017). In clinical practice, however, it is more common that patients seeking aesthetic enhancement will receive treatment for multiple areas of concern, as deemed appropriate by their physician. Given the multiple, distinct signs of facial aging, a variety of modalities may be administered as part of an integrated treatment plan agreed upon by patient and physician.

Few studies have characterized the humanistic benefits resulting from improvement in the signs of aging. A recent study investigated the impact of fillers and botulinum toxin in a pan-facial approach and demonstrated subject satisfaction, improved self-esteem, and a modest improvement in quality of life (Molina 2015).

A more comprehensive trial, the HARMONY Study, evaluated the impact of facial treatments using onabotulinum A toxin (BOTOX), dermal fillers, and bimatoprost (LATISSE) for inadequate eyelash length on subjects' self-image, self-esteem, and overall quality of life. Using validated patient-reported outcome measures, the study assessed the impact of a personalized, multimodal, minimally invasive treatment approach in 93 subjects. The results showed statistically significant physical, social, and psychological benefits following treatment, including a substantial improvement in subjects' perceived age (Dayan 2016).

The results of these studies support the potential benefits of aesthetic treatment that extends beyond treating lines, folds, and volume deficiencies. With the increase in the availability of minimally invasive tools to address signs of aging, it has become possible to take a holistic approach to facial rejuvenation. A pan-facial approach to treatment may yield greater overall benefit to patients, as it allows for a more balanced rejuvenation addressing multiple concerns.

2 Study Rationale

As often occurs, clinical practice has moved beyond what has been demonstrated in clinical trials. To date, no studies have evaluated the safety and impact of treatment with multiple approved aesthetic products. The objective of the initial HARMONY USA study was to observe overall aesthetic impact of treating subjects with several modalities in an attempt to achieve subjects' desired clinical outcome. The HARMONY Brazil study will expand upon the products tested, the facial areas treated, and the quantification of the psychological and emotional impact of the comprehensive aesthetic treatment provided and will ultimately be global in scope.

In the HARMONY Brazil study, subjects will be evaluated by the investigator to receive BOTOX, HArmonyCa Lidocaine facial filler, and Juvéderm facial fillers (JUVÉDERM VOLITE [redacted], JUVÉDERM VOLBELLA with Lidocaine, JUVÉDERM VOLIFT with Lidocaine, JUVÉDERM VOLUMA with Lidocaine, and JUVÉDERM VOLUX with Lidocaine). Selected subjects will receive staged treatment with the multiple products and will be evaluated using validated patient-reported outcome measurements to determine the psychological and emotional impact of an integrated treatment approach to reduce visible signs of aging.

The clinical hypothesis of this study is that subjects treated with a combination of BOTOX, HarmonyCa Lidocaine facial filler, and JUVÉDERM facial fillers will be satisfied with their overall facial appearance at the final study visit as measured by the change from baseline on the FACE-Q Satisfaction with Facial Appearance Overall Scale.

3 Study Objectives

3.1 Primary Objective

The primary objective of this study is to quantify the psychological, social, and emotional impact of comprehensive aesthetic treatment with a portfolio of the Sponsor's products by measuring the change in subject's satisfaction with facial appearance from baseline (before any treatment) to the final study visit (Appendix 4 FACE-Q™: Satisfaction with Facial Appearance). These products include BOTOX, HArmonyCa Lidocaine, and Juvéderm HA facial fillers, as described in Section 9.

3.2 Secondary Objectives

Secondary objectives are:

- To determine the subject's self-appraisal of age-related facial appearance (Appendix 4 FACE-Q©: Aging Appraisal), psychological function (Appendix 5 FACE-Q™: Psychological Function), social function (Appendix 6 FACE-Q™: Social Function) and overall satisfaction with skin (Appendix 7 FACE-Q™ Satisfaction with Skin Questionnaire).
- To quantify the investigator's and subject's assessment of aesthetic improvement.

4 Study Design

4.1 Study Design Overview

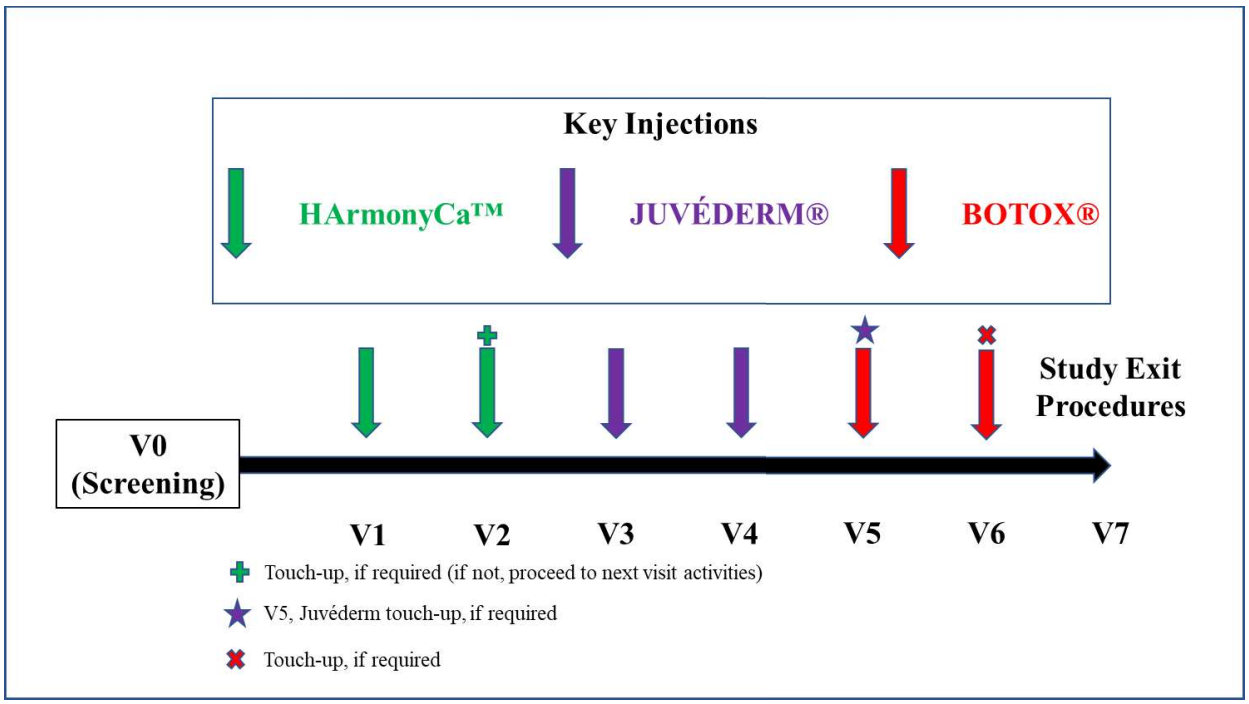
This Phase 4 study is a prospective, interventional, multicenter, combination medical device and drug post marketing study. Each subject will be in the study for up to approximately 5 months and act as his/her own control. All products will be used as per their license only. The investigators will perform all treatments and evaluations.

The study is planned to enroll 60 subjects consecutively at approximately 7 study sites in Brazil. Recruitment will also target men, who are typically under-represented in aesthetic studies.

Detailed descriptions of all study procedures by study visit and study treatment are presented in Table 6.1 and Section 6.

All subjects will sign an informed consent form (ICF) and begin at the screening visit (V0). Subjects will enter the study at V1 to begin treatment with facial fillers and will receive BOTOX starting at V3, as indicated in the study design diagram (Figure 4.1). In order to reduce the number of subject visits, Visit 0 can be combined with the initial treatment visit, if judged by the investigator to be appropriate and acceptable for the subject. Identical study procedures will not be repeated where the visits are combined.

Figure 4.1 Overall Study Design



4.2 Study Endpoints

4.2.1 Primary Endpoint

The primary endpoint is the change from before any treatment (baseline, V0) in the Rasch-transformed score of the FACE-Q Satisfaction with Facial Appearance Overall Scale to the final study visit (V7).

4.2.2 Key Secondary Endpoints

4.2.2.1 FACE-Q Questionnaires

- Subject's assessment of age-related facial appearance as measured by the change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Aging Appraisal to final study visit (V7)
- Subject's assessment of psychological well-being as measured by the change from baseline before any treatment in the Rasch-transformed score the FACE-Q Psychological Function Scale to final study visit (V7)
- Subject's assessment of social function as measured by the change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Social Function scale to final study visit (V7)
- Subject's assessment of overall satisfaction with skin as measured by the change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Satisfaction with Skin to final study visit (V7)

4.2.2.2 Self-Perception of Age Questionnaire

Subject's assessment of age-related facial appearance by the self-perception of age (SPA) measure at baseline before any treatment to final study visit (V7); responders are defined as having achieved a younger category.

4.2.3 Other Secondary Endpoints

4.2.3.1 Global Aesthetic Improvement Scale

- Investigator's assessment of global facial aesthetic improvement as measured by the 5-point global aesthetic improvement scale (GAIS) at final study visit (V7).
- Subject's assessment of global facial aesthetic improvement as measured by the 5-point GAIS at final study visit (V7).

4.2.3.2 Periorbital Aesthetic Appearance Questionnaire

- Change in subject's satisfaction with appearance of periorbital area as measured by the periorbital aesthetic appearance questionnaire (PAAQ) from baseline to final study visit (V7).

4.3 Safety

All adverse events (AEs) including injection site reactions (ISRs) will be collected from when the ICF is signed through to the last study visit (V7). Serious adverse events (SAEs) will be reported within the specified time and format directly to the Sponsor as described in Section 10.5.

4.4 Blinding and Randomization

Blinding and randomization are not applicable. This is an open-label, single-arm study. Subjects are enrolled consecutively based upon subject need and all subjects are intended to receive all treatments. Investigators will perform all treatments and evaluations.

5 Selection of Subjects

Approximately 60 subjects will be enrolled at approximately 7 sites in Brazil. Subjects will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria. Subjects who discontinue treatment will not be replaced.

5.1 Inclusion Criteria

The following are requirements for entry into the study.

1. 35 to 65 years of age, inclusive, at screening (male or female)
2. Accept the obligation not to receive any other facial procedures or treatments at any time during the study that are not related to the study
3. Women of childbearing potential must have a negative urine pregnancy test before each injectable treatment and practice a reliable method of contraception throughout the study
4. Willing to avoid direct and prolonged sun exposure to the facial skin, which includes tanning beds, for the duration of the study
5. Must qualify to receive BOTOX treatments, in at least one area, as per the approved Product Monograph including treatment of hyperkinetic lines for the glabellar, crow's feet, and forehead lines:
    - Glabellar injection: glabellar rhytides characterized as 2 (moderate) or 3 (severe) during maximum muscle contraction on the evaluation of the facial wrinkle scale (FWS)
    - CFLs characterized as 2 (moderate) or 3 (severe) during maximum smile on the evaluation of the FWS
    - FHLs of 2 (moderate) to 3 (severe) rating at maximum eyebrow elevation as assessed using the FWS
6. Must qualify to receive Juvéderm dermal filler treatments as per the approved Directions for Use. Subjects must use at least two different Juvéderm filler products in at least two different aesthetic anatomic areas. A summary of inclusion criteria by facial area for potential subjects for filler treatments is presented in Table 5.1.

Table 5.1 Summary of Inclusion Criteria by Facial Area for Potential Subjects for Filler Treatments

Product	Indication	Contra-indications
JUVÉDERM VOLBELLA with Lidocaine	Treatment of any fine lines and medium-sized skin depressions. Can also be used for enhancement and pouting of the lips to correct structural defects such as asymmetry, contour deformities, volume loss.	• Do not inject into the eyelids. The application in the bags under the eyes is reserved to specialists specifically trained in this technique and having a sound knowledge of the physiology for this particular area. • Do not inject into the blood vessels (intravascular). Intravascular injection may lead to embolization, occlusion of the vessels, ischemia, or infarction. • Do not overcorrect.
JUVÉDERM VOLIFT with Lidocaine	Intended for the treatment of any deep skin depressions due to conditions such as premature aging. Can also be used for face contouring and volume restoration to correct facial structural defects such as asymmetry, contour deformities, volume loss in the lips, cheeks, chin, lower face.	• Do not inject in the periorbital area (eyelids, under-eye area, crow's feet) and glabellar region. • Do not inject into the blood vessels (intravascular). Intravascular injection may lead to embolization, occlusion of the vessels, ischemia, or infarction. • Do not overcorrect.
JUVÉDERM VOLUMA with Lidocaine	Intended to restore volume of the face	• Do not inject in the periorbital area (eyelid, under-eye area, crow's feet), in the glabellar region or in the lips. • Do not inject into the blood vessels (intravascular). Intravascular injection may lead to embolization, occlusion of the vessels, ischemia, or infarction. • Do not overcorrect.
JUVÉDERM VOLITE [redacted]	Intended for treatment, by filling, of superficial cutaneous depressions such as fine lines and for additional improvement of skin quality attributes such as hydration and elasticity.	• Do not inject in the eyelids. • Do not inject into the blood vessels (intravascular). Intravascular injection may lead to embolization, occlusion of the vessels, ischemia, or infarction. • Do not overcorrect.
JUVÉDERM VOLUX with Lidocaine	Intended to restore and generate facial volume in chin and mandible areas	• Do not inject in the periorbital area (eyelid, under-eye area, crow's feet), in the glabellar region or in the lips. • Do not inject into the blood vessels (intravascular). Intravascular injection may lead to embolization, occlusion of the vessels, ischemia or infarction. • Do not overcorrect
HArmonyCa Lidocaine	Intended for facial soft tissue augmentation.	HArmonyCa Lidocaine is contraindicated: • in patients with a known sensitivity to any of the product components. • in patients suffering from skin disease or abnormal skin conditions. • in patients suffering from an infection or inflammation (either acute or chronic) at or near the treatment site. • in patients susceptible to keloid formation, hypertrophic scarring, or developing inflammatory skin conditions.

Product	Indication	Contra-indications
		• in patients with impaired wound healing due to systemic disorders, medicinal drugs, or unhealthy or poorly-vascularized tissue. • in patients suffering from prolonged bleeding or tissue healing due to medical conditions or medicinal drugs. • in patients with a history of anaphylactic reactions and/or multiple severe allergies. • in patients with a known sensitivity to steroids, or who are contraindicated to be treated with steroids. • for injection into the glabellar or periocular areas. • for injection into the lips and perioral region. • for injection into regions containing foreign bodies. • in patients presenting with herpes. • in patients with autoimmune diseases. • for injection into blood vessels and to highly vascularized areas. • for injection into the epidermis or superficial dermis. • in breastfeeding or pregnant women. • in patients below the age of 18.

The investigator should not inject greater than 20 mL of filler (Juvéderm and HArmonyCa) per 60 kg (130 lbs.) body mass per year for a single subject.

5.2 Exclusion Criteria

The following criteria exclude potential subjects from participating in the study:

1. Body mass index (BMI) > 30 kg/m^2
2. Known allergy or sensitivity to the study products or their components
3. Pregnant, lactating, or planning to become pregnant at any time during the study
4. Received BOTOX or treatment with any other botulinum toxin product for any condition within 6 months before enrollment
5. Received (or is planning to receive) anticoagulation, antiplatelet or thrombolytic medications (e.g., warfarin) or other substances known to increase coagulation time from 10 days prior to injection and up to 3 days post-injection
6. Undergone plastic surgery of the face and/or neck, tissue grafting, or tissue augmentation with silicone, fat, or other permanent dermal fillers, or be planning to undergo any of these procedures at any time during the study
7. Has undergone temporary or semi-permanent facial or neck dermal filler treatment (e.g., hyaluronic acid, calcium hydroxylapatite, poly-L-lactic acid) within 12 months before enrollment
8. Received mesotherapy, skin resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or non-ablative procedures) in the face or neck within 6 months prior to study enrollment

9. Marked facial asymmetry, brow or eyelid ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or an inability to substantially lessen the resting GLs and CFLs/facial rhytides by physically spreading them apart
10. Lip tattoos, facial hair or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments
11. At any proposed injection site, presence of inflammation, infection at any injection site or systemic infection (study entry may be postponed until one week following recovery), noticeable acne scarring, cancerous or pre-cancerous lesion, or unhealed wound or have undergone radiation treatment in the area to be treated
12. Received any investigational product within 60 days prior to study enrollment or planning to participate in another investigation during the course of this study
13. An employee (or a relative of an employee) of the investigators, the Sponsor, or representative of the Sponsor
14. Condition or in a situation that, in the investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study
15. Current use of oral corticosteroids
16. Current use of nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., aspirin, ibuprofen), from 10 days prior to injection up to 3 days post-injection
17. Prescription topical retinoid therapy and/or topical hormone cream applied to the face, for potential subjects who have not been on a consistent dose regimen for at least 6 months prior to enrollment and who are unable to maintain regimen for the study
18. Systemic retinoid therapy within one year prior to study enrollment
19. History or current symptoms of dysphagia
20. Medical condition that may increase the risk of exposure to botulinum toxin including diagnosed myasthenia gravis, Eaton-Lambert Syndrome, amyotrophic lateral sclerosis, or any other disease that might interfere with neuromuscular function
21. Current use of aminoglycoside antibiotics, curare-like agents, or agents that might interfere with neuromuscular (skeletal) function
22. Profound atrophy/excessive weakness of muscles in target areas of injection
23. History of facial nerve palsy
24. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study treatment)
25. Very thin skin in the mid-facial region
26. Tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, i.e., significant convexity or projection from the infraorbital fat pads
27. Mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (e.g., juvenile dermatomyositis), partial lipodystrophy (e.g., Barraquer-Simons syndrome), inherited disease, or human immunodeficiency virus–related disease

28. Undergone oral surgery or other dental procedures (e.g., tooth extraction, orthodontia, or implantation) within 30 days prior to enrollment or be planning to undergo any of these procedures during the study
29. Subjects with neuromuscular disorders including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise
30. Subjects with a history of allergies or hypersensitivity to hyaluronic acid or lidocaine

5.3 Summary of Required Washout Periods

Potential study subjects may have used the following products and procedures (Table 5.2) that have specified washout periods prior to baseline visits for all subjects.

