NCT03712449

Study ID: CMO-MA-FAS-0579

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

Protocol Date: 24Oct2018

Clinical Study Protocol

Canada Global HARMONY: 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-0579

Drug Development Phase:	Phase 4, Postmarketing
Investigational Products:	BOTOX Cosmetic®, BELKYRA®, JUVÉDERM® VOLITE®, JUVÉDERM® VOLBELLA® with Lidocaine, JUVÉDERM® VOLIFT® with Lidocaine, JUVÉDERM® VOLUMA® with Lidocaine
Indications:	Glabellar Lines, Crow's Feet Lines, Forehead Lines, Nasolabial Folds, Facial Volume Loss, Lip Augmentation, Perioral Rhytides, Submental Fat, and/or Forehead/Cheek/Neck Cutaneous Depressions or Fine Lines
Sponsor:	Allergan Inc. 85 Enterprise Boulevard, Suite 500 Markham, Ontario, Canada L6G 0B5 Tel: 905-940-1660
Version and Date	Version 2, 24th October 2018

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.

[redacted]

Protocol Approval Signature Page

Sponsor: Allergan

I have read and understand the contents of this clinical protocol for Study No. CMO-MA-FAS-0579 dated 24th October 2018 and agrees to meet all obligations of Allergan 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]

[redacted] Associate Director, Phase IV

Principal Investigator's Agreement

I have read and understand the contents of this clinical protocol for Study No. CMO-MA-FAS-0579 dated 24th October 2018 and will adhere to the study requirements as presented, including all statements regarding confidentiality.

I agree to:

- Implement and conduct this study diligently and in strict compliance with the protocol, good clinical practices (Allergan has certified GCP training completed) and all applicable laws and regulations.
- Maintain all information supplied by Allergan in confidence and, when this information is submitted to 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:**
Allergan Inc. 85 Enterprise Blvd., Suite 500, Markham, Ontario, Canada	BOTOX Cosmetic®, BELKYRA®, JUVÉDERM® VOLITE®, JUVÉDERM® VOLBELLA® with Lidocaine, JUVÉDERM® VOLIFT® with Lidocaine, JUVÉDERM® VOLUMA® with Lidocaine	Phase 4, Postmarketing

Title of Study: Canada Global HARMONY: 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-0579

Number of Subjects and Study Center(s): 60 subjects at 7 study centers in Canada

Indication:

1. BOTOX Cosmetic is indicated for the treatment of upper facial rhytides, including forehead, lateral canthus, and glabellar lines.
2. BELKYRA® is indicated for the improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults.
3. JUVÉDERM® VOLITE® is indicated for the treatment, by filling, of superficial cutaneous depressions such as fine lines.
4. JUVÉDERM® VOLBELLA® with Lidocaine is indicated for enhancement and pouting of the lips to correct volume loss and to treat perioral lines and oral commissures, and infraorbital area
5. JUVÉDERM® VOLIFT® with Lidocaine is indicated for the treatment of nasolabial folds.
6. JUVÉDERM® VOLUMA® with Lidocaine is indicated to restore volume of the face (i.e. cheek, chin, and malar area).

Primary Study Objective:

To quantify the psychological and emotional impact of comprehensive aesthetic treatment with a portfolio of Allergan products by measuring the change in subject's satisfaction with facial appearance from baseline (before any treatment) to the final study visit.

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.

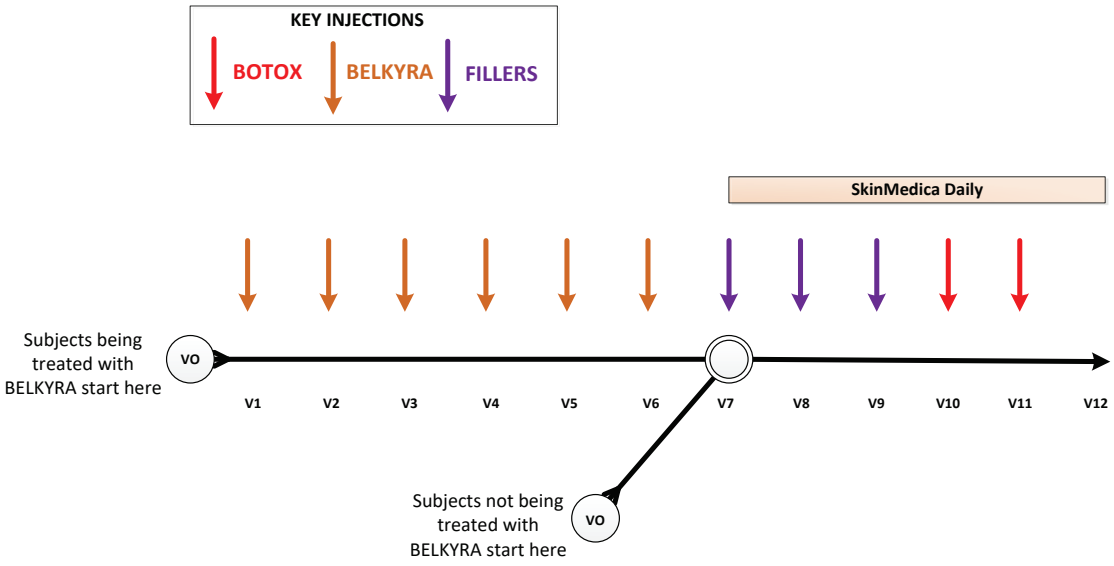
Methodology:

This Phase 4 study is a prospective, interventional, multicenter, combination medical device, drug, and skin care postmarketing study. Each subject will be in the study for up to

11 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 6 study sites in Canada. The ratio of subjects treated with BELKYRA to subjects without BELKYRA treatment will be approximately 1:2 (ie, approximately 20 BELKYRA subjects and 40 subjects without BELKYRA) based on clinical indication and the decision of the subject and investigator. Thus, approximately one-third of all subjects will receive BELKYRA treatment. Recruitment will also target men, who are typically under-represented in aesthetic studies. Allergan may stop recruitment into one group to ensure these approximate representations.

Overall Study Design



All subjects will sign an informed consent form (ICF), and begin the study at the screening visit (V0). Subjects receiving BELKYRA treatment will enter the study at V1 continuing on through V12. There will be no less than 1 month between repeat BELKYRA treatments and the final BELKYRA treatment. Subjects not receiving BELKYRA following screening (V0) will enter the study at V7 to begin treatment with fillers, SkinMedica, and BOTOX Cosmetic as indicated in the study design diagram above.

All adverse events (AEs) including 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 Allergan and SkinMedica within 24 hours.

Criteria for Evaluation:

<u>Primary Endpoint</u>

The primary endpoint is the change from screening (V0) before treatment in the Rasch-transformed score of the FACE-Q Satisfaction with Facial Appearance Overall Scale to the final study visit (V12).

Key Secondary Endpoints

- Subject's assessment of expectations of life change as measured by the mean change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Expectations scale to final study visit (V12)
- Subject's assessment of age-related facial appearance as measured by the mean change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Aging Appraisal to final study visit (V12)
- Subject's assessment of psychological well-being as measured by the mean change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Psychological Function Scale to final study visit (V12)
- Subject's assessment of social function as measured by the mean change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Social Function Scale to final study visit (V12)
- Subject's assessment of overall satisfaction with skin as measured by the mean change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Satisfaction with Skin to final study visit (V12)
- 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 (V12); responders are defined as having achieved a younger category.