Table 5.2 Products and Procedures with Washout Periods Taken by Potential Subjects Prior to Study Enrollment

Product or Procedure	Washout Prior to Baseline
• Anticoagulation, antiplatelet or thrombolytic medications (e.g., warfarin) or other substances known to increase coagulation time[1] • NSAIDs (e.g., aspirin, ibuprofen) [1]	10 days, and to 3 days post injection
• Systemic retinoids	1 year
• Prescription topical retinoid and/or hormone cream (if not a consistent dose regimen)	6 months
• Current use of aminoglycoside antibiotics, curare-like agents, or agents that might interfere with neuromuscular (skeletal) function • Systemic corticosteroids • Oral surgery or other dental procedures	30 days
• Received any other investigational product	60 days
• Mesotherapy or Skin resurfacing (e.g., laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or non-ablative procedures) in the face or neck • History of ocular surgery	6 months
• BOTOX or any other botulinum toxin product	6 months
• Temporary or semi-permanent facial or neck dermal filler treatment (e.g., hyaluronic acid, calcium hydroxylapatite, poly-L-lactic acid)	12 months

Abbreviations: NSAIDs = non-steroidal anti-inflammatory drugs

[1] For subjects being treated for cardiac conditions with aspirin and/or anti-coagulants, approval from a cardiologist is required prior to enrollment in the study.

5.4 Other Restrictions and Precautions

5.4.1 Prohibited Medications and/or Treatments

Subjects must not undergo any type of facial plastic or reconstructive surgery or cosmetic procedure (e.g., plastic surgery; tissue grafting; tissue augmentation with silicone, fat, or other permanent, semi-permanent, or temporary dermal fillers; neuromodulator injections; or mesotherapy; or ablative procedures) at any time during this study.

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 the Sponsor's representative should be notified before a prohibited medication/treatment is administered. Prior to attending study visits, subjects must not apply facial cosmetics.

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.), treatment of AEs, estrogens, androgens, anti-androgenic agents, vitamins, iron supplements, folate, and herbal supplements. Medications should be taken consistently throughout the study and at the investigator's discretion.

Concomitant medications as defined for this study include dietary supplements, over-the counter medications, and oral herbal preparations, as well as changes in dosages of current prescription medications. Concomitant medications will be documented for each subject at each scheduled visit. A detailed history of medications will be documented at screening. Subsequently, at each study visit, subjects will be asked what medication, if any, they have taken since the previous visit. All concomitant medications will be recorded on electronic case report forms (eCRFs).

5.4.2 Definition of Females of (Non-)Childbearing Potential and/or Acceptable Contraceptive Methods

Women of childbearing potential must have a negative urine pregnancy test before any injections or other treatments are given. A reliable method of contraception must be practiced throughout the study. Women of childbearing potential comprises women who have experienced menarche and who have not undergone successful surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy) or who are not post-menopausal. The investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study.

5.4.3 Special Diet or Activities

Within the first 24 hours after any filler treatment (HArmonyCa or Juvéderm) 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.

6 Study Plan and Procedures

6.1 Study Subject Number

Subjects who meet all inclusion/exclusion criteria will be assigned a subject enrollment number via the electronic data system that will serve as the subject identification number on all study documents.

6.2 Description of Study Days

Study procedures, treatments, and assessments will be performed at the study visits as listed below and as shown in Table 6.1.

Table 6.1 Schedule of Study Procedures, Treatments, and Assessments

Study Visit	V0[1]	V1	V2	V3	V4	V5	V6[2]	V7[3]
	Screening	Day 1	Day 30	Day 60	Day 90	Day 120	Day 135	Day 150
Visit window	(Day -14 to Day -1)	N/A	(30 ± 7 days after V1)	(30 ± 7 days after V2)	(30 ± 7 days after V3)	(30 ± 7 days after V4)	(15 + 7 days after V5)	(15 ± 7 days after V6)
	STUDY TREATMENTS							
HarmonyCa Injections[4, 13]		X	X[14]					
Juvéderm Injections[4]				X	X	X[5]		
BOTOX[4]						X	X[6]	
	STUDY PROCEDURES							
Provide subject information; review/verify study criteria	X							
Informed consent form	X							
Demographics	X							
Medical history	X							
Weight/BMI[7]	X							X
Pregnancy test[8]	X	X	X	X	X	X	X[9]	
Concomitant medications	X	X	X	X	X	X	X	X
2D facial photography	X							X
Standardized digital video	X							X
Adverse events	X	X	X	X	X	X	X	X
Fitzpatrick Skin Phototype	X							
Subject diary		X	X[10]	X	X	X[10]		

Study Visit	**V0[1]**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6[2]**	**V7[3]**
	Screening	**Day 1**	**Day 30**	**Day 60**	**Day 90**	**Day 120**	**Day 135**	**Day 150**
Visit window	(Day -14 to Day -1)	N/A	(30 ± 7 days after V1)	(30 ± 7 days after V2)	(30 ± 7 days after V3)	(30 ± 7 days after V4)	(15 + 7 days after V5)	(15 ± 7 days after V6)
	STUDY RATING SCALES AND QUESTIONNAIRES							
Self-perception of age (SPA)	X							X
FACE Q[11]	X							X[12]
Periorbital aesthetic appearance questionnaire (PAAQ)	X							X
FWS – glabellar lines (GLs)	X							
FWS – crow's feet lines (CFLs)	X							
FWS –forehead lines (FHLs)	X							
Investigator global aesthetic improvement scale (GAIS)								X
Subject GAIS								X

1 Screening and Visit 1 can be combined in order to reduce the total number of visits, if judged by the investigator to be appropriate and acceptable for the subject. Identical study procedures will not be repeated where the visits are combined.

2 If no BOTOX touch-up is required, the subject will still return for V7.

3 All subjects attend V7 for study exit procedures and assessments.

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

5 Juvéderm filler, if required

6 BOTOX touch-up if required

7 BMI > 30 is exclusionary. Body weight will be measured at screening and end of study (V7) for all subjects. Drastic weight loss or gain may skew assessments of "before" and "after" photos.

8 Required for women of childbearing potential

9 Pregnancy test not required at V6 if no BOTOX touch-up is needed.

10 New subject diary only administered at touch-up if injection occurred. Collect completed diary at the next scheduled visit.

11 FACE-Q Scales include Satisfaction with Facial Appearance Scale, Expectations Scale (baseline only), Aging Appraisal, Psychological Function Scale, Social Function Scale, and Satisfaction with Skin Questionnaire.

12 FACE-Q Expectations subscale will not be collected at End of Study.

13 If HArmonyCa injections are not to be administered to a subject, the subject will begin at Day 1 with V3 study activities (i.e., Juvéderm fillers).

14 HArmonyCa touch-up, if required. If not required, proceed with V3 study activities.

6.2.1 Study Procedures for Screening Visit (V0)

- Provide subject information; review / verify study criteria.
- Collect ICF.
- Collect subject demographics, including age and gender.
- Collect medical history, including a detailed history of prior cosmetic procedures, with start and stop dates, if applicable, as well as any discontinuations due to intolerability or toxicity.
- Confirm that inclusion/exclusion criteria are met; document status of all washout periods that apply.
- Measure body weight and height and calculate BMI. Body mass index > 30 kg/m^2 is exclusionary.
- Perform urine pregnancy test for women of childbearing potential.
- Record concomitant medications.
- Perform 2D facial photography.
- Perform standardized digital video.
- Determine Fitzpatrick Skin Phototype
- Record adverse events (AEs) occurring since signing consent.
- Perform the following study assessments:
  - SPA
  - FACE-Q
  - PAAQ
  - FWS (GLs, CFLs, FHLs)

6.2.2 Visit V1 and V2 (HArmonyCa Lidocaine)

Screening Visit (V0) and first study treatment (V1) may occur on the same day if all screening procedures are completed, results received, and all eligibility criteria (inclusion and exclusion) are confirmed prior to treatment administration. But the subject must be in agreement to do this and must have had sufficient time to understand the study, and the investigator also must judge that the subject had enough time to consider the study. It will be a subject and investigator decision together - in the event of any doubt, the subject should not be treated on the same day.

Subjects who have successfully completed screening (V0) will enter the study at V1. If no HArmonyCa will be administered to the subject, please proceed with study activities for V3 as outlined in Section 6.2.3 and Table 6.1.

The following activities will be performed at V1 if HArmonyCa Lidocaine is administered:

- Record concomitant medications.
- Perform urine pregnancy test for women of childbearing potential.
- Record AEs.
- Dispense subject diary to record AEs; counsel subject on diary entries that are needed during the next 30 days.
- Perform facial HArmonyCa Lidocaine injections into areas that the subject desires and qualified for per the inclusion/exclusion criteria and within the approved clinical indications (Section 5.1 and Section 5.2, respectively).

At V2, HArmonyCa Lidocaine touch-up treatment may be performed. If touch-up is not performed, please proceed with study activities for V3 as outlined in Section 6.2.3 and Table 6.1. If touch-up for HArmonyCa Lidocaine is performed, perform the following activities:

- Record concomitant medications.
- Perform urine pregnancy test for women of childbearing potential.
- Record AEs.
- Dispense subject diary to record AEs; counsel subject on diary entries that are needed during the next 30 days.
- Perform facial HArmonyCa Lidocaine touch-up injections into areas that the subject desires and qualified for per the inclusion/exclusion criteria and within the approved clinical indications (Section 5.1 and Section 5.2, respectively).

6.2.3 Visit V3 and V4 (Juvéderm)

V3 will occur 30 ± 7 days after previous treatment. If HArmonyCa is not given to the subject, the subject may begin with Juvéderm filler injections and V3 activities as outlined in this section and in Table 6.1. If no HArmonyCa is administered, please see guidance regarding screening and first treatment occurring on the same day outlined in Section 6.2.2. V3 and V4 are mandatory regardless of whether further filler treatment is expected. The following study procedures and treatments will be performed at V3 and V4:

- Record concomitant medications.
- Perform urine pregnancy test for women of childbearing potential.
- Record AEs.
- Dispense subject diary to record AEs; counsel subject on diary entries that are needed during the next 30 days
- Perform facial Juvéderm filler injections.

- Facial filler injections (JUVÉDERM VOLBELLA with Lidocaine, and/or JUVÉDERM VOLIFT with Lidocaine, and/or JUVÉDERM VOLUMA with Lidocaine, and/or JUVÉDERM VOLITE [redacted] and/or JUVÉDERM VOLUX with Lidocaine) will be administered into areas that the subject desires and qualified for per the inclusion/exclusion criteria and within the approved clinical indications (Section 5.1 and Section 5.2, respectively).

6.2.4 Visit V5 (Juvéderm Touch-up and BOTOX)

V5 will occur 30 ± 7 days following V4.

- Record concomitant medications.
- Perform urine pregnancy test for women of childbearing potential.
- Record AEs.
- If Filler touch up is given, dispense subject diary to record AEs; counsel subject on diary entries that are needed during the next 30 days
- Administer BOTOX treatment.

6.2.5 Visit V6 (BOTOX Touch-up, if needed)

V6 will occur 15 + 7 days following V5.

- Collect diary from V5, if Filler treatment was given.
- Record concomitant medications.
- Record AEs.
- Perform urine pregnancy test for women of childbearing potential (omit if no BOTOX touch up required at V6).
- Administer touch up BOTOX treatment if needed.

6.2.6 Visit V7 (Final Study Visit)

V7 will occur 15 ± 7 days following V6.

- Measure body weight and calculate BMI.
- Record concomitant medications.
- Perform 2D facial photography.
- Perform standardized digital video.
- Record AEs.

- Perform the following study assessments for all subjects:
  - SPA
  - PAAQ
  - FACE-Q (except for Expectations subscale)
  - Investigator GAIS
  - Subject GAIS

If a subject discontinues the study before V7, the subject will be asked to have this final study visit for collecting all clinical data required during this visit.

6.2.7 Unscheduled/Missed Visits

Each time the subject returns to the study site, the investigator (or designee) will solicit and record information about ISRs, other AEs, and concomitant medications. An interim or unscheduled visit may replace a scheduled visit if it occurs within the acceptable time window for a scheduled visit or if the scheduled visit was missed. All applicable procedures should be performed.

7 Methods of Assessment and Endpoints

7.1 Clinical Scales for Treatment Inclusion Only

- Investigator's assessment of the severity of GLs at maximum frown using the FWS with photonumeric guide (Appendix 10)
- Investigator's assessment of the severity of CFLs at maximum smile using the FWS with photonumeric guide (Appendix 11)
- Investigator's assessment of the severity of FHLs at maximum eyebrow elevation using the FWS with photonumeric guide (Appendix 12)
- Subject's assessment of expectations of life change as measured by the FACE-Q Expectations Scale (Appendix 3)

7.2 Efficacy Endpoint Measurements

7.2.1 FACE-Q

- Subject's assessment overall facial appearance as measured by the FACE-Q Satisfaction with Facial Appearance Scale (Appendix 2)
- Subject's assessment of age-related facial appearance as measured by the FACE-Q Aging Appraisal (Appendix 4)
- Subject's assessment of psychological well-being as measured by the FACE-Q Psychological Function Scale (Appendix 5)
- Subject's assessment of social function as measured by the FACE-Q Social Function Scale (Appendix 6)
- Subject's assessment of overall satisfaction with skin as measured by the FACE-Q Satisfaction with Skin Questionnaire (Appendix 7)

7.2.2 Self-Perception of Age Questionnaire

- Subject's assessment of age-related facial appearance as measured by the SPA Questionnaire (Appendix 1)

7.2.3 Global Aesthetic Improvement Scale

- Investigator's assessment of global facial aesthetic improvement as measured by the 5-point GAIS (Appendix 13)
- Subject's assessment of global facial aesthetic improvement as measured by the 5-point GAIS (Appendix 13)

7.2.4 Periorbital Aesthetic Appearance Questionnaire

- Subject's assessment of periorbital area as measured by the PAAQ (Appendix 9)

8 Discontinuation Criteria

8.1 Early Discontinuation of the Study

An investigator may stop the study at his/her study site at any time. The Sponsor may discontinue the study (and/or participation of a single study site) for any reason with appropriate notification. If conditions arise during the study that indicate that the study or an investigational site should be terminated, the Sponsor, the investigator, the study monitor, REB, and/or regulatory agencies will take appropriate action after consultation. Conditions that may warrant termination of the study or investigational site include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing or evaluation of the study treatment
- Failure of an investigator to comply with pertinent national or state regulations, REB-imposed conditions, or protocol requirements
- Submission of knowingly false information to the Sponsor, study monitor, the REB, or any regulatory agency by the investigator

If the study is prematurely terminated or suspended due to safety issues, the Sponsor will inform all investigators and applicable regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The REB is also to be informed promptly and provided the reason(s) for the termination or suspension by the Sponsor or by the investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, the Sponsor shall remain responsible for providing resources to fulfill the protocol obligations and existing agreements for follow-up of subjects enrolled in the study, and each investigator or authorized designee will promptly inform enrolled subjects, if applicable.

8.2 Early Discontinuation of Individual Subjects

A subject may voluntarily withdraw from the study at any time. Notification of early subject discontinuation from the study and the reason for discontinuation will be made to the sponsor and will be clearly documented on the appropriate eCRF. In the event of subject discontinuation, every effort should be made to have the subject complete the primary endpoint FACE-Q Satisfaction with Facial Appearance Overall questionnaire.

It is the right and responsibility of the investigator to discontinue a subject's participation when the subject's health or well-being is threatened by continuation in the study. In the event of premature discontinuation, the investigator should determine the primary reason for discontinuation.

A subject who is withdrawn from the study prior to initiation of treatment may be replaced. Discontinued subjects will not be replaced.

The following are circumstances that could result in a subject's discontinuation from the study:

- AEs or SAEs that render the subject unable to continue study participation
- Protocol violation
- Subject voluntarily withdraws consent
- Non-compliance with study requirements
- Discretion of investigator (must document reason on eCRF)
- Progressive injury (at the discretion of the investigator)
- Changes in the subject's condition that render the subject unacceptable for further participation, in the judgment of the investigator
- Pregnancy (required discontinuation)
- Lost to follow-up
- Unable to physically or mentally tolerate the use of the test treatment
- Exclusion criterion met

9 Treatments

The study treatments are:

- **BOTOX**: The dose and the number of injection points may be adapted to the needs of the subject, based on their characteristics and location of the muscles to be treated. Subjects will receive at least one BOTOX treatment in the following areas: GLs, CFLs, and FHLs.)
- **HArmonyCa Lidocaine**:The investigator will determine the appropriate volume to be injected during initial and touch-up treatments based on his/her clinical experience. The maximum total volume of HArmonyCa Lidocaine allowed per subject for the initial and touch-up treatment combined is 4 syringes (5 mL).
- **JUVÉDERM**: The investigator will determine the appropriate volume to be injected during initial and touch-up treatments based on his/her clinical experience
  - JUVÉDERM VOLITE [redacted]: The maximum total volume of JUVÉDERM VOLITE [redacted] allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).
  - JUVÉDERM VOLBELLA with Lidocaine: The maximum combined total volume allowed per subject for all facial areas treated for both the initial and touch-up treatments combined is 2 syringes (2 mL).
  - JUVÉDERM VOLIFT with Lidocaine: The maximum total volume of JUVÉDERM VOLIFT with Lidocaine allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).
  - JUVÉDERM VOLUMA with Lidocaine: The maximum total volume of JUVÉDERM VOLUMA with Lidocaine allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).
  - JUVÉDERM VOLUX with Lidocaine: The maximum total volume of JUVÉDERM VOLUX with Lidocaine allowed per subject for the initial and touch-up treatments combined is 4 syringes (4 mL).