Other Secondary Endpoints

- Change in investigator's assessment of global facial aesthetic improvement as measured by the 5-point global aesthetic improvement scale (GAIS) at final study visit (V12)
- Change in subject's assessment of global facial aesthetic improvement as measured by the 5-point GAIS at final study visit (V12)
- Change in subject's satisfaction with appearance of periorbital area as measured by the periorbital aesthetic appearance questionnaire (PAAQ)

[redacted]

[redacted]

Key Inclusion Criteria:

[redacted]

1. 30 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. Mild to moderate facial photo damage based on a score of 1 to 9 on the SkinMedica overall photodamage scale (SOPS)
5. Willing to avoid direct and prolonged sun exposure to the facial skin, which includes tanning beds, for the duration of the study
6. Must qualify to receive BOTOX Cosmetic as per the approved Product Monograph:is indicated: for the treatment of upper facial rhytides, including forehead, lateral canthus, and glabellar 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

7. Must qualify to receive facial filler treatments as per the approved Directions for Use

Key Exclusion Criteria:

[redacted]

2. Body mass index (BMI) > 30
3. Known allergy or sensitivity to any study products or their components
4. Pregnant, lactating, or planning to become pregnant at any time during the study
5. Received BOTOX Cosmetic or treatment with any other botulinum toxin product for any condition within 6 months before enrollment
6. Received (or is planning to receive) anti-coagulation, anti-platelet or thrombolytic medications (eg, warfarin) or other substances known to increase coagulation time from 10 days prior to injection and up to 3 days post-injection
7. 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
8. 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
9. 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

[redacted]

11. Lip tattoos, facial hair, or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments

12. 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
13. Received any investigational product within 60 days prior to study enrollment or planning to participate in another investigation during the course of this study
14. An employee (or a relative of an employee) of the investigators, Allergan, or representative of Allergan
15. 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
16. Current use of oral corticosteroids
17. Current use of nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, aspirin, ibuprofen), from 10 days prior to injection up to 3 days post-injection
18. 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
19. Systemic retinoid therapy within one year prior to study enrollment

[redacted]

21. 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
22. Current use of aminoglycoside antibiotics, curare-like agents, or agents that might interfere with neuromuscular (skeletal) function
23. Profound atrophy/excessive weakness of muscles in target areas of injection
24. History of facial nerve palsy
25. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study treatment)
26. Very thin skin in the mid-facial region
27. Tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, ie, significant convexity or projection from the infraorbital fat pads
28. Mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (eg, juvenile dermatomyositis), partial lipodystrophy (eg, Barraquer-Simons syndrome), inherited disease, or human immunodeficiency virus–related disease
29. Undergone oral surgery or other dental procedures (eg, tooth extraction, orthodontia, or implantation) within 30 days prior to enrollment or planning to undergo any of these procedures during the study
30. Subjects with neuromuscular disorders including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise
31. Subjects with a history of allergies or hypersensitivity to HA or lidocaine

Products, Dose, and Mode of Administration:

BELKYRA

Inject 0.2 mL in each site, 1 cm apart, up to 50 injections into the subcutaneous fat. The planned treatment area should be outlined with a surgical pen and a 1 cm injection grid applied to mark the injection sites. The maximum dose should not exceed 100 mg (10 mL) in a single treatment. The number of treatment sessions needed to achieve a satisfactory response depends on the individual patient. Up to 6 treatments spaced at intervals of no less than 1 month apart. are recommended based on the clinical trial efficacy and safety data. Patients should receive the minimum number of injections over a minimum number of treatment sessions to achieve a satisfactory result. More frequent dosing with BELKYRA has not been clinically evaluated for safety and effectiveness and is not recommended. The investigator will determine the number of treatment sessions based on his/her clinical experience and the subject's aesthetic goals.

SkinMedica Products

During Visit 7 to Visit 12, all subjects will receive a combination of the following SkinMedica products, to be applied daily for approximately 4 months, as per the investigator's discretion:

- Facial Cleanser
- TNS Essential Serum®
- Rejuvenative Moisturizer
- Optional: Total Defence + Repair Broad Spectrum Sunscreen SPF34 may be used at the subjects' discretion

BOTOX Cosmetic

Subjects will receive at least one of the following BOTOX Cosmetic dosing regimens:

- 20 U total to GLs area consisting of 5 injection sites (2 in each corrugator and one in the procerus), and/or
- CFLs: 2-6 U should be injected bilaterally at each of 1-3 injection sites and/or
- 24U total to FHLs area consisting of 4 injection sites in the frontalis muscle.

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 volume that may be injected for initial and top-up treatments combined is 2 mL for lips injection, 1.5 mL for oral commissure injection, 1.2 mL for perioral line injection and 1.5 mL per eye for infraorbital injection.

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 (4.0 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. Do not inject more than 2 mL per treatment area during each session.

JUVÉDERM VOLITE 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 VOLITE with Lidocaine allowed per subject for the initial and touch-up treatments combined is 4 syringes (4.0 mL).

The investigator should not inject greater than 20 mL of filler per 60kg (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 approximately 11 months depending on the treatments they receive.

Statistical Methods:

Three analysis populations are defined in Section 11. Unless otherwise specified in the SAP, efficacy analyses will be based on the Evaluable Population, safety analyses will be based on the Safety Analysis Population, and all other analyses will be based on the Full Analysis Population

Primary Efficacy Analysis

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

[redacted]

Table of Contents

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List of Abbreviations

Abbreviation	Definition
AE	adverse event
BMI	body mass index
CFLs	crow's feet lines (also known as lateral canthal lines in BOTOX product literature)
DCA	deoxycholic acid
eCRF	electronic case report form
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 Harmonisation
ISR	injection site reaction
LFS	lip fullness score
MITT	modified intent-to-treat
NLF	nasolabial fold
NSAIDs	nonsteroidal anti-inflammatory drugs
OTC	over-the-counter
PAAQ	periorbital aesthetic appearance questionnaire
REB	research ethics board
SAE	serious adverse event
SAP	statistical analysis plan
SMF	submental fat
SMFRS	submental fat rating scale
SOPS	SkinMedica overall photodamage scale
SPA	self-perception of age
SSRS	subject self-rating scale
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 interactionsThese 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 including use of botulinum toxin as well as hyaluronic acid fillers are used to improve the signs of aging such as addressing presence of both static and dynamic wrinkles, myomodulation

In addition, a recently approved injectable agent, BELKYRA, has been demonstrated as safe and effective in the reduction of undesirable excess submental fat (SMF) (McDiarmid 2014, Jones 2016, Ascher 2014, Humphrey 2016). SMF may cause an unappealing fullness, which can affect overall facial appearance. Before the approval of BELKYRA, the procedures used to cure the SMF were surgical, eg, liposuction or fat excision, which may lead to serious complications (Jones 2016, Wollina 2015).

BELKYRA contains an injectable proprietary formulation of synthetically derived deoxycholic acid (DCA), a cytolytic agent that can induce adipocytolysis when injected directly into fat. Multiple treatment sessions spaced at least a month apart are generally needed for full response, with most subjects requiring 3 to 5 treatments (BELKYRA™ Product Monograph).

Botulinum toxins have been approved by Health Canada for the treatment of moderate to severe glabellar lines, lateral canthal rhytides, and forehead lines (BOTOX Cosmetic® Product Monograph). Onabotulinumtoxin A (BOTOX Cosmetic) 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 Health Canada–approved to temporarily treat facial wrinkles and volume loss (Jones 2013, JUVÉDERM VOLUMA® with Lidocaine Directions for Use, Lupo 2008, Pinsky 2008). 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.

Health Canada has approved the following filler products as indicated:

- JUVÉDERM VOLBELLA with Lidocaine is indicated for enhancement and pouting of the lips to correct volume loss and to treat perioral lines and oral commissures and correction of infraorbital skin depressions.
- JUVÉDERM VOLIFT with Lidocaine is indicated for the treatment of nasolabial folds.
- JUVÉDERM VOLUMA with Lidocaine is indicated to restore volume of the face (ie, cheek, chin, and malar area).
- JUVÉDERM VOLITE is indicated for the treatment of face (cheek and forehead) and neck, by filling of superficial cutaneous depressions such as fine lines and for additional improvement of hydration

In clinical trials, each product mentioned above has been demonstrated to be safe and effective for its approved indication (Carruthers 2004a, Jones 2013, Lupo 2008, Pinsky 2008, Wollina 2015, Ascher 2014). 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 onabotulinumA toxin (BOTOX Cosmetic), 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 Health Canada–approved aesthetic products. The objective of the initial USA HARMONY study was to observe the safety and overall aesthetic impact of treating subjects with several modalities in an attempt to achieve subjects' desired clinical outcome. The Canada Global HARMONY 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 Global HARMONY study, subjects will be evaluated by the investigator to receive BOTOX Cosmetic, BELKYRA, Juvéderm facial fillers (JUVÉDERM VOLITE, JUVÉDERM VOLBELLA with Lidocaine, JUVÉDERM VOLIFT with Lidocaine, and JUVÉDERM VOLUMA with Lidocaine), and SkinMedica products. 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 Cosmetic, BELKYRA, JUVÉDERM facial fillers, and SkinMedica products will have a significantly higher satisfaction with their overall facial appearance at the final study visit when compared with baseline, pre-treatment satisfaction scores, as measured by the mean 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 Allergan products by measuring the change in subject's satisfaction with facial appearance from baseline (before any treatment) to the final study visit ([redacted] FACE-Q™: Satisfaction with Facial Appearance). These Allergan products include BOTOX Cosmetic, BELKYRA, Juvéderm HA facial fillers, and SkinMedica® topical nonprescription skin care products, as described in Section 9.

3.2 Secondary Objectives

Secondary objectives are:

- To determine the subject's self-appraisal of expectations of life change ([redacted] FACE-Q™: Expectations), age-related facial appearance [redacted] FACE-Q©: Aging Appraisal), psychological function ([redacted] FACE-Q™: Psychological Function), social function ([redacted] FACE-Q™: Social Function) and overall satisfaction with skin ([redacted] 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, drug, and skin care postmarketing study. Each subject will be in the study for up to 11 months depending on the treatments given, 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.

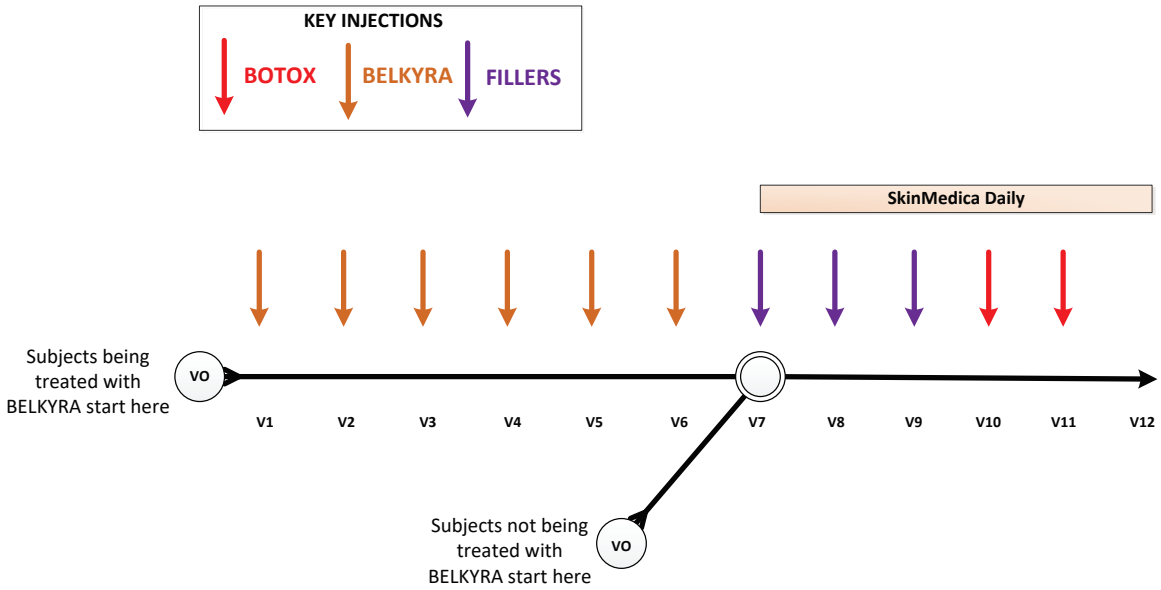
The study is planned to enroll 60 subjects consecutively at approximately 6 study sites in Canada. The ratio of subjects treated with BELKYRA to subjects without BELKYRA treatment will be approximately 1:2 (ie, approximately 20 BELKYRA subjects and 40 subjects without BELKYRA) based on clinical indication and the decision of the subject and investigator. Thus approximately one-third of all subjects will receive BELKYRA treatment. 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 receiving BELKYRA treatment will enter the study at V1 continuing on to V12. There will be at least 1 month between repeat BELKYRA treatments and the final BELKYRA treatment.

Subjects not receiving BELKYRA following screening (V0) will enter the study at V7 to begin treatment with Juvéderm HA facial fillers, SkinMedica, and BOTOX Cosmetic, as indicated in the study design diagram (Figure 4.1).

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 (screening, V0) in the Rasch-transformed score of the FACE-Q Satisfaction with Facial Appearance Overall Scale to the final study visit (V12).

4.2.2 Key Secondary Endpoints

4.2.2.1 FACE-Q Questionnaires

- Subject's assessment of expectations of life change as measured by the mean change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Expectations scale to final study visit (V12)
- Subject's assessment of age-related facial appearance as measured by the mean change from screening before any treatment in the Rasch-transformed score of the FACE-Q Aging Appraisal to final study visit (V12)
- Subject's assessment of psychological well-being as measured by the mean change from screening before any treatment in the Rasch-transformed score the FACE-Q Psychological Function Scale to final study visit (V12)
- Subject's assessment of social function as measured by the mean change from baseline before any treatment in the Rasch-transformed score of the FACE-Q Social Function scale to final study visit (V12)

- Subject's assessment of overall satisfaction with skin as measured by the mean change from screening before any treatment in the Rasch-transformed score of the FACE-Q Satisfaction with Skin to final study visit (V12)

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 (V12); responders are defined as having achieved a younger category.

4.2.3 Other Secondary Endpoints

4.2.3.1 Global Aesthetic Improvement Scale

- Change in investigator's assessment of global facial aesthetic improvement as measured by the 5-point global aesthetic improvement scale (GAIS) at final study visit (V12)
- Change in subject's assessment of global facial aesthetic improvement as measured by the 5-point GAIS at final study visit (V12)

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)

[redacted]

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 (V12). Serious adverse events (SAEs) will be reported within the specified time and format directly to Allergan and SkinMedica as described in Section 10.8.1.