The investigator should not inject greater than 20 mL of filler (Juvéderm and HArmonyCa) per 60 kg (130 lbs.) body mass per year for a single subject.

The chemical compositions for each of the study products intended for subject treatment are provided in Appendix 8.

All study drugs/devices must be stored in a secure area, accessible only to study personnel. The sponsor will provide each study site with sufficient study treatments (study drugs and devices) for all study subjects, including back-up study treatments.

The sponsor will provide the most recent country-specific Directions for Use and Product Monographs for each product to each investigator to be used in study treatment. Details of formulation, storage, and handling, and complete instructions for administration of treatments can be found in the respective product information for each study drug/device.

All unused study treatments should be retained for return to the sponsor.

All products will be used as per their license only. Further details on the products can also be found in the currently approved Directions for Use and Product Monographs.

9.1 Rescue Medications

No product licensed in Brazil is approved as a rescue medication. Administration of hyaluronidase is considered to be "off-label" and it has not been provided as a part of the study regimen. It should only be used if in the investigator's judgment it is deemed to be necessary to inject hyaluronidase for the safety of the subject, in that situation, the investigator may inject at his/her discretion as a concomitant medication, capturing relevant information.

9.2 Treatment 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 REB 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 drug and device accountability records for compliance with the protocol, e.g., subject eligibility criteria, volume of product injected, procedures performed, and follow-up visit schedule.

10 Adverse Events

Throughout the course of the study (from the date of informed consent), all AEs will be monitored and recorded 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 or until follow-up is no longer possible.

10.1 Drug Adverse Events

An AE from a drug is defined as any undesired medical occurrence in a subject receiving a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable sign 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.

Adverse events 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 AEs 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 AEs will be documented on the AE eCRF.

10.2 Medical Device Adverse Events

An AE from a medical device 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 considered related to the procedure or the product. Adverse events 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.

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.

10.3 Injection Site Reactions

Injection site reactions following treatment with dermal fillers include redness, pain after injection, tenderness to touch, firmness, swelling, lumps/bumps, bruising, itching, and discoloration. Subjects will maintain a diary record of the presence, location, frequency, severity, and duration of any ISR for 30 days after each filler treatment.

Subjects will indicate the occurrence of an ISR and severity (none, mild, moderate, severe) of the event. NOTE: ISRs that persist longer than 30 days should be recorded and followed to resolution on the AE eCRF. If an ISR is ongoing or appears after the subject’s last study visit, it will be followed up by the sponsor Product Surveillance separate from this study protocol.

10.4 Unusual Failure in Efficacy

Unusual Failure in Efficacy is defined as failure of a health product to produce the expected/intended effect, which may result in an adverse outcome for the patient, including an exacerbation of the condition for which the health product is being used. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription. Another example of a case that should be reported on an expedited basis is a life-threatening infection where the failure in efficacy seems to be due to the development of a newly resistant strain of bacterium previously regarded as susceptible.

Any unusual failure in efficacy reported during the conduct of the study should be immediately reported to a sponsor representative and recorded in the appropriate eCRFs.

The Investigator must:

1. Notify the sponsor immediately. For Emergency Phone Numbers see front of protocol. Fax completed Unusual Failure in Efficacy reporting form to: 1-714-796-9504.
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.

10.5 Serious Adverse Events

10.5.1 Serious Adverse Events Definition

An SAE is any AE that either led to death; resulted in a life-threatening illness or injury; resulted in a permanent impairment of a body structure or a body function; required in-patient hospitalization or prolongation of existing hospitalization; resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function; led to fetal distress, fetal death or a congenital abnormality or birth defect.

Pre-planned surgeries or procedures for pre-existing, known medical conditions for which a subject requires hospitalization are not reportable as an SAE. Any pre-planned surgery or procedure should be clearly documented in the site source documents by the investigator at the time of the subject's entry into the study.

NOTE: the sponsor considers all cancer AEs as SAEs. Pregnancy by itself is not generally considered an AE.

10.5.2 Serious Adverse Event Reporting Requirements

Any SAE occurring during the study period (beginning with informed consent) and through 30 days after study exit must be reported within 24 hours to the sponsor on 2 SAE forms. The drug, and device SAE forms must be recorded and e-mailed per this protocol section. All subjects with an SAE must be followed up and the outcomes reported.

The principal investigator must supply the sponsor and the REB with any additional requested information (e.g., hospital discharge summary, autopsy reports and terminal medical reports) only upon request. The sponsor will evaluate all SAEs for both drug and device. Device SAEs will be documented in writing as to whether they meet the definition of an USADE. These will be reported to all participating investigators, the regulatory authorities, and the REB.

In the event of an SAE, the investigator must:

1. Notify the sponsor immediately (within 24 hours) using the SAE reporting forms. Emergency phone numbers and relevant sponsor personnel contacts are below.

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.

Provide the sponsor with a complete, written case history (AE report form), including copies of supporting reports (e.g., progress notes, laboratory reports), upon request 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.

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

10.5.3 Serious Adverse Event Contact Information

SAE Reporting Information: BOTOX®	Fax: 1-714-796-9504 Back-up fax: 1-714-246-5295 Email: IR-Clinical-SAE@abbvie.com
SAE Reporting Information: JUVÉDERM® VOLBELLA® with Lidocaine, JUVÉDERM® VOLIFT with Lidocaine, JUVÉDERM® VOLUMA® with Lidocaine, and JUVÉDERM® VOLITE® [redacted] and JUVÉDERM® VOLUX®, HArmonyCa Lidocaine	Fax: 1-714-796-9567 Email: LC-Medical_Safety@abbvie.com Fax: +1 (877) 605-4524 or Back-up Fax +1 (714) 796-9567

10.6 Unanticipated Serious Adverse Device Effects

An unanticipated serious adverse device effect (USADE) 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 USADE 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 sponsor within 24 hours of any device malfunction and a representative will provide instruction for the return of any faulty syringe for evaluation.

10.7 Assessment of Adverse Events

10.7.1 Severity

Assessment of severity of an AE will be rated according to the definitions in Table 10.1 and the worst grade documented. 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.

The term "severe" is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., "severe headache"). This is not the same as "serious." Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a subject's life or functioning.

Table 10.1 Classification of Adverse Events by Intensity

Grade 1 (Mild)	The symptom is barely noticeable to the study subject and does not influence performance or functioning. Concomitant medication is not ordinarily indicated for relief of mild AEs.
Grade 2 (Moderate)	The symptom is of sufficient severity to make the study subject uncomfortable and to influence performance of daily activities. Concomitant medication may be indicated for relief of moderate AEs.
Grade 3 (Severe)	The symptom causes severe discomfort, sometimes of such severity that the study subject cannot continue in the study. Daily activities are significantly impaired or prevented by the symptom. Concomitant medication may be indicated for relief of severe AEs.
Not applicable	In some cases, an AE/ISR may be an "all-or-nothing" finding that cannot be graded.

Abbreviations: AE = adverse event, ISR = injection site reaction.

10.7.2 Relationship to Study Product

A determination will be made, by the investigator, of the relationship, if any, between an AE and any study product, anesthesia employed, the study device, or the injection procedure, as applicable, using the guidelines presented in Table 10.2.

Table 10.2 Guidelines for Determining the Relationship Between Adverse Event and the Study Product

Highly Probable	This causal relationship is assigned if the AE starts a reasonable time after the administration of study product, stops/improves when the study product is stopped, and could reasonably be explained by known characteristics of the study product.
Probable	This causal relationship is assigned when the AE starts a reasonable time after the administration of study product, stops/improves when the study product is stopped, and could not be reasonably explained by known characteristics of the subject's clinical state.
Possible	This causal relationship is assigned when the AE starts a reasonable time after the administration of study product but could be produced by the subject's clinical state or other modes of therapy administered to the subject.
Not Related	This causal relationship is assigned when the time association or the subject's clinical state is such that the study product was not likely to have had an association with the observed AE.

Abbreviations: AE = adverse event.

10.7.3 Adverse Event Follow-up

All AEs (including SAEs) must be recorded on the appropriate eCRF. All AEs that are treatment-related and unexpected (not listed as treatment-related in the current package insert or directions for use) must be reported to the governing REB as required by the REB, local regulations, and the governing health authorities. Any AE that is marked "ongoing" at the exit visit must be followed up as appropriate.

10.8 Exposure to Investigational Product during Pregnancy

Marketing Authorization Holders (MAHs) are expected to follow up all pregnancy reports from health professionals and consumers where the embryo/fetus could have been exposed to one of its health products. For consumer reports, it is appropriate to seek permission to only follow up with the health professional. The MAH must apply all principles outlined in this guidance document and the regulations pertaining to reporting requirements, including determination of seriousness and minimal criteria for submitting an adverse reaction (AR) report. Reports of pregnancy exposure with no associated ARs should not be reported as ARs. When an active substance, or one of its metabolites, has a long half-life, this should be taken into account when considering whether a fetus could have been exposed (e.g., if health products taken before the gestational period should be considered).

Pregnancy by itself is not generally considered an AE. The occurrence of an adverse pregnancy outcome may constitute an AE or an SAE, making the collection of pregnancy-related data and pregnancy outcomes valuable. Inpatient hospitalization for a normal vaginal delivery or elective abortion of a normal fetus does not constitute a SAE. If no serious injury occurred to the mother or fetus, then there is no reason to qualify pregnancy in the setting of hospitalization as a SAE. Accidental, therapeutic, or spontaneous abortion should always be classified as a SAE and

expeditiously reported to the Sponsor. Some examples of pregnancy related SAEs are, but not limited to, the following conditions: placental abruption, placenta previa, pre-eclampsia, prematurity, fetal death, congenital anomaly, or birth defects.

10.8.1 Female Subjects Who Become Pregnant

- The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a subject's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication will be reported as an AE or SAE. A spontaneous abortion or elective termination is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.5.2. While the investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

10.8.2 Male Subjects with Partners Who Become Pregnant

- The investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive study product.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

11 Statistical Methods

11.1 General Statistical Considerations

A brief summary of the general statistical analysis methods is 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).

Hypothesis testing will be performed at 0.025 significance level (1-sided). Conclusions related to study outcomes will be focused on the overall results of each outcome.

Two critical time points, baseline and end of study, 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, V7 (after approximately 5 months of treatment). Subjects who discontinue prematurely will be asked to return for the last clinical visit for end-of-study data collection.

11.1.1 Analysis Populations

The following analysis populations will be used:

- mITT (modified Intent-to-Treat) Population - all subjects who enrolled and had at least one post-baseline efficacy assessment.
- Evaluable Population– all subjects as defined in the mITT Population who have received both study products as treatments in this study, had at efficacy assessment at the final visit (V7) and no major protocol violations or deviations.
- Safety Population – all subjects who received any product used as treatment in this study.

The mITT Population will be used for subject disposition, demographics and baseline characteristics summary, efficacy and the Safety Population will be used for safety analyses. The Evaluable Population will be used on key efficacy endpoints.

11.1.2 Subgroups

Subgroup analysis will be performed by:

- Gender: As male and female subjects may have differing expectations/perceptions of aesthetic improvement; they will be examined separately.
- Treatment touch-ups: subjects with no touch-ups, Juvéderm only, Botox only, Juvéderm and Botox

Additional subgroup analysis will be discussed in the SAP.

11.2 Demographics and Baseline Characteristics

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

11.3 Exposure and Concomitant Therapies

Subject study product exposure and compliance will be summarized using descriptive statistics for each product, combination of multiple products, and overall exposure respectively.

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.

11.4 Efficacy Analyses

Unless stated otherwise, all efficacy analyses will be based on the mITT and Evaluable Populations.

11.4.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline in the overall Rasch-transformed scores of the FACE-Q Satisfaction with Facial Appearance Scale to the final study visit (V7). This will be analyzed using one sample t-test (or sign test if normality assumptions are not met).

11.4.2 Analysis of All Other Efficacy Endpoints

The same analysis procedures and methods used for the primary efficacy endpoint will be used for the other FACE-Q efficacy endpoints (FACE-Q Aging Appraisal, FACE-Q Psychological Function Scale, FACE-Q Social Function Scale, FACE-Q Satisfaction with Skin). Details will be documented in the SAP.

11.4.3 Missing Data

The missing data strategy will be documented in the SAP.

11.5 Adverse Events

Device-related AEs will be captured with TrackWise Enterprise Quality Management Software and coded using AE term codes. Treatment-emergent AEs will also be summarized by serious AEs (SAEs), AE severity, AE leading to treatment or study early termination, and relationship to study drugs/devices and procedures. SAEs will be coded using MedDRA version 21.0 or higher and presented by system organ class and preferred term.

11.6 Interim Analyses and Data Monitoring

No formal interim analyses are planned for this study.

11.7 Determination of Sample Size

A sample size of 48 subjects will provide 90% power to detect if change from baseline to end-of-study visit in the FACE-Q Satisfaction with Facial Appearance Overall Scale Rasch-transformed score is different from zero, assuming a mean change of 12.0 and a standard deviation of 25.0. This calculation is based on a one-sample, 1-sided t-test at 0.025 significance level. The assumptions of mean and standard deviation are based on FACE-Q results from the HARMONY Study GMA-CMB-14-001. Anticipating a potential 20% drop-out rate (for early withdrawals and/or subjects who failed to duly complete the FACE-Q Satisfaction with Facial Appearance Overall Scale assessment at end of study), 60 subjects will be enrolled.

PASS 2008 software was used to calculate the sample size.

11.8 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.

11.9 Exploratory Imaging Analysis

Exploratory analysis may be performed on the collected video and photographs as part of this study only. This could include lay panel review of photographs and videos on specific variables such as age, health, and attractiveness. In addition, more advanced facial mapping of wrinkles may be performed. Analysis will be detailed in the statistical analysis plan.

12 Regulatory, Ethical, and Legal Obligations

12.1 Declaration of Helsinki

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

12.2 Good Clinical Practice

The study will be conducted according to the study protocol and to Standard Operating Procedures that meet ICH GCP guidelines for clinical studies.

12.3 Research Ethics Board

Before implementing this study, the protocol, the proposed subject ICFs, and other information for the subjects must be reviewed by a properly constituted committee or committees responsible for approving clinical studies. The REB-written and -signed approval letter/form must contain approval of the designated investigator, the protocol (identifying protocol title, date, and version number), and of the subject ICF (date, version).

12.4 Regulatory Authority Approval

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

12.5 Informed Consent

Written informed consent is to be obtained from the subject prior to enrollment into the study.

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. No protocol-specific procedures, including screening procedures, will be performed until the subject has signed and dated an REB-approved ICF. Study participation will start with the signing and dating of the ICF.

The investigator must ensure that the subject is given full and adequate oral and written information about the nature, purpose, and 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.

In case of a clinical trial protocol amendment, the subject information sheet and ICF need to be revised to reflect the changes, if needed. Also, if the subject information sheet and ICF are revised, they must be reviewed and approved by the responsible REB and signed by all subjects subsequently enrolled in the clinical trial as well as those currently enrolled in the clinical trial.

12.6 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 or the

governing health authorities including the Brazilian Health Regulatory Agency if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

In accordance with Brazilian privacy 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.

12.7 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, blinding, size, and endpoints of the study. This will be detailed in the study monitoring plan.

Authorized representatives of the sponsor 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.

12.8 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 ICF. All information on the eCRFs must be traceable to these source documents in the subject's file. Data without a written or electronic record will be defined before study start and will be recorded directly on the eCRFs which will be documented as being the source data.

12.9 Collection of Study Data

This study will be conducted in compliance with Brazilian Health Regulatory Agency requirements. 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 should personally sign for the eCRFs (as indicated in the eCRFs) to ensure that the observations and findings are recorded on the eCRFs correctly and completely. The eCRFs are to be submitted to the sponsor in a timely manner at the completion of the study, or as otherwise specified by the sponsor.

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.

12.10 Disclosure of Information

This study will be registered, and results posted on www.ClinicalTrials.gov. The sponsor has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study investigators and the sponsor 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 the sponsor.

12.11 Discontinuation of the Study

It is agreed that, for reasonable cause, either the investigator or the sponsor may terminate the investigator's participation in this study after submission of a written notice. The sponsor may terminate the study at any time upon immediate notice for any reason, including the sponsor's belief that discontinuation of the study is necessary for the safety of subjects.

12.12 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. Essential documents specific to the sponsor 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 the sponsor.