4.4 Blinding and Randomization

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

5 Selection of Subjects

Approximately 60 subjects will be enrolled at approximately 7 sites in Canada. 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.

Applies to BELKYRA Subjects Only

1. Clinical report of Grade 2 or 3 on the submental fat rating scale (SMFRS; [redacted]).
2. Subject report of dissatisfaction with submental area; rating of 0, 1, or 2 using the subject self-rating scale (SSRS; [redacted]).

Applies to All Subjects

1. 30 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

[redacted]

5. Willing to avoid direct and prolonged sun exposure to the facial skin, which includes tanning beds, for the duration of the study

[redacted]

[redacted]

5.2 Exclusion Criteria

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

Applies to BELKYRA Subjects Only

1. History of any intervention to treat SMF (eg, liposuction, surgery, or lipolytic agents)
2. History of trauma associated with the chin or neck areas that in the judgment of the investigator may affect evaluation of safety or efficacy of treatment
3. An anatomical feature (eg, predominant subplatysmal fat, loose skin in the neck or chin area, prominent platysmal bands) for which reduction in SMF may, in the judgment of the investigator, result in an aesthetically unacceptable outcome

4. Evidence of any cause of enlargement in the submental area (eg, thyroid enlargement, cervical adenopathy, ptotic submandibular gland) other than localized SMF
5. Any medical condition (eg, respiratory, cardiovascular, hepatic, neurological disease, or thyroid dysfunction) that would interfere with assessment of safety or efficacy or compromise the subject's ability to undergo study procedures or give informed consent

Applies to All Subjects

[redacted]

2. Body mass index (BMI) > 30
3. Known allergy or sensitivity to the study products or their components
4. Pregnant, lactating, or planning to become pregnant at any time during the study
5. Received BOTOX Cosmetic or treatment with any other botulinum toxin product for any condition within 6 months before enrollment
6. Received (or is planning to receive) anticoagulation, antiplatelet or thrombolytic medications (eg, warfarin) or other substances known to increase coagulation time from 10 days prior to injection and up to 3 days post-injection
7. 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
8. 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
9. 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

[redacted]

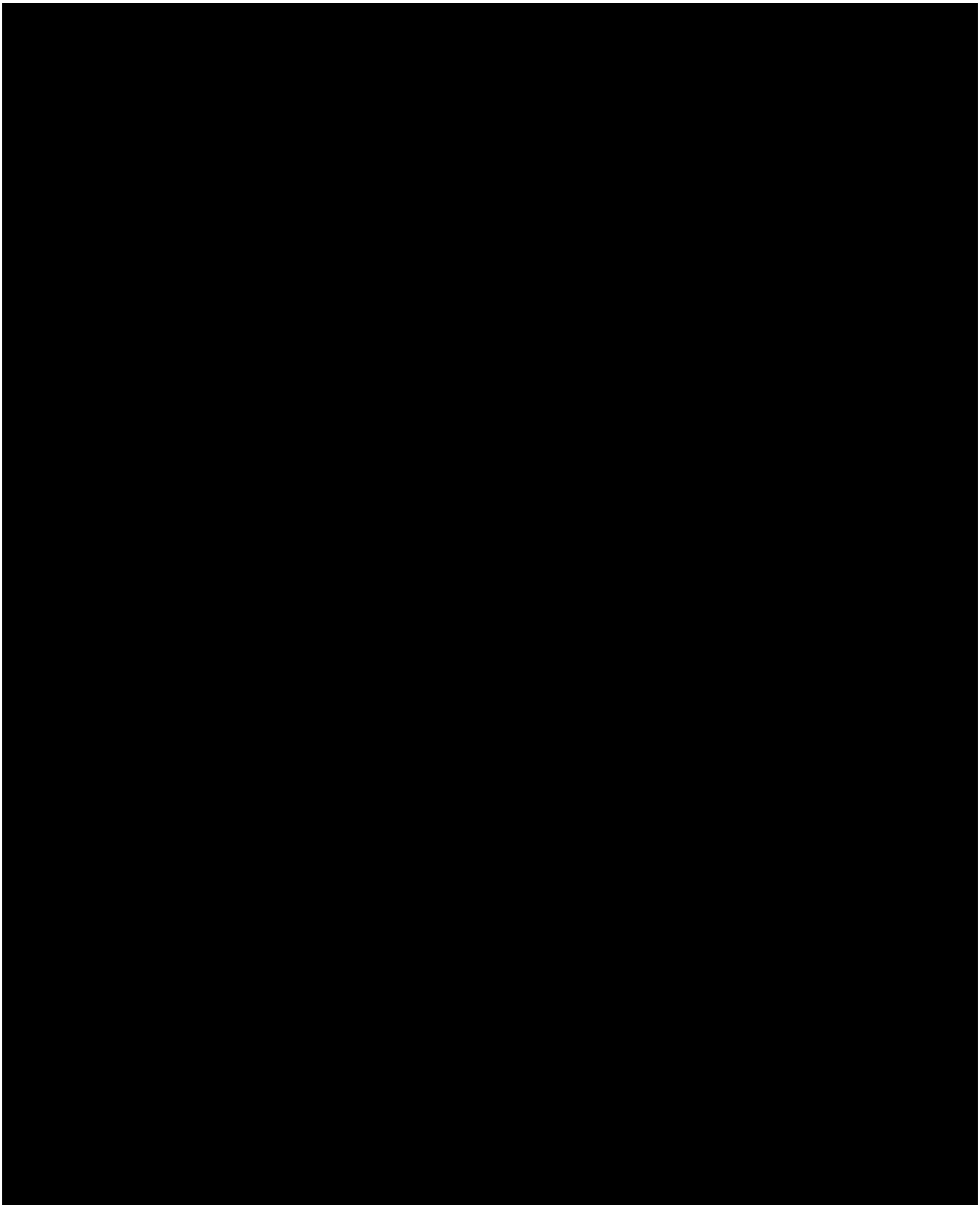
11. Lip tattoos, facial hair or scars that would interfere with visualization of the lips and perioral area for the effectiveness assessments
12. At any proposed injection site, presence of inflammation, infection at any injection site or systemic infection (study entry may be postponed until one week following recovery), noticeable acne scarring, cancerous or pre-cancerous lesion, or unhealed wound or have undergone radiation treatment in the area to be treated
13. Received any investigational product within 60 days prior to study enrollment or planning to participate in another investigation during the course of this study
14. An employee (or a relative of an employee) of the investigators, Allergan, or representative of Allergan
15. 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
16. Current use of oral corticosteroids
17. Current use of nonsteroidal anti-inflammatory drugs (NSAIDs) (eg, aspirin, ibuprofen), from 10 days prior to injection up to 3 days post-injection
18. 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
19. Systemic retinoid therapy within one year prior to study enrollment

[redacted]

21. 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
22. Current use of aminoglycoside antibiotics, curare-like agents, or agents that might interfere with neuromuscular (skeletal) function
23. Profound atrophy/excessive weakness of muscles in target areas of injection
24. History of facial nerve palsy
25. Anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study treatment)
26. Very thin skin in the mid-facial region
27. Tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, ie, significant convexity or projection from the infraorbital fat pads
28. Mid-face volume deficit due to congenital defect, trauma, abnormalities in adipose tissue related to immune-mediated diseases such as generalized lipodystrophy (eg, juvenile dermatomyositis), partial lipodystrophy (eg, Barraquer-Simons syndrome), inherited disease, or human immunodeficiency virus–related disease
29. Undergone oral surgery or other dental procedures (eg, tooth extraction, orthodontia, or implantation) within 30 days prior to enrollment or be planning to undergo any of these procedures during the study
30. Subjects with neuromuscular disorders including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise
31. Subjects with a history of allergies or hypersensitivity to HA 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.



6 Study Plan and Procedures

6.1 Study Subject Number

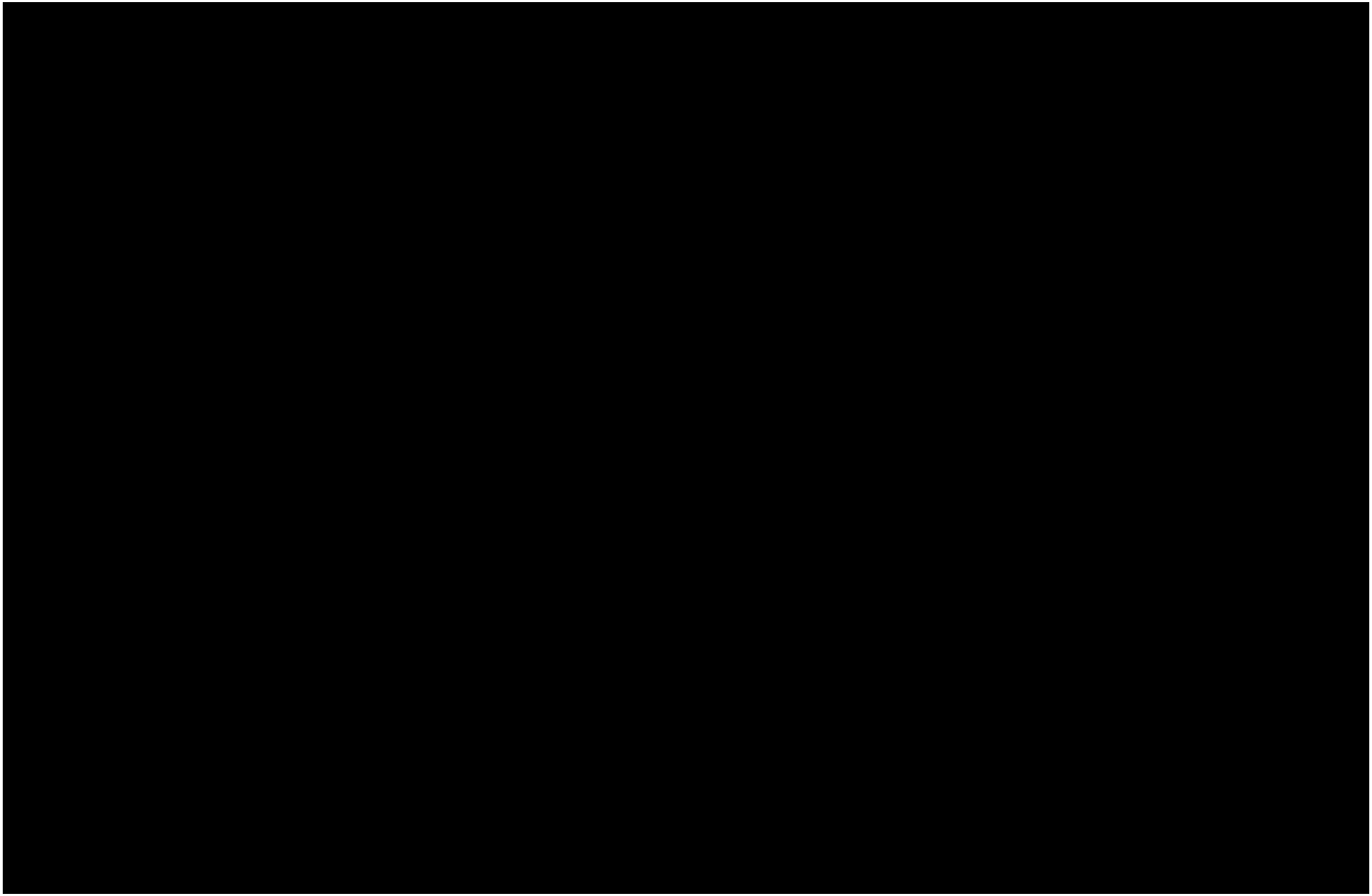
Subjects who meet all inclusion/exclusion criteria will be assigned a subject enrollment number via the electronic data system that will serve as the subject identification number on all study documents.