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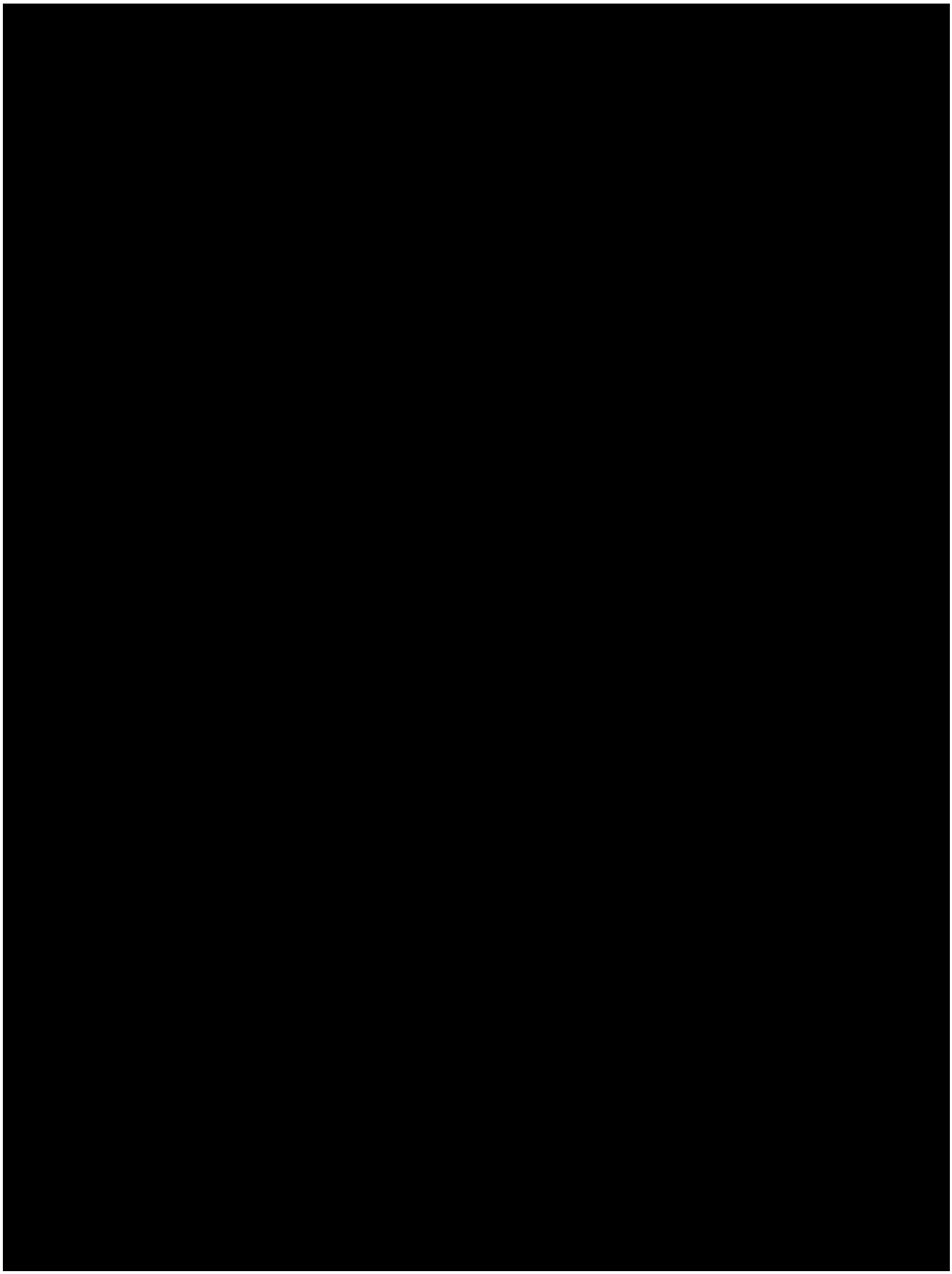
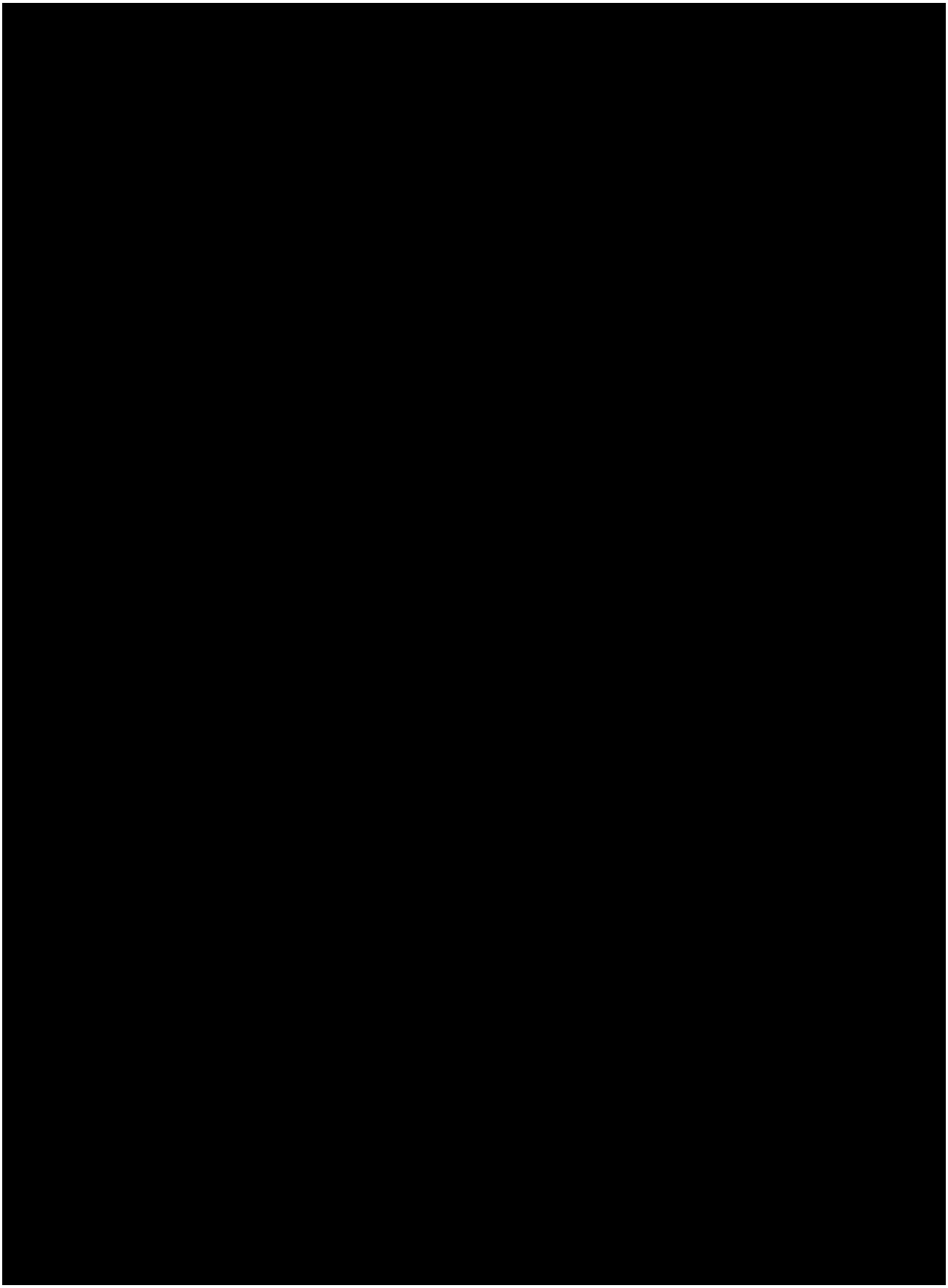
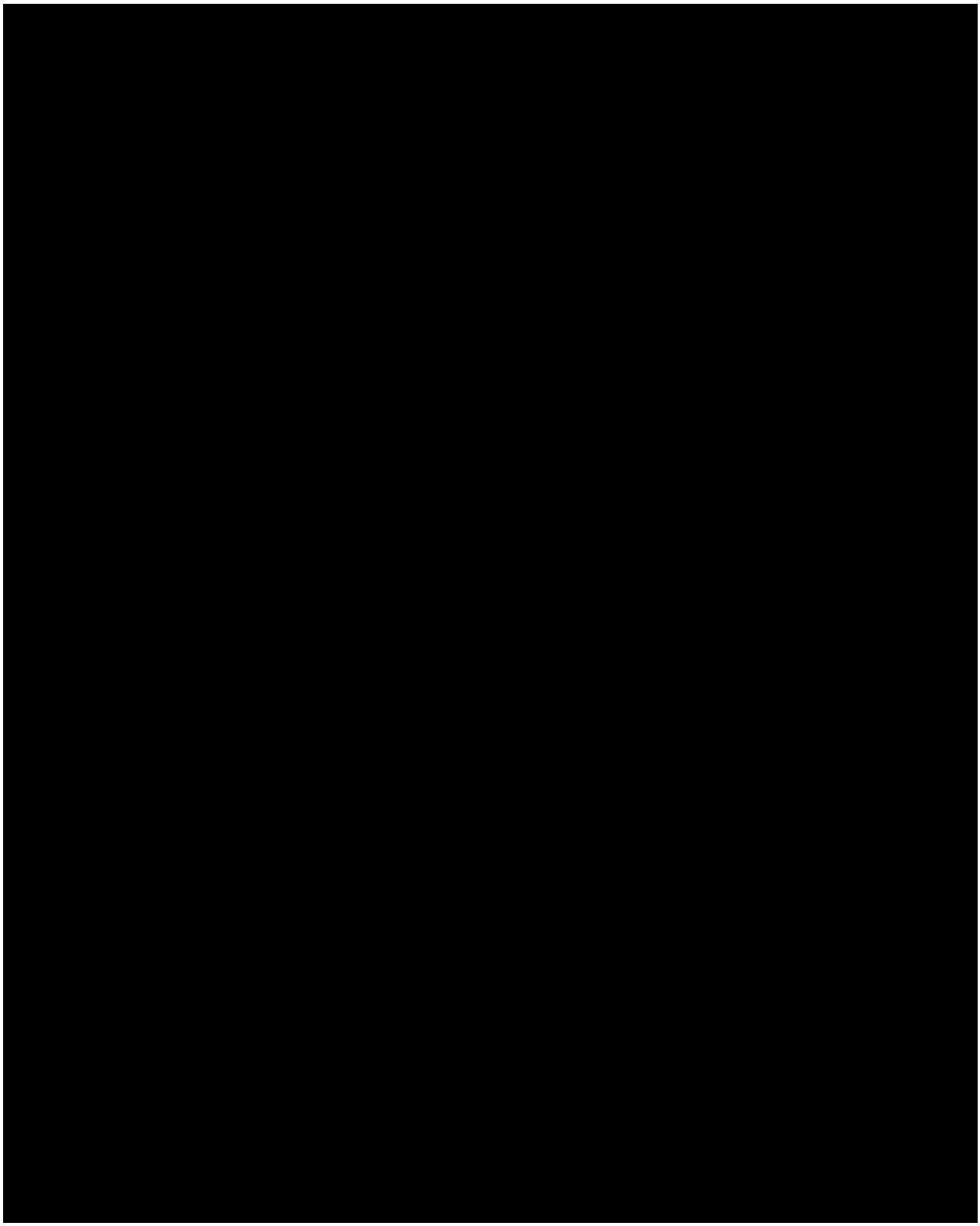
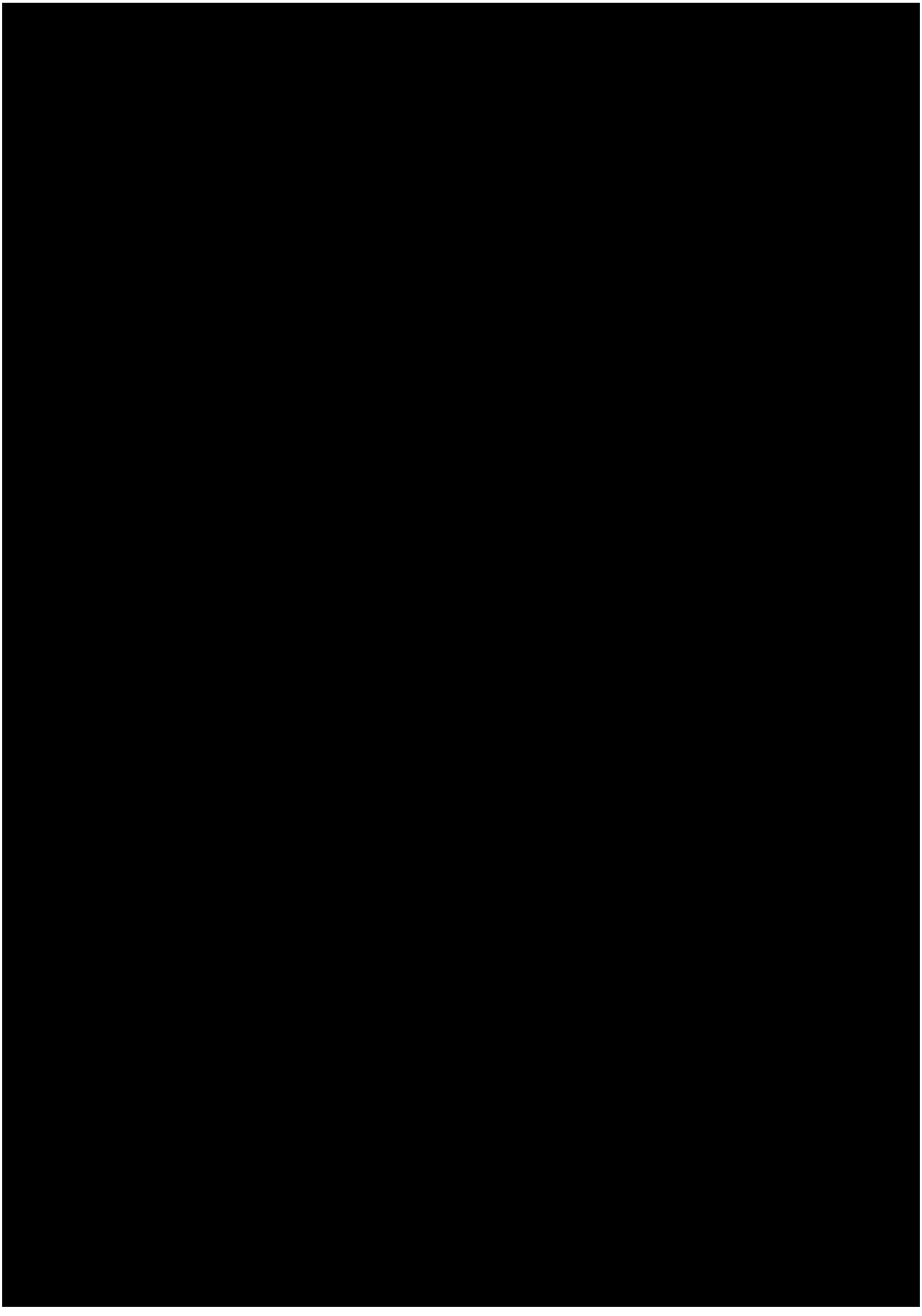
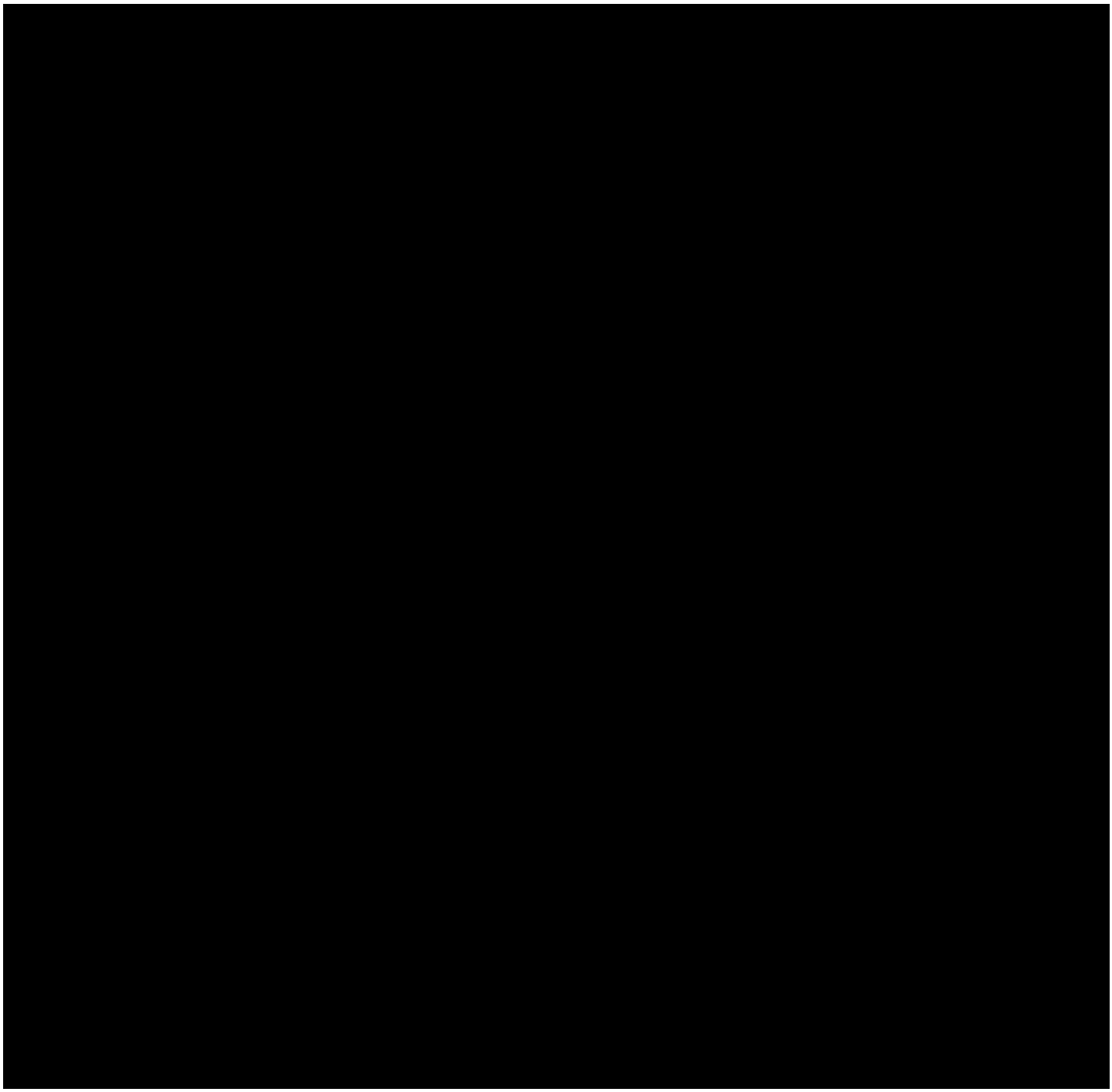
14 APPENDICES