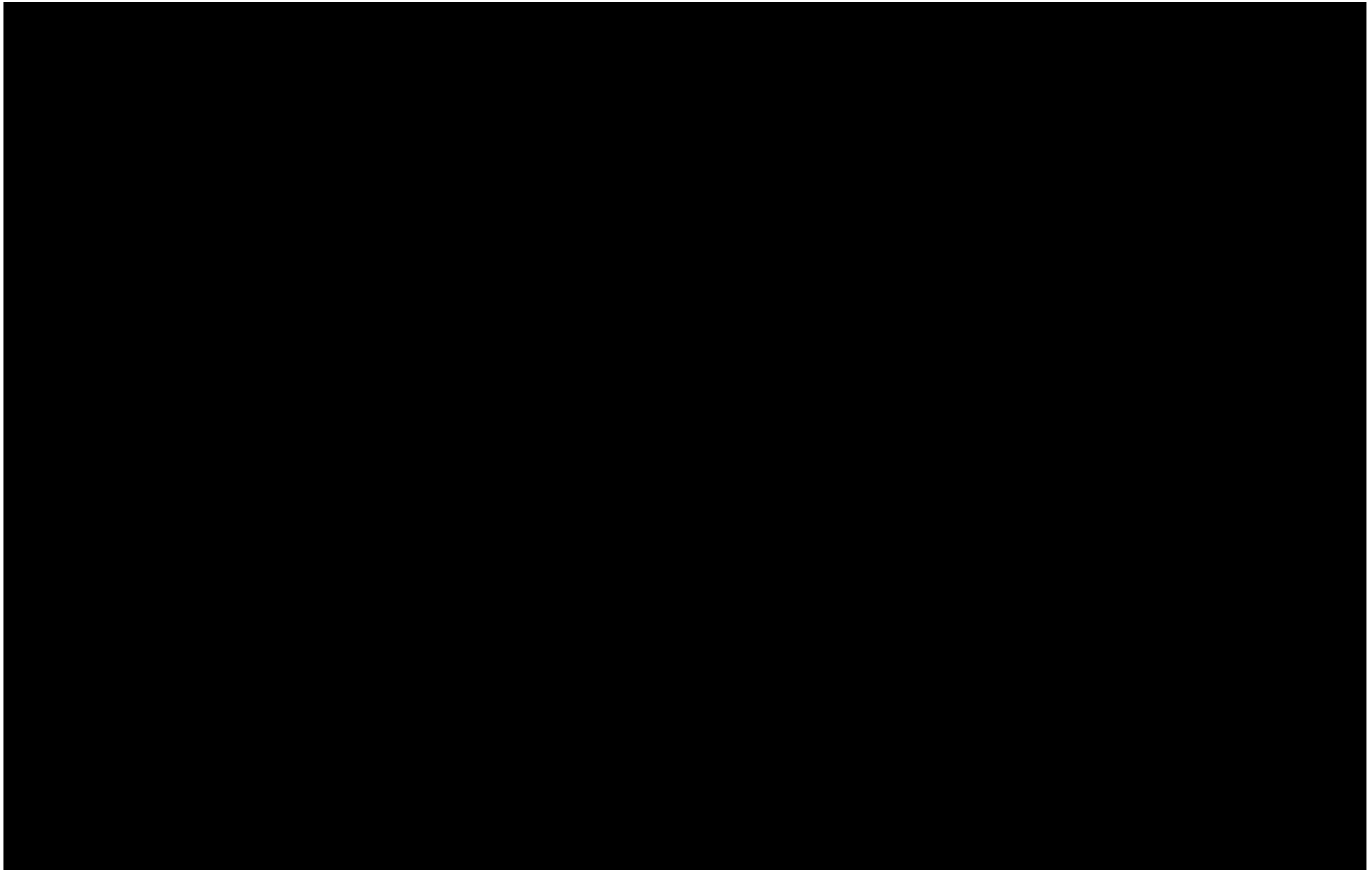
6.2 Description of Study Days

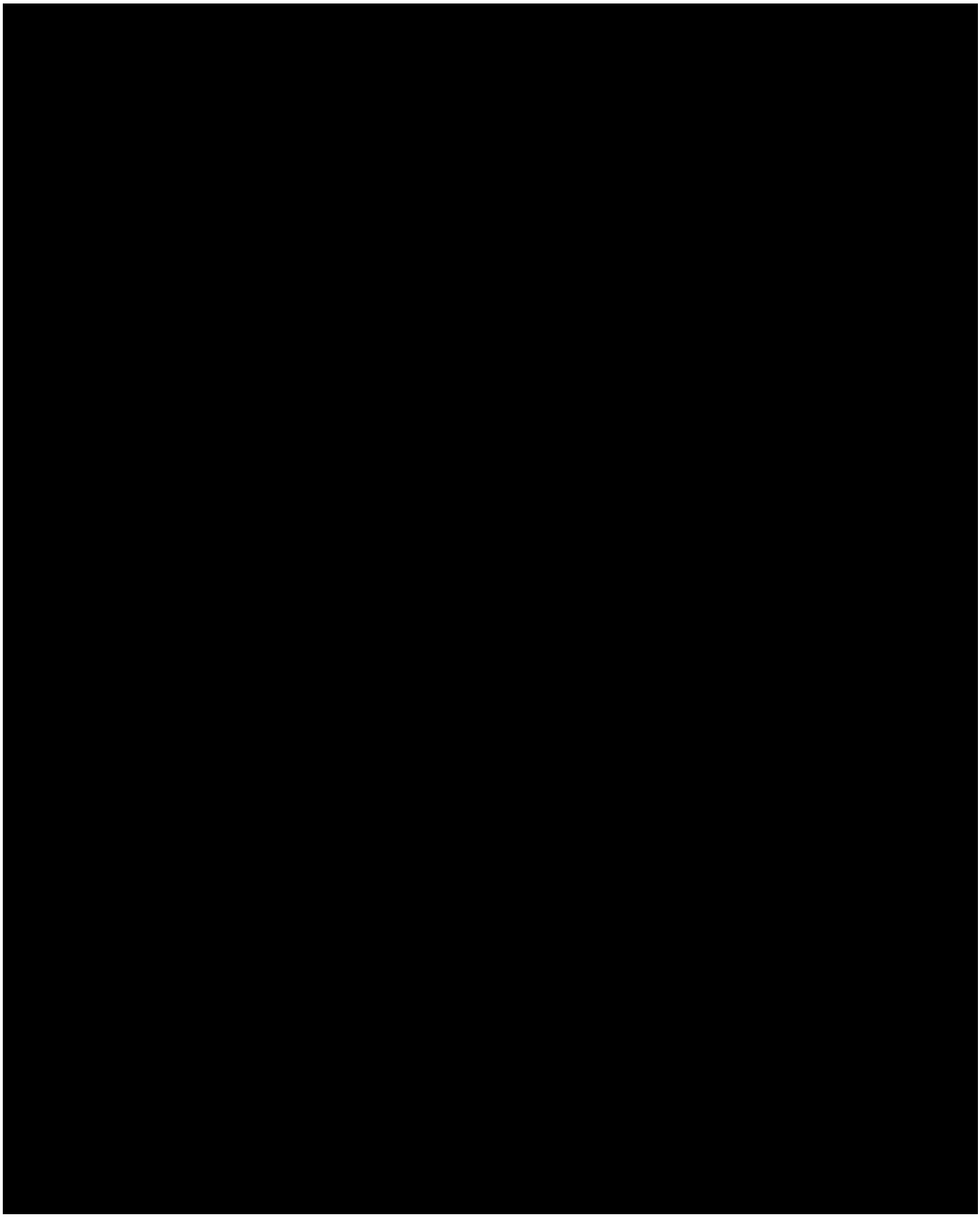
Study procedures, treatments, and assessments will be performed at the study visits as listed below and as shown in Table 6.1.

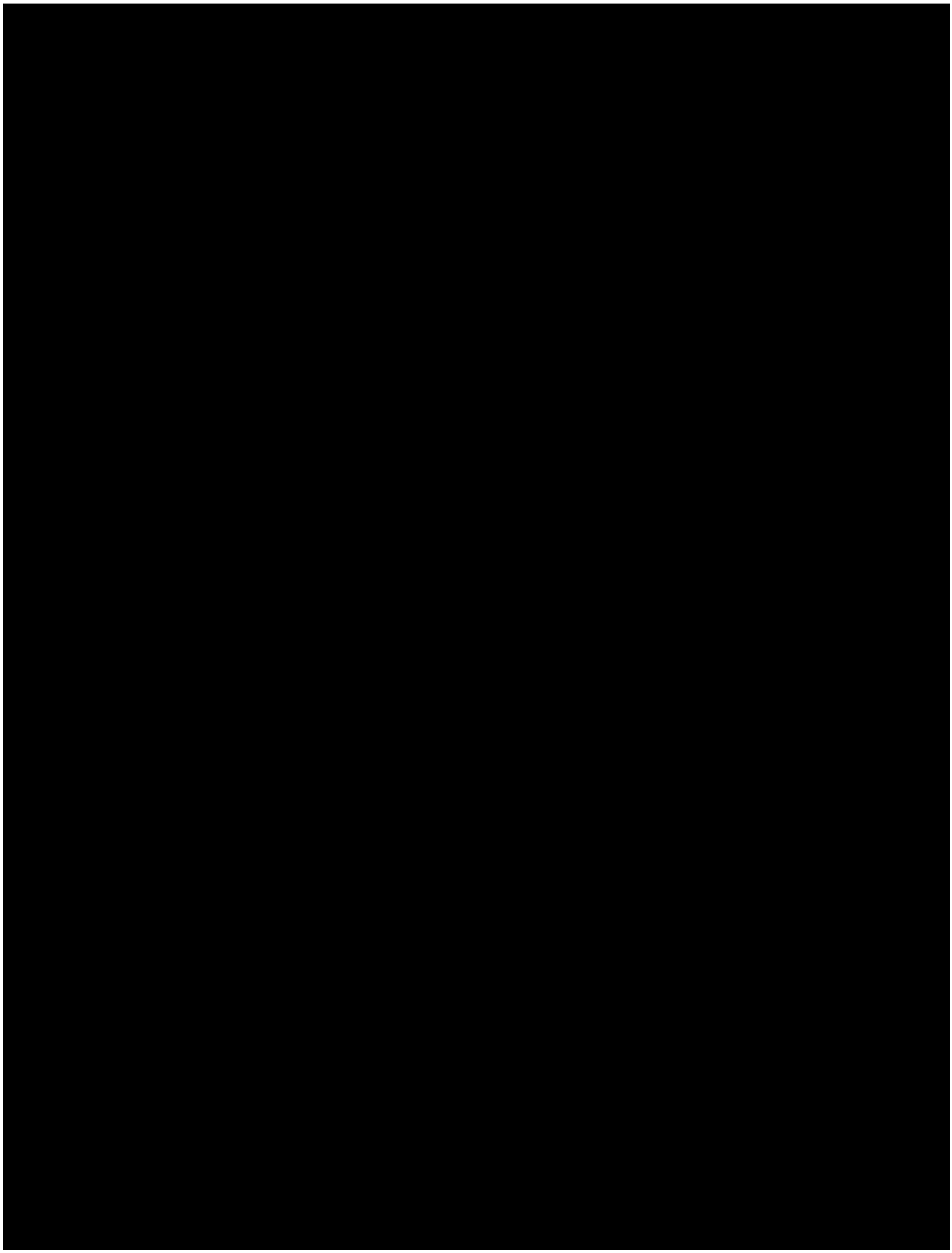
Table 6.1 Schedule of Study Procedures, Treatments, and Assessments

[redacted]









[redacted]

6.2.4 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.

6.2.5 Restrictions and Precautions

6.2.5.1 Prohibited Medications and/or Treatments

Subjects must not undergo any type of facial plastic or reconstructive surgery or cosmetic procedure (eg, 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, Allergan or Allergan's

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

6.2.5.2 Special Diet or Activities

Within the first 24 hours after filler treatment, on V7, and if a touch-up treatment is performed on V8 and V9, 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.

7 Methods of Assessment and Endpoints

7.1 Demographic Data

At the Screening Visit (V0), subject demographic data will be collected. These data include age and gender.

7.2 Medical History

At the Screening Visit (V0), a medical history will be obtained from each subject. Medical history includes a detailed history of prior cosmetic procedures, with start and stop dates, if applicable, as well as any discontinuations due to intolerability or toxicity.

7.3 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.

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).

7.4 Pregnancy

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.

7.5 Clinical Scales for Treatment Inclusion Only

- Investigator's assessment of the severity of GLs at maximum frown using the FWS with photonumeric guide ([redacted])
- Investigator's assessment of the severity of CFLs at maximum smile using the FWS with photonumeric guide ([redacted]
- Investigator's assessment of the severity of FHLs at maximum eyebrow elevation using the FWS with photonumeric guide ([redacted])

- Investigator's assessment of the subject's facial photodamage severity using the 10-point SOPS ([redacted]
- Investigator's assessment of the subject's SMF using the 5-point SMFRS [redacted]
- Subject's assessment of self-appearance using the 7-point SSRS ([redacted]

7.6 Efficacy Endpoint Measurements

7.6.1 FACE-Q

- Subject's assessment overall facial appearance as measured by the FACE-Q Satisfaction with Facial Appearance Scale [redacted]
- Subject's assessment of expectations of life change as measured by the FACE-Q Expectations Scale ([redacted]
- Subject's assessment of age-related facial appearance as measured by the FACE-Q Aging Appraisal ([redacted]
- Subject's assessment of psychological well-being as measured by the FACE-Q Psychological Function Scale ([redacted]
- Subject's assessment of social function as measured by the FACE-Q Social Function Scale ([redacted]
- Subject's assessment of overall satisfaction with skin as measured by the FACE-Q Satisfaction with Skin Questionnaire ([redacted]

7.6.2 Self-Perception of Age Questionnaire

- Subject's assessment of age-related facial appearance as measured by the SPA Questionnaire ([redacted]

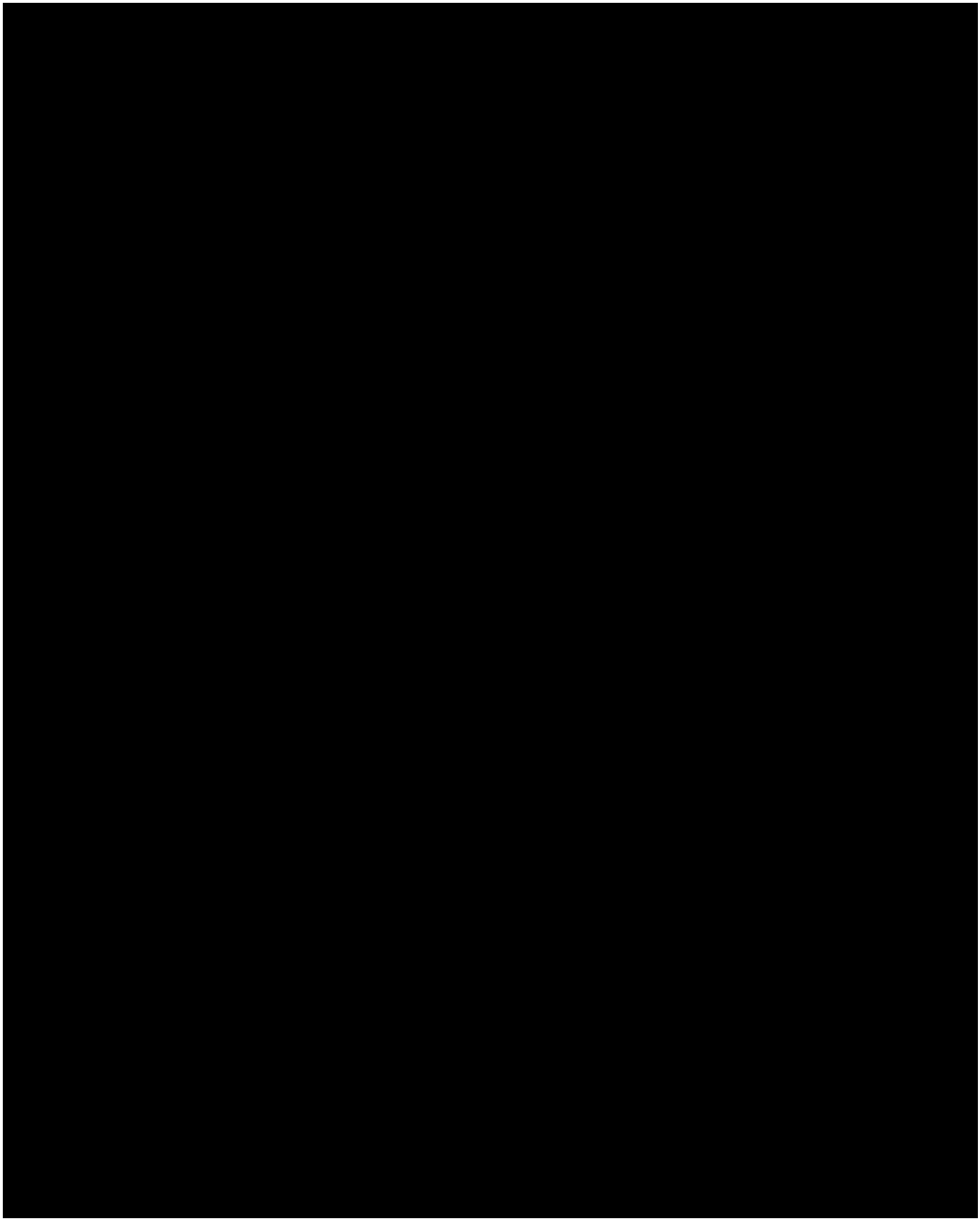
7.6.3 Global Aesthetic Improvement Scale