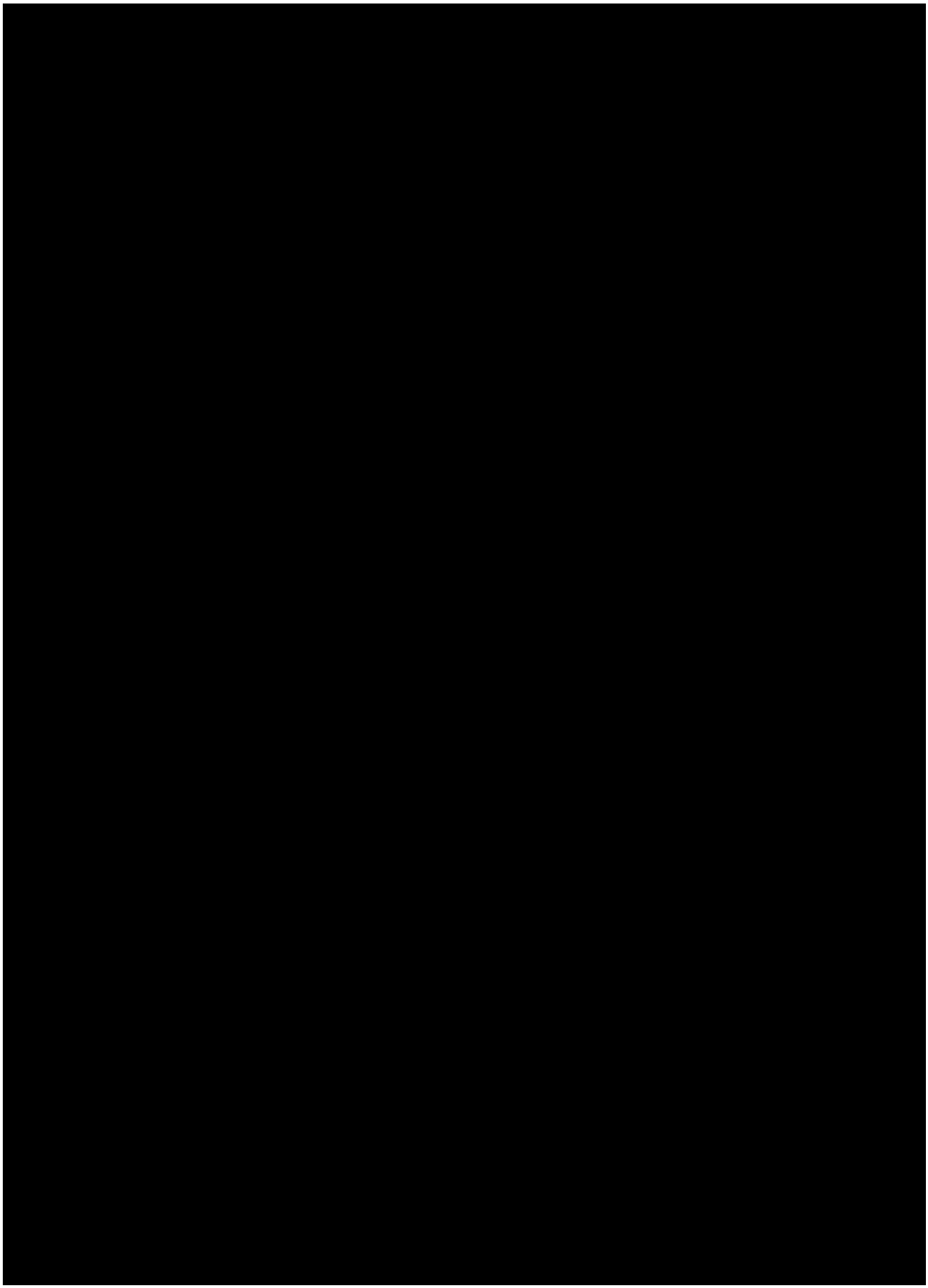
APPENDIX 8 Chemical Ingredients of the Study Products

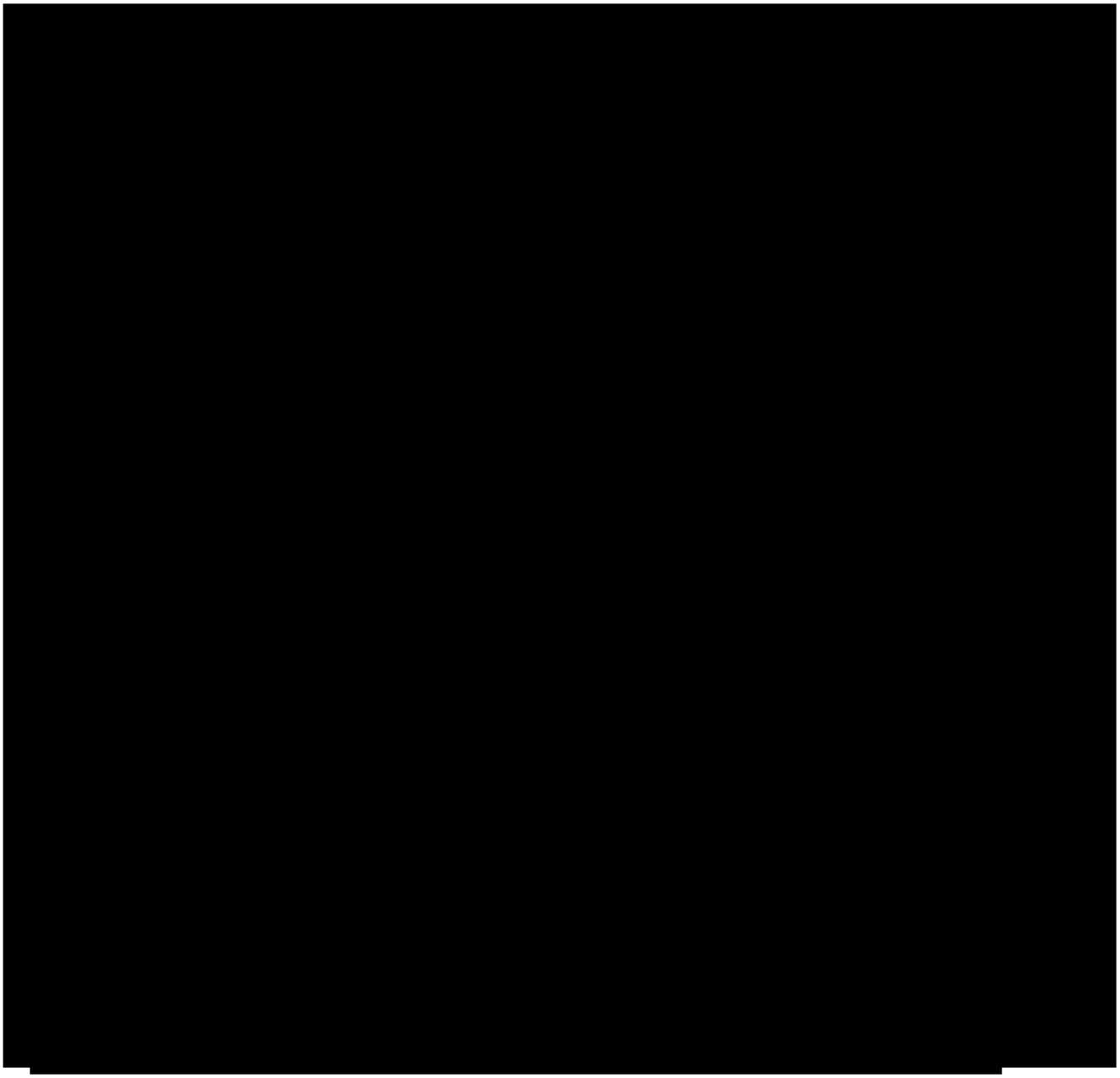
Study Drugs:

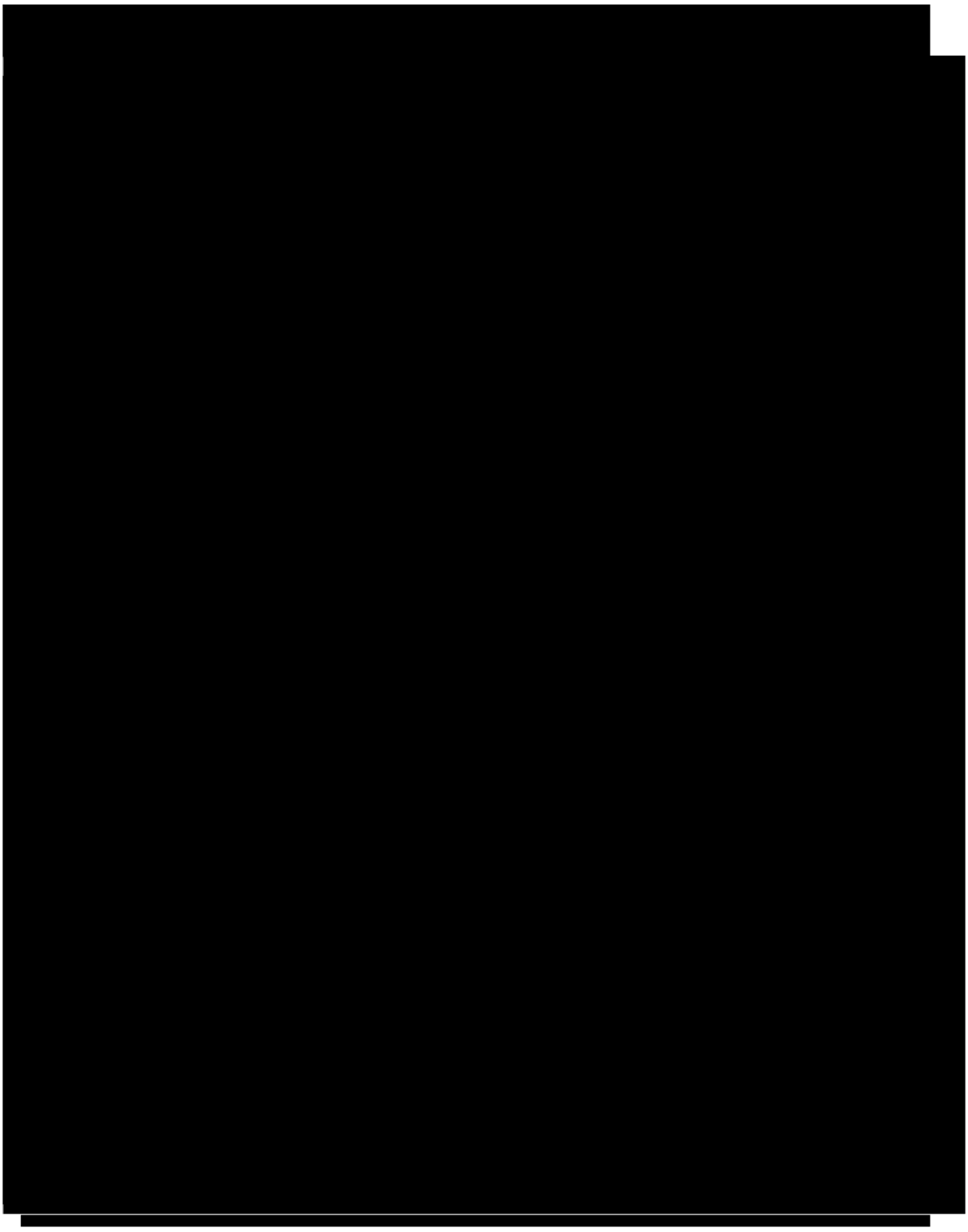
- BOTOX (onabotulinumtoxinA) purified neurotoxin complex

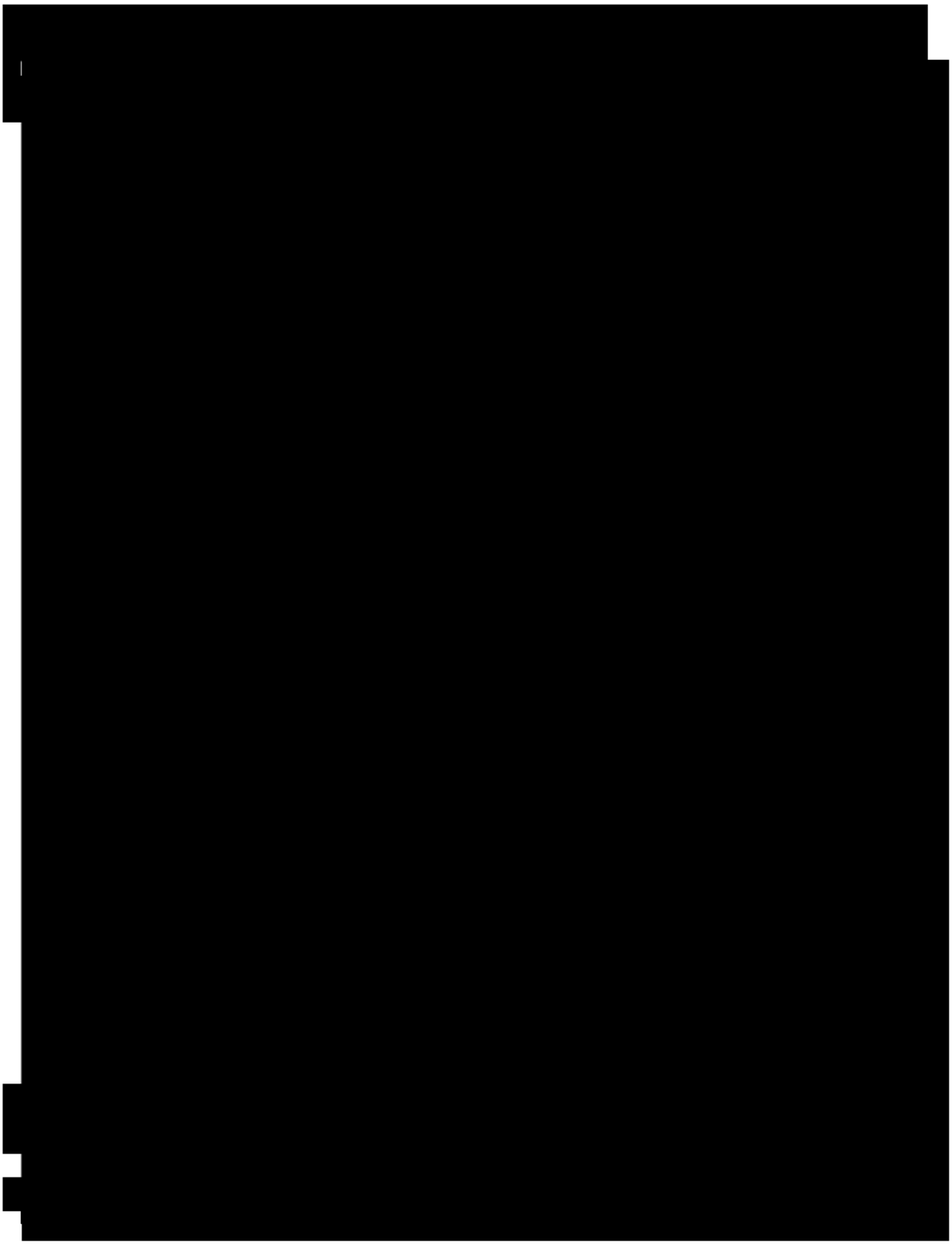
Study Devices:

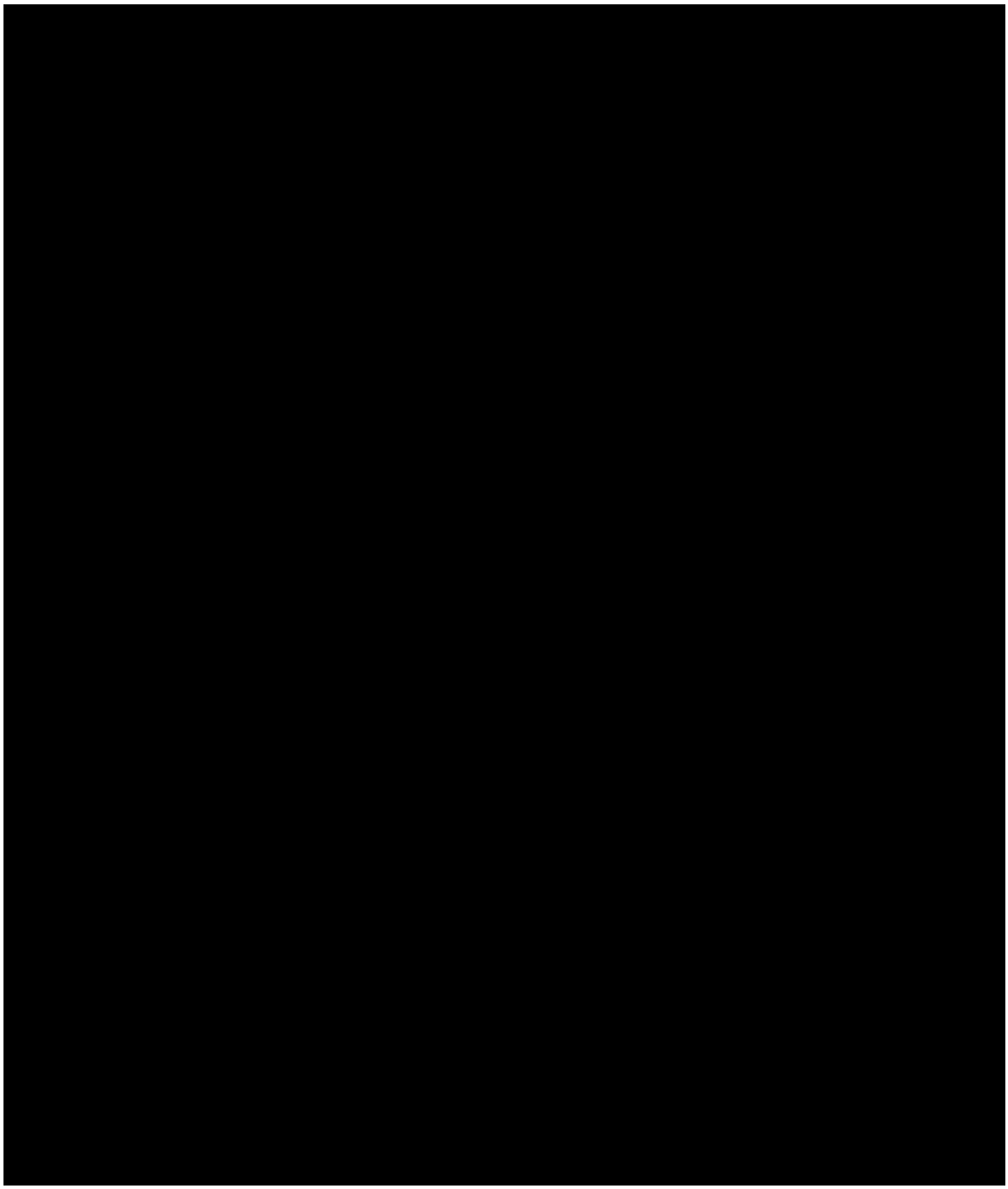
- JUVÉDERM® VOLITE® is a sterile non-pyrogenic physiological solution of cross-linked hyaluronic acid which is not of animal origin. It consists of cross-linked HA produced by *Streptococcus* of bacteria, formulated to a concentration of 12 mg/mL and 0.3% w/w lidocaine, HCl, in a phosphate buffer.
- JUVÉDERM® VOLBELLA® with Lidocaine injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogeneous gel implant. It consists of cross-linked HA produced by *Streptococcus* of bacteria, formulated to a concentration of 15 mg/mL and 0.3% w/w lidocaine, HCl, in a phosphate buffer.
- JUVÉDERM® VOLIFT® with Lidocaine is a sterile non-pyrogenic physiological solution of cross-linked hyaluronic acid which is not of animal origin. It consists of cross-linked HA produced by *Streptococcus* of bacteria, formulated to a concentration of 17.5 mg/mL and 0.3% w/w lidocaine, HCl, in a phosphate buffer.
- JUVÉDERM® VOLUMA® with Lidocaine is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized, HA gel implant (dermal filler). It consists of crosslinked HA formulated to a concentration of 20 mg/ml, suspended in a physiological buffer. The HA is mixed with phosphate buffer and 0.3% lidocaine, HCl, and crosslinked by adding BDDE to form a 3-dimensional HA gel.
- JUVÉDERM® VOLUX® with Lidocaine is a sterile, pyrogenic physiological solution of cross-linked hyaluronic acid that is not of animal origin. It consists of crosslinked HA gel 25 mg and 3 mg lidocaine, HCl, in a phosphate buffer.
- HArmonyCa Lidocaine™ is a dermal filler consisting of synthetic calcium hydroxyapatite microspheres, formulated to a concentration of 55.7% (w/w), embedded in a cross-linked sodium hyaluronate gel (0.886% [w/w] HA) from a non-animal source with 0.3% (w/v) lidocaine HCl.