- Investigator's assessment of global facial aesthetic improvement as measured by the 5-point GAIS ([redacted]
- Subject's assessment of global facial aesthetic improvement as measured by the 5-point GAIS ([redacted]

7.6.4 Periorbital Aesthetic Appearance Questionnaire

- Subject's assessment of periorbital area as measured by the PAAQ ([redacted]

[redacted]



8 Discontinuation Criteria

8.1 Early Discontinuation of the Study

An investigator may stop the study at his/her study site at any time. Allergan, as 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, Allergan, 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 Allergan 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 Allergan, study monitor, the REB, or any regulatory agency by the investigator

If the study is prematurely terminated or suspended due to safety issues, Allergan 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 Allergan or by the investigator, as specified by the applicable regulatory requirements. If a premature termination or suspension occurs, Allergan 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 Allergan 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 Cosmetic
- BELKYRA
- JUVÉDERM VOLITE, JUVÉDERM VOLBELLA with Lidocaine, JUVÉDERM VOLIFT with Lidocaine, and/or JUVÉDERM VOLUMA with Lidocaine
- SkinMedica products

[redacted]

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

Allergan 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 Allergan.

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 and Concomitant Treatments

No product licensed in Canada is approved as a rescue medication. Administration of hyaluronidase is considered to be "off-label" and has not been provided as a part of the study regimen and 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, then 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 Allergan. A representative of Allergan 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, eg, 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

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 temporarily 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 (ie, 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.

The daily skin care products (SkinMedica) utilized by subjects are not considered to be investigational products in this study. SkinMedica-related AEs will be handled per SkinMedica Standard Operating Procedures for Postmarketing Safety.

10.2 Medical Device

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 it is 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, discoloration, and other. 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 be recorded and followed to resolution on the AE eCRF. If an ISR is ongoing or appears 30 days after the subject's last study visit, it will be followed up by Allergan 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 an Allergan Inc. representative and recorded in the appropriate CRFs.

The Investigator must:

1. Notify Allergan Inc. immediately. For Emergency Phone Numbers see front of protocol. Fax completed Unusual Failure in Efficacy reporting form to: [redacted]
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

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: Allergan considers all cancer AEs as SAEs. Pregnancy by itself is not generally considered an AE. The occurrence of an adverse pregnancy outcome may constitute 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.

10.6 Unanticipated Serious Adverse Device Effects

An unanticipated 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 Allergan 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, eg, 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 (eg, "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.

10.8 Adverse Events and Pregnancy

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 AR report. Reports of pregnancy exposure with no associated adverse reactions 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).

10.8.1 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.

10.8.2 Pregnancies

The investigator and each subject will determine the appropriate method of contraception for the subject during the participation in the study.

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.

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 or elective abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.4. 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.

10.9 Serious Adverse Event Reporting

10.9.1 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 Allergan on 2 SAE forms. The drug, and device SAE forms must be recorded and e-mailed per this protocol section (including to the SkinMedica Safety Contact below from V7 to V12). All subjects with an SAE must be followed up and the outcomes reported.

The principal investigator must supply Allergan and the REB with any additional requested information (eg, hospital discharge summary, autopsy reports and terminal medical reports) only upon request. Allergan 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 Allergan immediately (within 24 hours) using the SAE reporting forms. Emergency phone numbers and relevant Allergan personnel contacts are below.
2. Obtain and maintain in his/her files of all pertinent medical records, information, and medical judgments from colleagues who assisted in the treatment and follow-up of the subject.
3. Provide Allergan with a complete, written case history (AE report form), including copies of supporting reports (eg, 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.
4. 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.

10.9.2 Serious Adverse Event Contact Information

SAE Reporting Information: BOTOX® Cosmetic, and BELKYRA

[redacted]

SAE Reporting Information: JUVÉDERM® VOLBELLA® with Lidocaine, JUVÉDERM® VOLIFT with Lidocaine, JUVÉDERM® VOLUMA® with Lidocaine, and JUVÉDERM® VOLITE®, BELKYRA Skin Grid

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 a 0.05 significance level (2-sided). In this study, BELKYRA and without BELKYRA is the major treatment difference between enrolled subjects. Hence, unless specified, all endpoints will be summarized by those two groups (BELKYRA and without BELKYRA) and overall respectively. However, this study is not designed to compare the efficacy and safety outcomes between subjects treated with BELKYRA and those treated without BELKYRA. All discussion and interpretation related to study outcomes will be mainly focused on the overall results.

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. For BELKYRA subjects who complete this study, the final visit will be their V12 visit; for subjects who will not be treated with BELKYRA, this visit will also be the V12 visit after approximately 5 months of treatment. Subjects who discontinue 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:

- Full Analysis Population – all subjects who have met all eligibility criteria at the screening visit (V0) and received any product used as treatment in this study.
- Safety Population – defined the same as Full Analysis Population.
- Evaluable Population– all subjects as defined in the Safety Population who have had at least one post-treatment efficacy assessment at the final visit (V12).

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

11.1.2 Subgroups

Two subgroups will be examined separately:

- Gender: As male and female subjects may have differing expectations/perceptions of aesthetic improvement, they will be examined separately.
- BELKYRA: As it is expected that approximately two-thirds of the enrolled population will not be treated with BELKYRA, subjects treated and not treated with BELKYRA will be examined separately.

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 compare post-treatment assessment values to the subject's corresponding baseline assessment value, and will be based on the Evaluable Population.

11.4.1 Primary Efficacy Analysis

The primary efficacy endpoint is the change from baseline to the final visit (V12) in the overall Rasch-transformed scores of the FACE-Q Satisfaction with Facial Appearance Scale. This will be analyzed using paired t-test (or Wilcoxon signed-rank test if normality assumptions are not met).

[redacted]

11.4.3 Missing Data

Missing data strategy will be documented in the SAP.

11.4.4 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. SAEs will be coded using MedDRA version 17.0 or higher, and presented by system organ class and preferred term.

11.5 Interim Analyses and Data Monitoring

No formal interim analyses are planned for this study.

11.6 Determination of Sample Size

A sample size of 48 subjects will provide 90% power to detect whether 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 20.0. This calculation is based on a 1-sample, 2-sided t-test at 5% significance level. The assumptions of mean and standard deviation are based on FACE-Q results from Allergan HARMONY Study GMA-CMB-14-001. With a 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. From the 60 subjects planned to enroll in this study, approximately 20 subjects will be treated with BELKYRA.

PASS 2008 software was used to calculate the sample size.

11.7 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.

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, Allergan, or the governing health authorities including Health Canada if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

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

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 Health Canada 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 Allergan in a timely manner at the completion of the study, or as otherwise specified by Allergan.

The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing. Any change or correction to data reported on an eCRF shall be dated, initialed and explained, if necessary, and shall not obscure the original entry (ie, 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. Allergan, as the sponsor, has proprietary interest in this study. Authorship and manuscript composition will reflect joint cooperation between study investigators and Allergan personnel. Authorship will be established prior to the writing of the manuscript. As this study involves multiple centers, no individual publications will be allowed prior to completion of the final report of the multicenter study except as agreed with Allergan.

12.11 Discontinuation of the Study

It is agreed that, for reasonable cause, either the investigator or Allergan may terminate the investigator's participation in this study after submission of a written notice. Allergan may terminate the study at any time upon immediate notice for any reason, including the Allergan'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. Allergan-specific essential documents are to be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents are to be retained for a longer period, however, if required by the applicable regulatory requirements or if needed by Allergan.

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