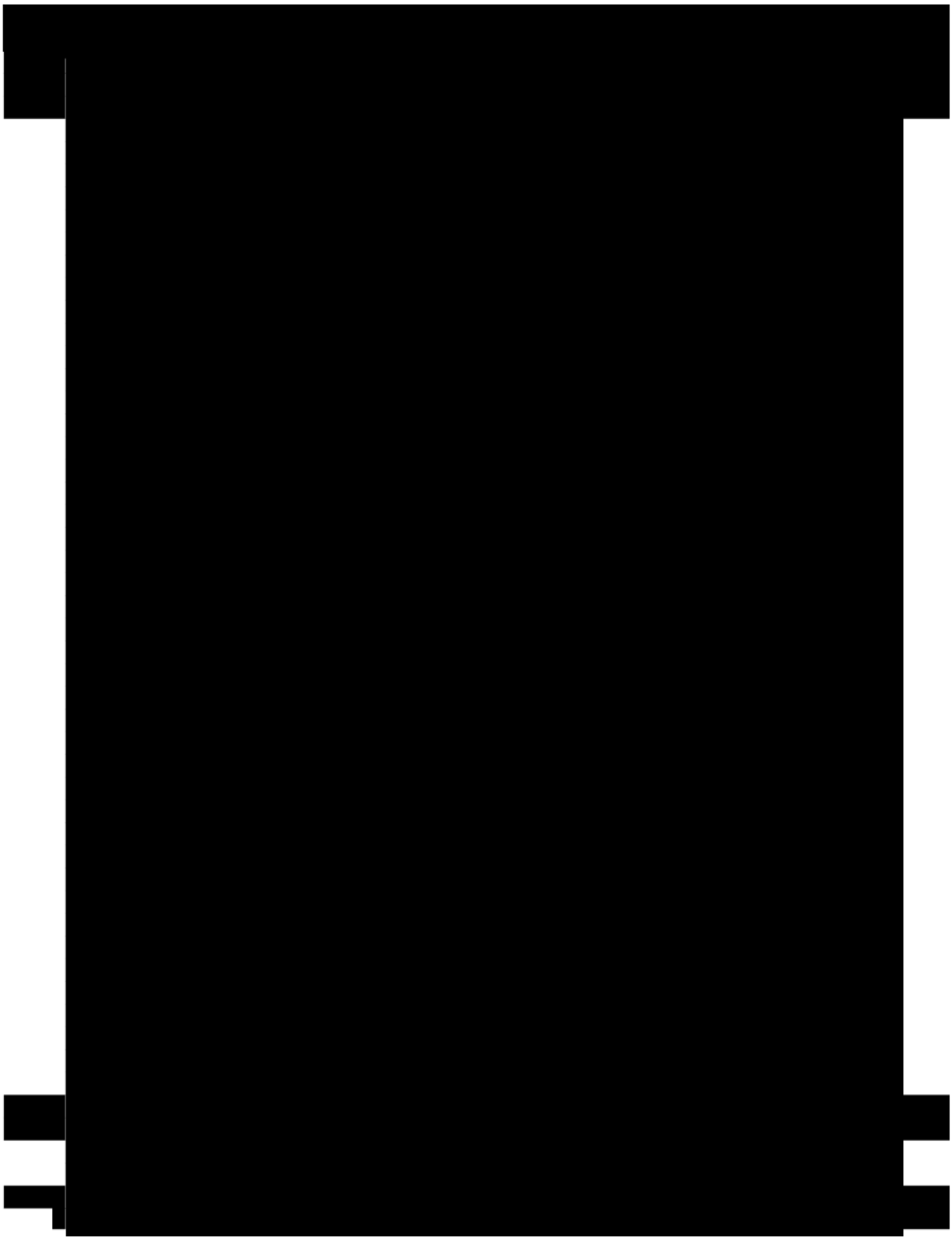


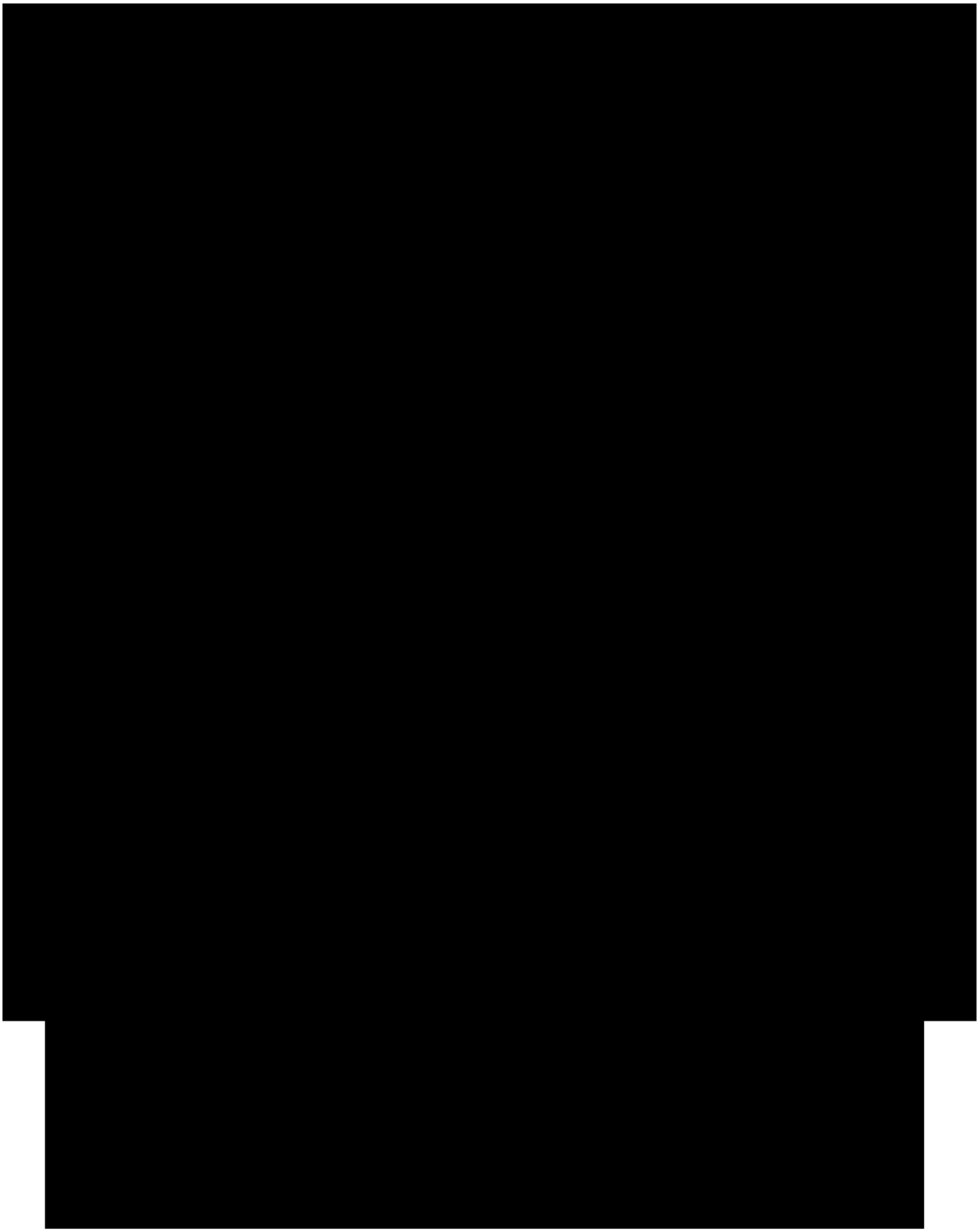


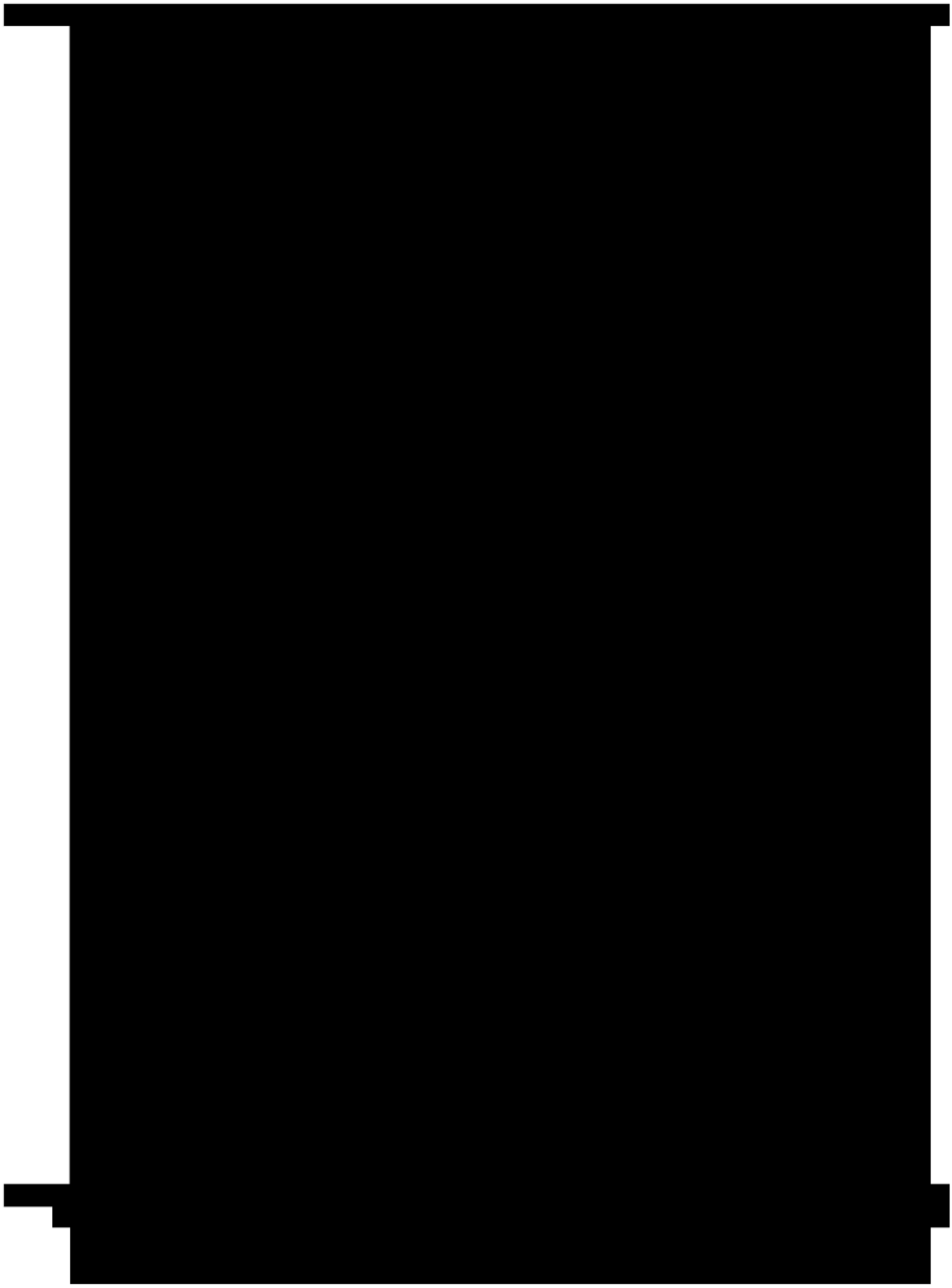


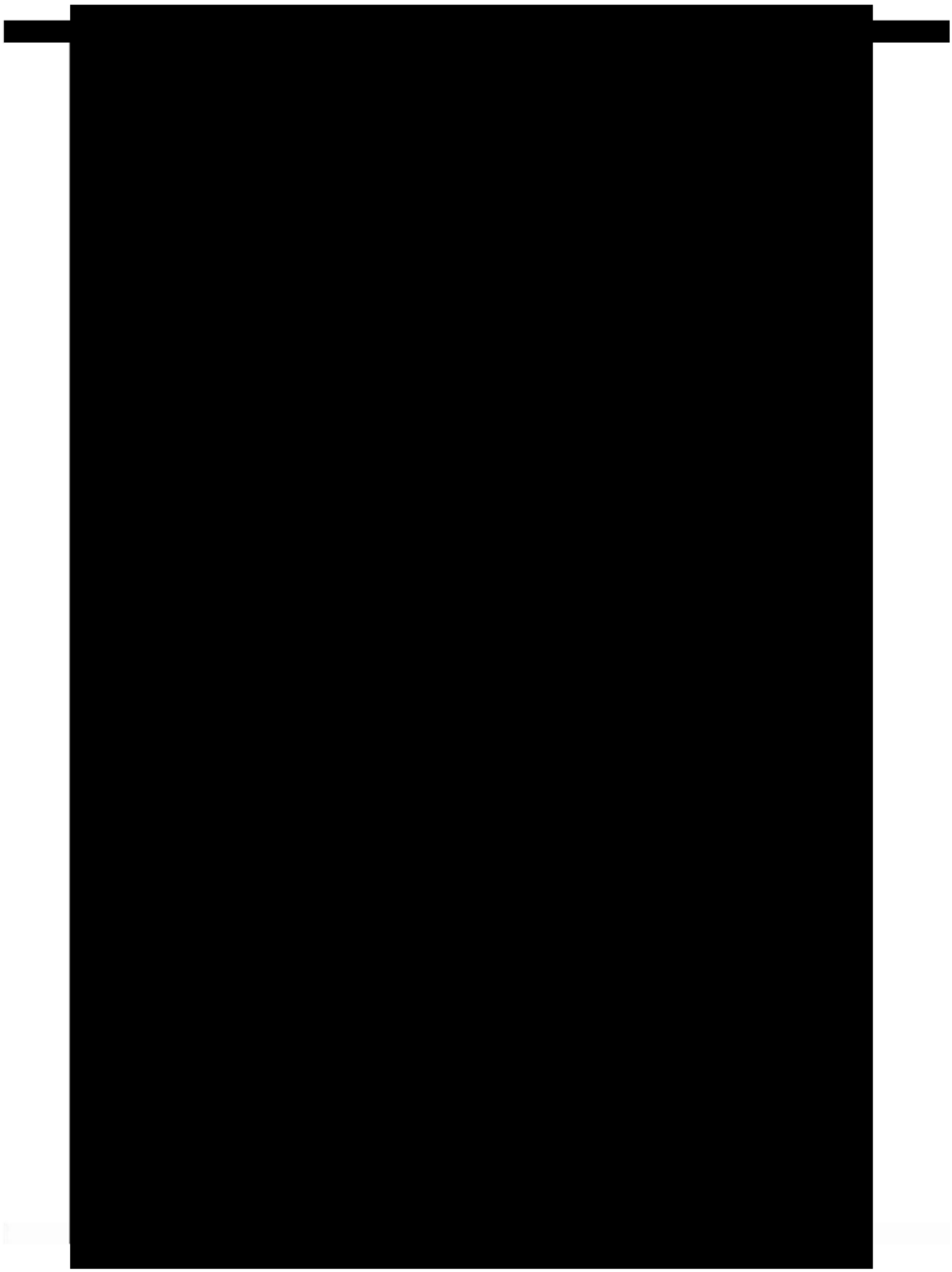


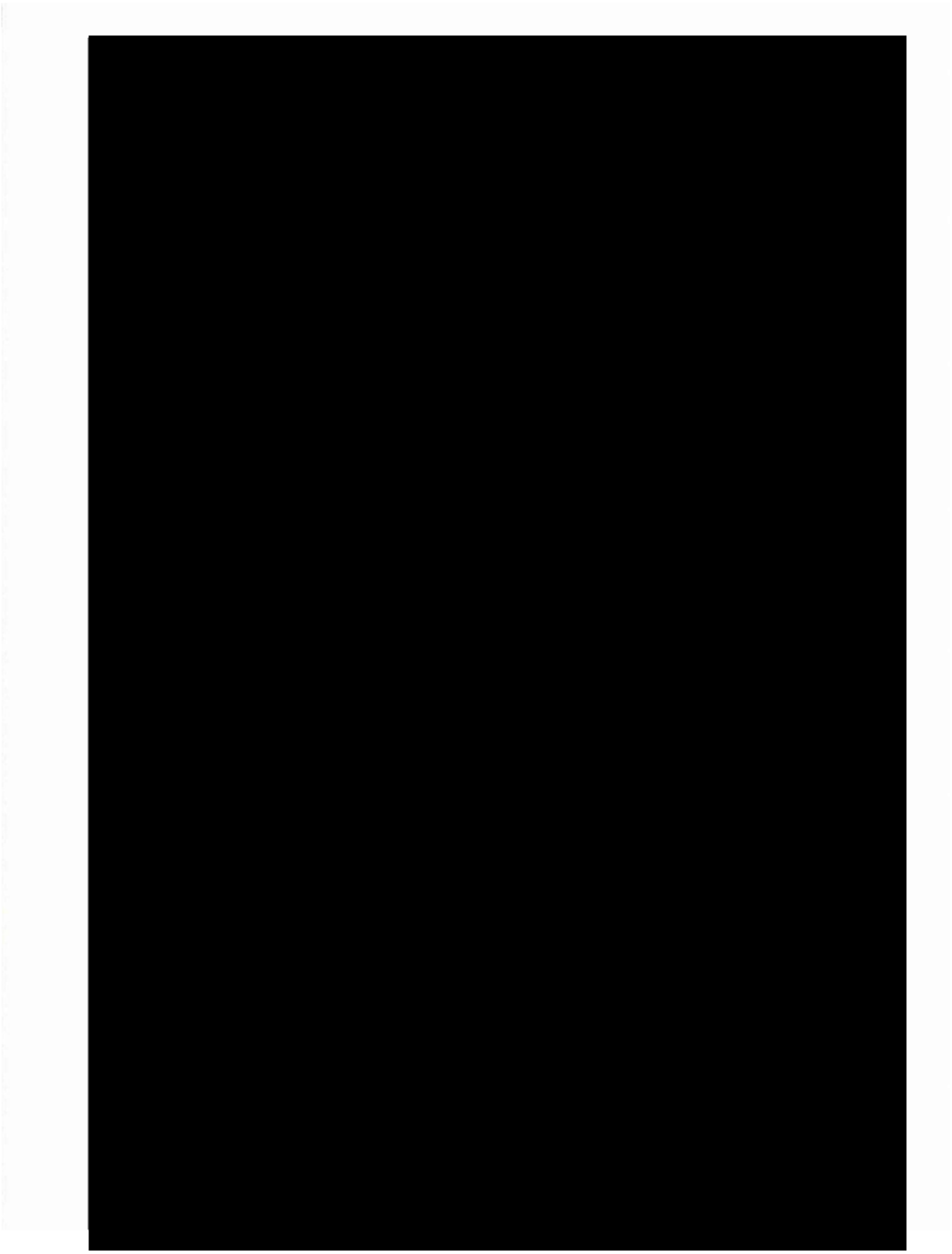


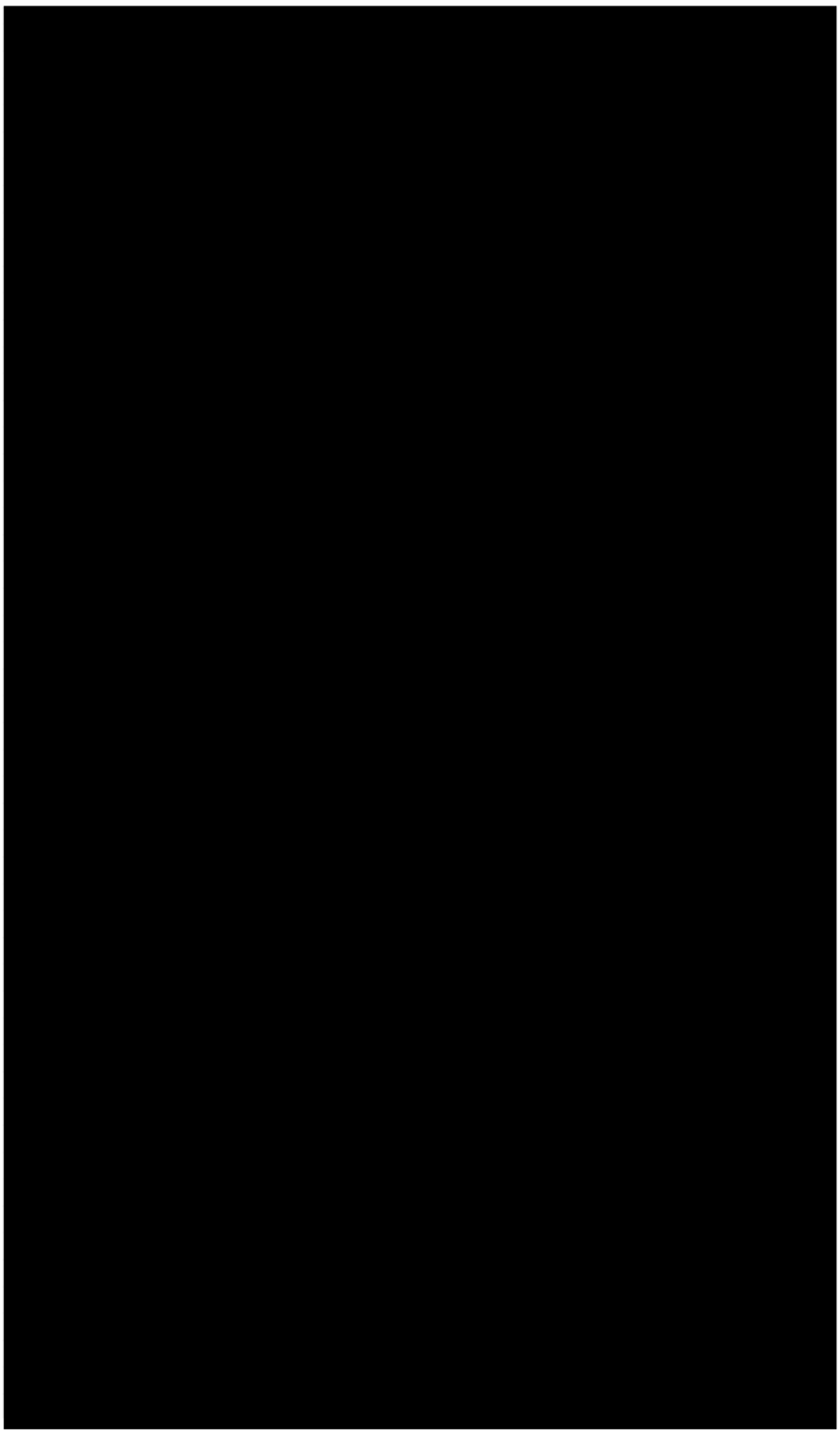


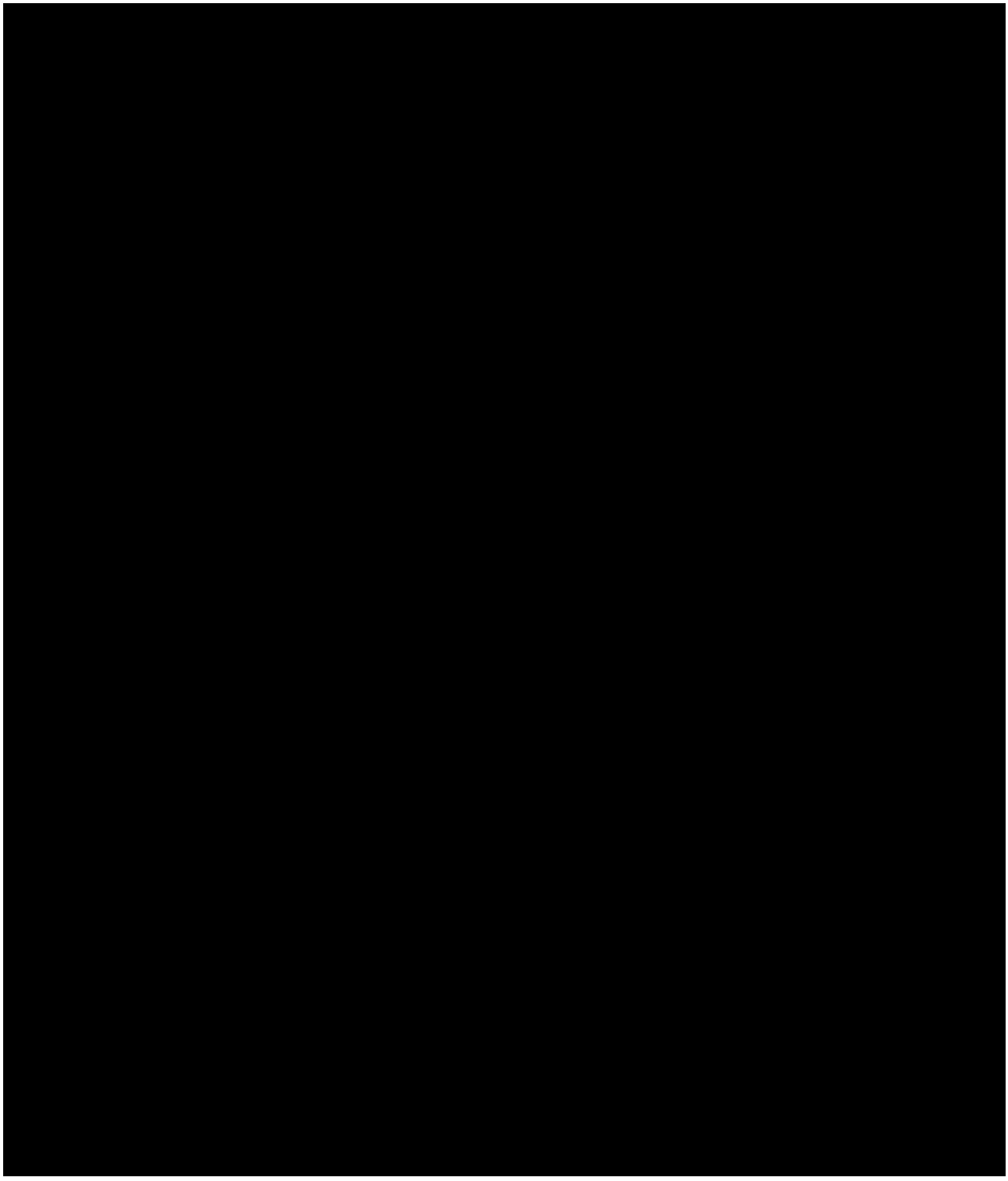


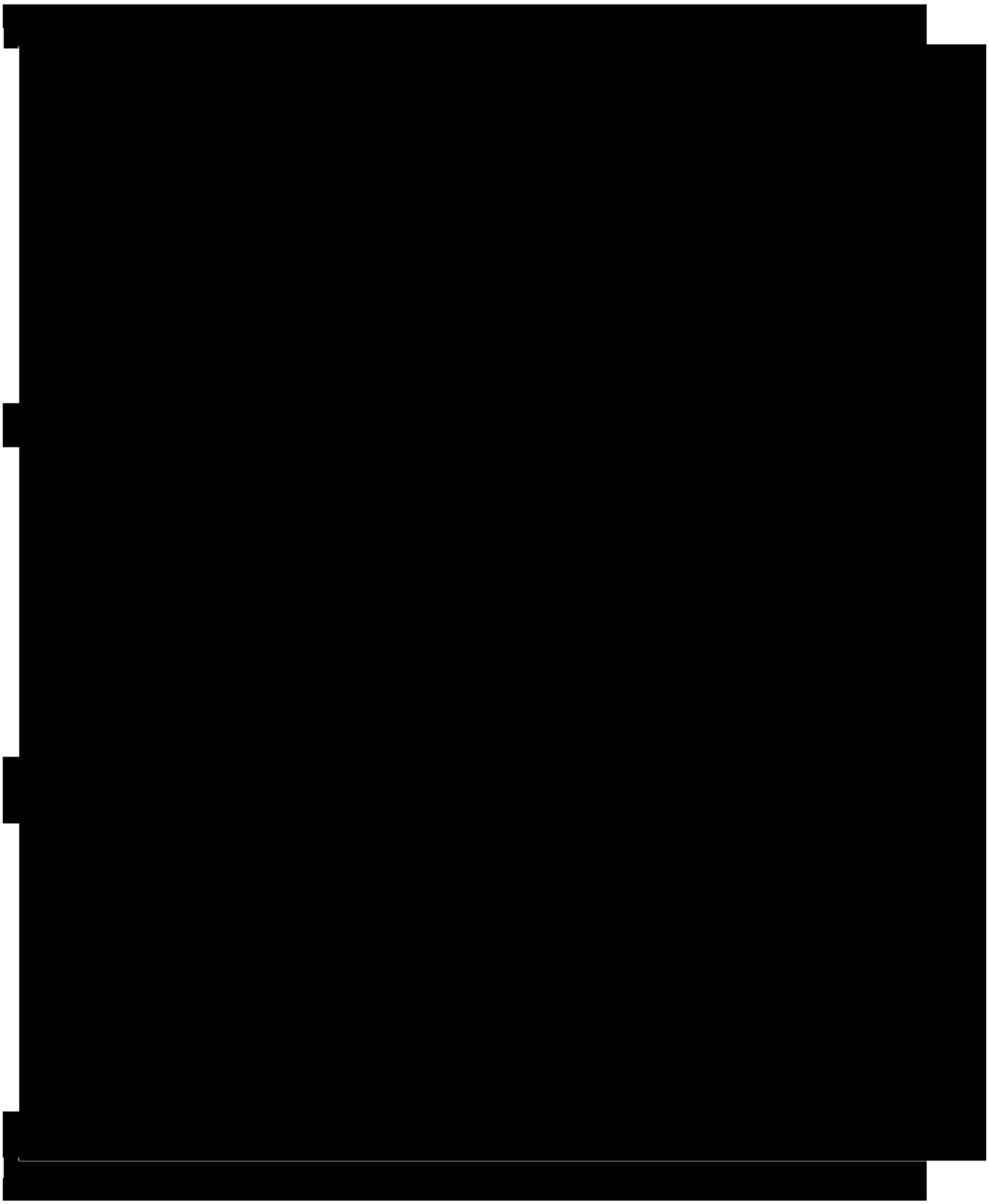


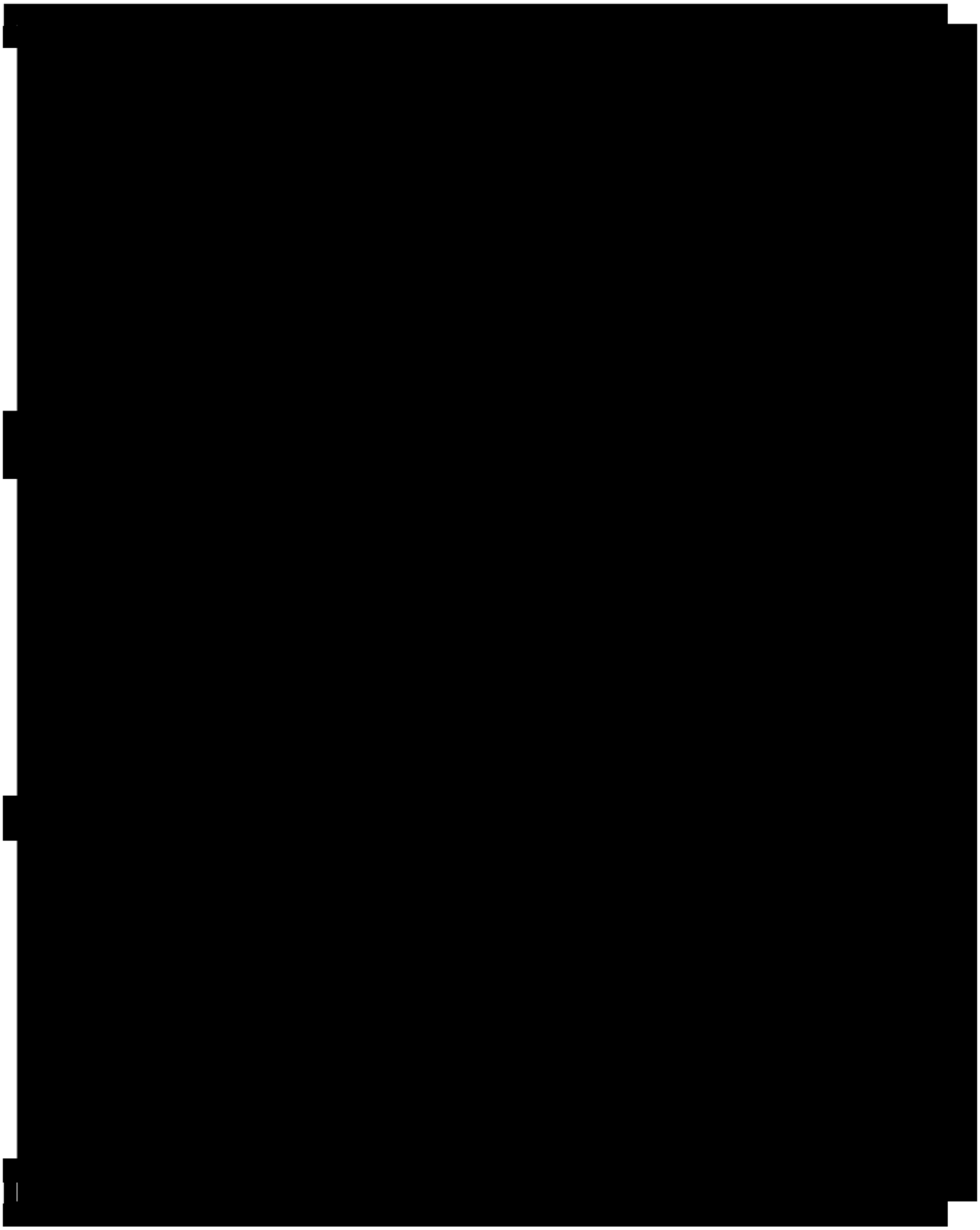


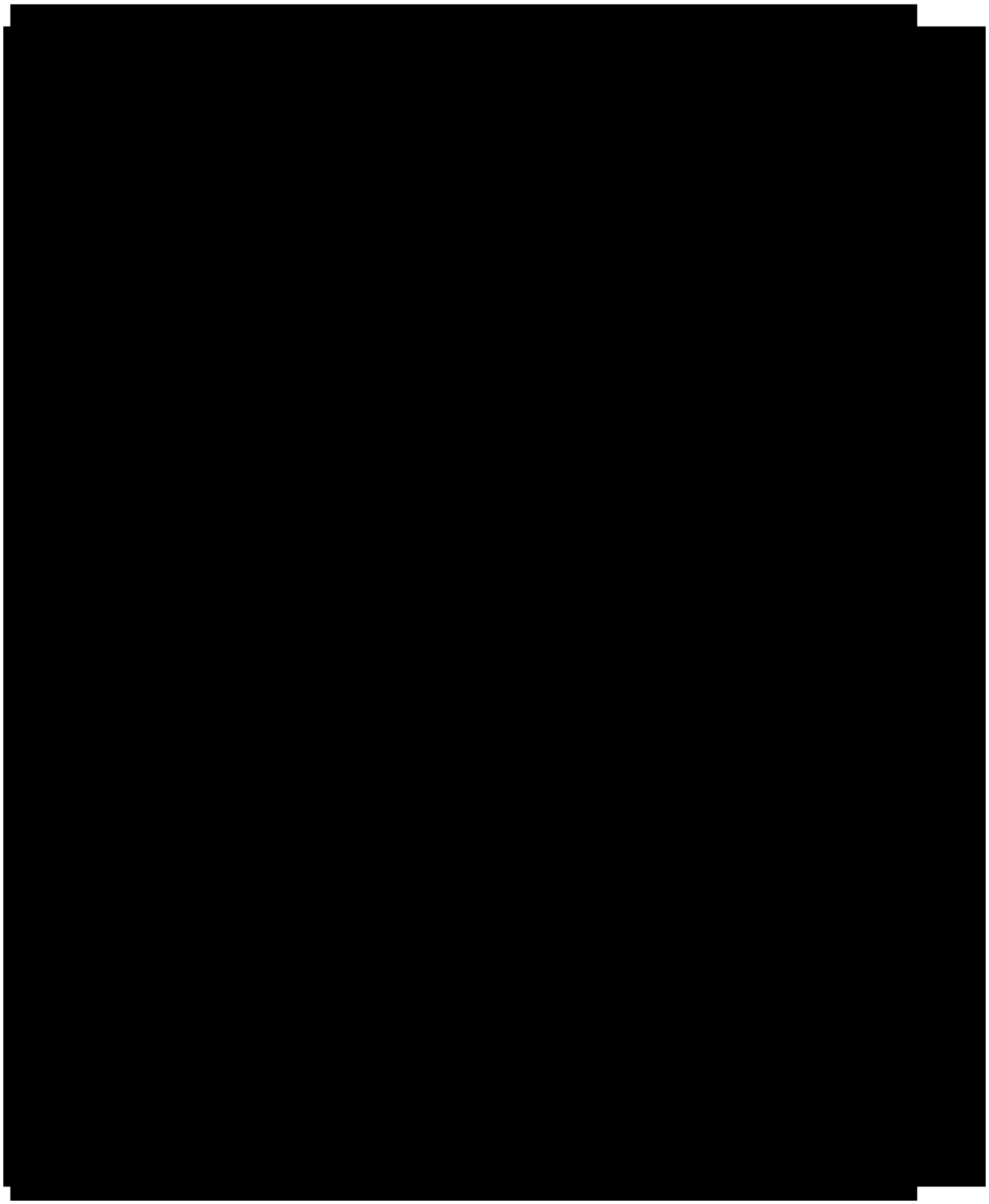


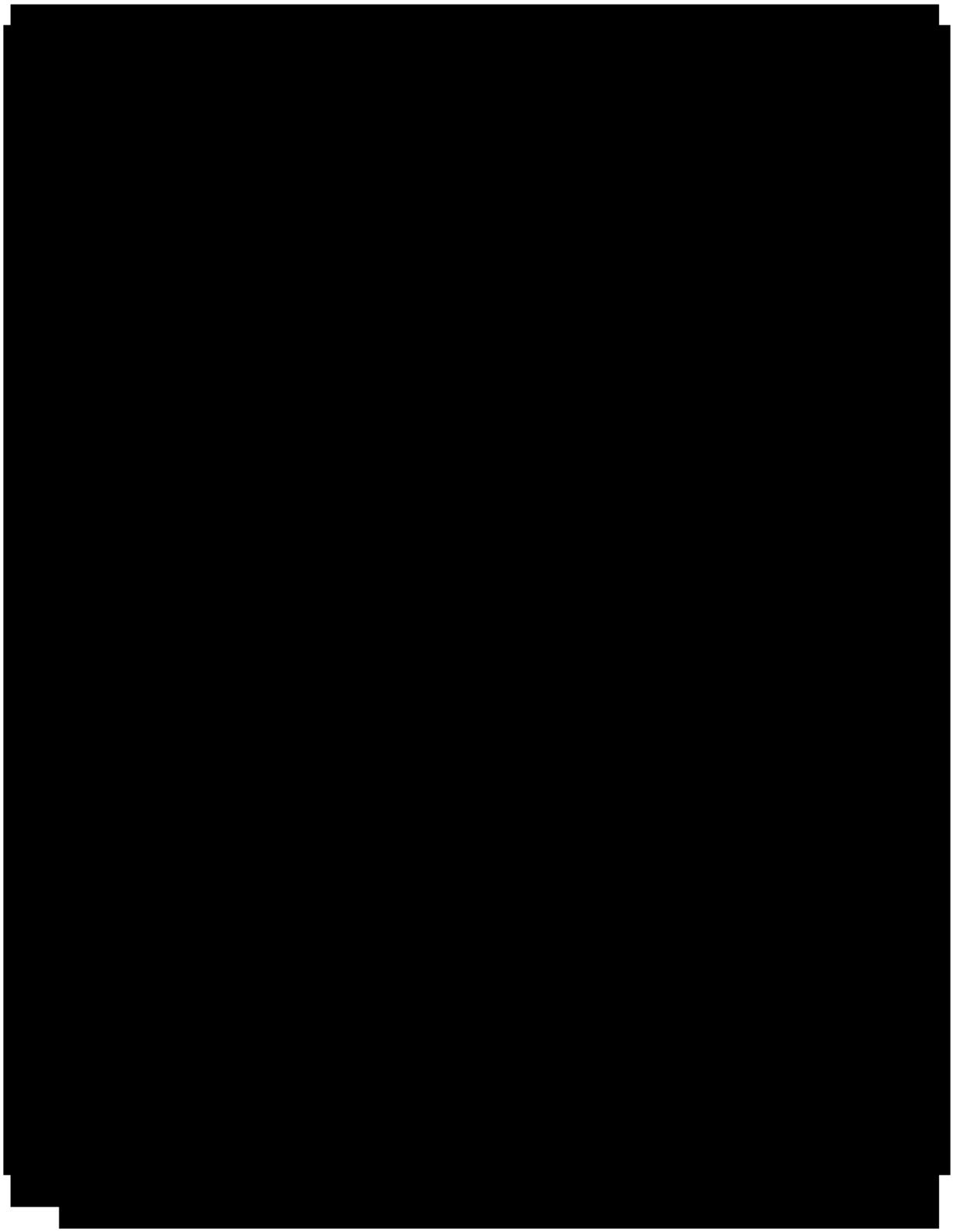


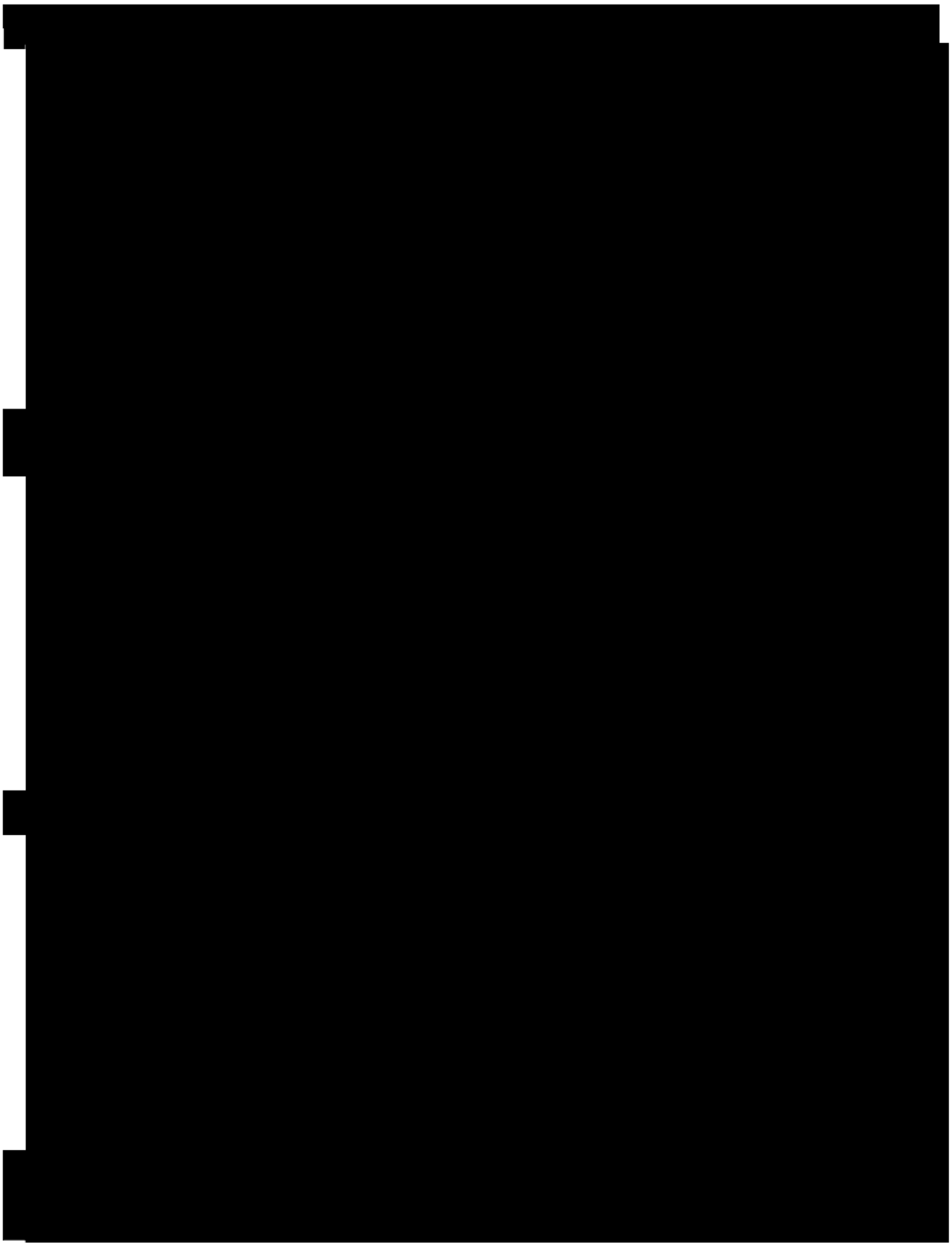


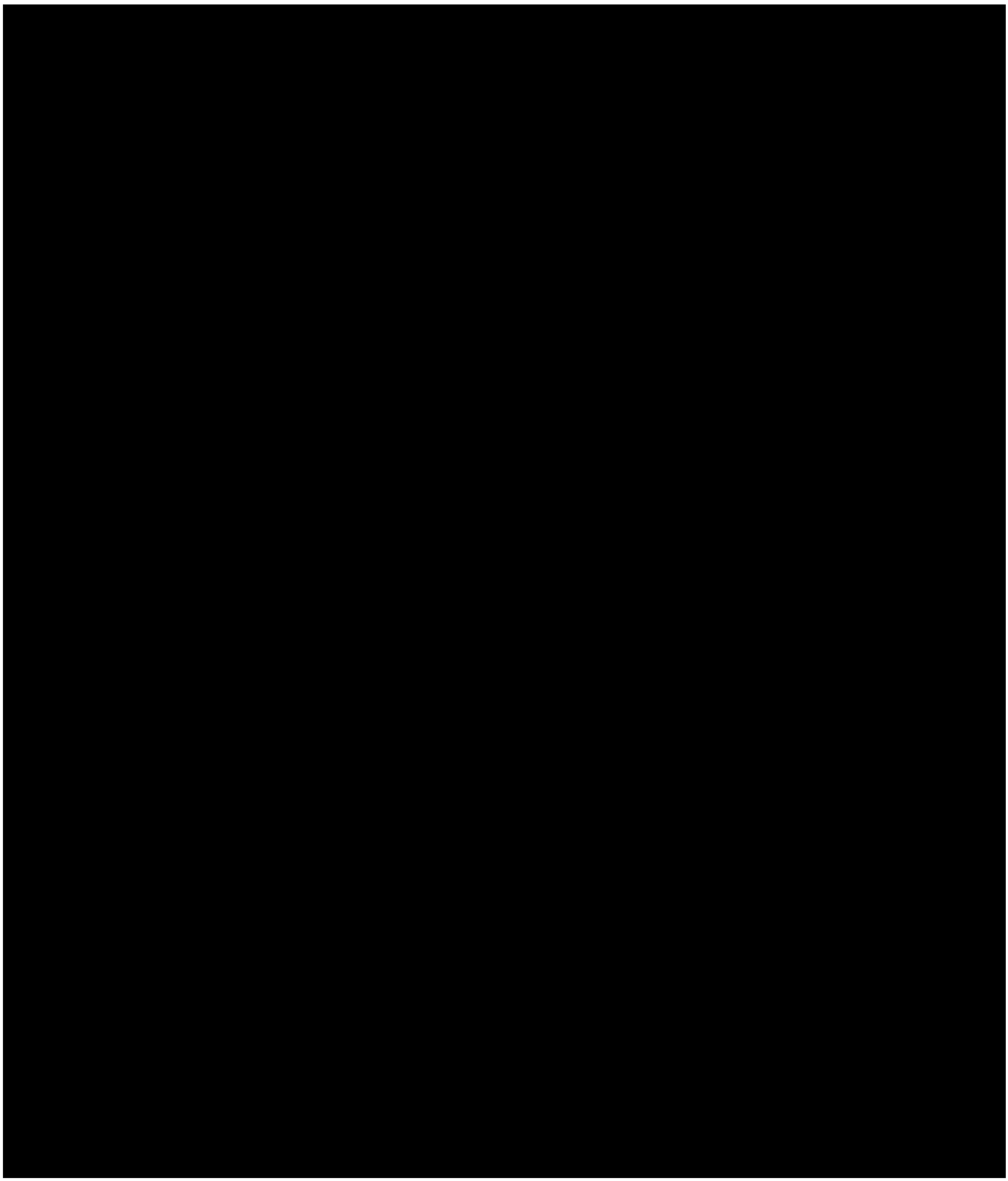












APPENDIX 14 Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Version 2	October 2021
Version 1 (Original Protocol)	May 2020

Version 2 (October 2021)

Overall Rationale for the Amendment:

HArmonyCa Lidocaine was approved for use in Brazil in April 2020. This provides the opportunity to include HArmonyCa Lidocaine in Study CMO-MA-FAS-0580 that evaluates combined facial treatment in subjects. All changes in the table below reflect the addition of HArmonyCa lidocaine to this study design.

Section # and Name	Description of Change	Brief Rationale
Global	Addition of HArmonyCa Lidocaine to the study design.	Per the overall rationale for the amendment to include HArmonyCa Lidocaine in this post market study, several sections throughout the protocol were updated, including study design, inclusion/exclusion criteria, study plan and procedures, etc.
Global	Editorial changes	Editorial changes throughout