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General and Plastic Surgery Devices Panel

FDA Advisory Committee Briefing Document

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JUVÉDERM VOLUMA™ XC

PMA P110033

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4. TERMS AND ABBREVIATIONS

Term/Abbreviation	Definition
AE	Adverse event
BDDE	1,4-butanediol diglycidyl ether
CFR	Code of Federal Regulations
COC	Cyclicolefin co-polymer
CRF	Case report form
CTR	Common treatment site response
DCF	Data clarification form
EI	Evaluating Investigator
FAE	Facial Appearance Evaluation
FLO	Facial Lines Outcome
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice
HA	Hyaluronic acid
IDE	Investigational Device Exemption
Initial Treatment	First treatment session
Initial Treatment Period	Initial Treatment + Touch-up Treatment, separated by approximately 30 days
IRB	Institutional Review Board
LAF	Look and Feel
LAFM	Look and Feel of Mid-Face
MFVDS	Mid-Face Volume Deficit Scale
mITT	Modified intent-to-treat
NLF	Nasolabial fold
NLFS	NLF Severity Scale
OAFM	Other Aesthetic Features of the Mid-Face
PP	Per protocol
PRO	Patient reported outcomes
Repeat Treatment	Optional, complimentary treatment offered 12-24 months after initial treatment period
SAE	Serious adverse event
SPA	Self-Perception of Age
TI	Treating Investigator
Touch-up Treatment	Treatment to reach optimal correction, if necessary, performed within the initial treatment period

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5. EXECUTIVE SUMMARY

This briefing document summarizes the data from the Allergan Premarket Approval (PMA) application for JUVÉDERM VOLUMA™ XC injectable gel, hereafter referred to as VOLUMA™ XC, for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face. This PMA is currently under review by the Office of Device Evaluation (ODE) within the Center for Devices and Radiological Health (CDRH) of the US Food and Drug Administration (FDA).

One of the effects of aging is the gradual formation of wrinkles, folds, and lines, and loss of volume loss, resulting in dramatic changes to the overall contour of the face. Mid-face volume deficit is one of the changes that takes place in varying degrees as people age, with lost soft tissue revealing the bony structural elements of the face. The appearance and condition of facial skin may communicate not only age, but also vitality.[1] A youthful appearance has been associated with increased self-esteem and improved social relations.[2] Thus, patients and physicians seek safe and effective treatment options which are specific for the facial region being addressed to help them fulfill their individual treatment goals.

The clinical need to replace lost facial volume is reflected in FDA approval of the first dermal filler device over 30 years ago. Since that time, multiple dermal fillers have been approved for injection into the mid to deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds). Due to its highly favorable safety and effectiveness profile, the majority of these approvals have been for hyaluronic acid fillers.

Recently, a more comprehensive understanding of the effects of the aging process on tissue volumes has led to increased focus on volume restoration to correct tissue sagging and address fat loss in the face. Addressing overall volume loss has begun to take the place of merely filling winkles and folds. This paradigm shift in the approach to facial rejuvenation prompted the development and evaluation of VOLUMA™ XC for the correction of age-related mid-face volume deficit. The proposed indication statement for VOLUMA™ XC is as follows:

> JUVÉDERM VOLUMA™ XC is indicated for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face.

VOLUMA™ XC is a transparent, biodegradable, sterile, crosslinked, hyaluronic acid hydrogel formulated to neutral pH in a physiological buffer. Similar to members of the

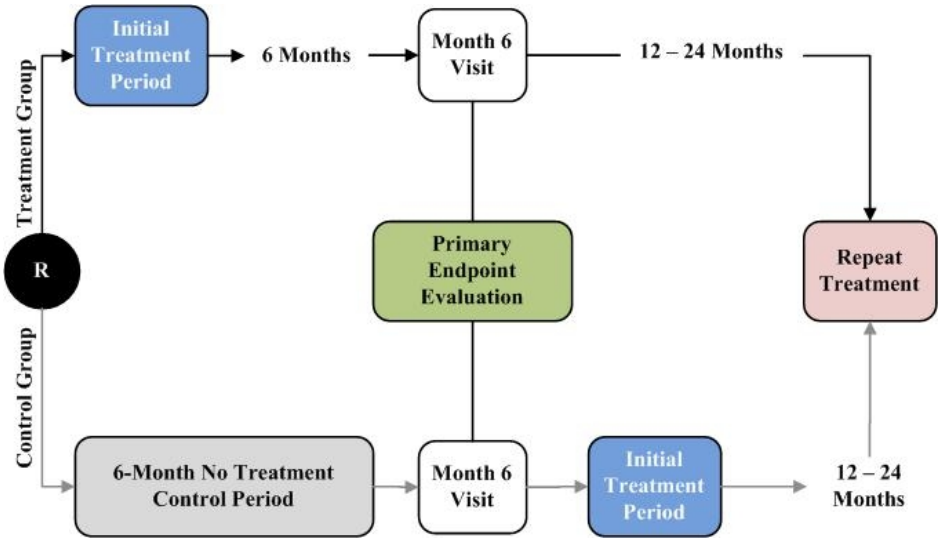
JUVÉDERM® family, approved and marketed in the US and worldwide for correction of moderate to severe wrinkles, VOLUMA™ XC is composed of hyaluronic acid biosynthesized by *Streptococcus equi*, chemically crosslinked with 1,4 butanediol diglycidyl ether, includes 0.3% lidocaine to reduce pain upon injection, and is provided in a 1 mL plastic syringe. However, VOLUMA™ XC differs from the members of the JUVÉDERM® family in strategic physical and chemical characteristics that make it better suited for the prospective indication: restoration of age-related mid-face volume deficit.

In preclinical testing, the biocompatibility of VOLUMA™ XC was evaluated in accordance with the International Standards Organization (ISO) 10993. The results demonstrated that VOLUMA™ XC is non-cytotoxic, a non-irritant, non-toxic, non-sensitizing, non-genotoxic, non-pyrogenic, and well tolerated.

Based on these positive biocompatibility results and an extensive data package presented to countries outside the US, the VOLUMA™ formulation without lidocaine was first approved for use in Europe starting in 2005. World-wide approval of VOLUMA™ XC (identical in formulation, but with lidocaine incorporated) began in 2009. As of December 31, 2012, VOLUMA™ and VOLUMA™ XC have been approved in over 60 countries including Canada and countries in the EU, and more than 520,000 syringes of VOLUMA™ and VOLUMA™ XC have been sold. Post-market surveillance data has revealed a similar safety profile to other marketed hyaluronic acid based dermal fillers.

A clinical trial of VOLUMA™ XC (protocol VOLUMA-002) has been conducted in the US and Canada to support US FDA approval. The primary objective of VOLUMA-002 was to evaluate the safety and effectiveness of VOLUMA™ XC for age-related cheek augmentation in the mid-face. Subjects with moderate to severe age-related mid-face volume deficit were followed for up to 24 months following treatment with VOLUMA™ XC. Under the study design, subjects were assigned to either receive treatment with VOLUMA™ XC, or to participate in a “no-treatment” control group, where treatment would be delayed until after the primary 6-month follow-up period. At the end of the 12-24 month follow-up period, an optional repeat treatment with an additional 12 months scheduled follow-up was offered to all subjects (Figure 1).

Figure 1. VOLUMA-002 Clinical Study Design



In this study, a responder was defined as a subject with a ≥1 grade improvement on the validated photometric Mid-Face Volume Deficit Scale (MFVDS) compared to baseline. VOLUMA™ XC was determined to be clinically effective if the treatment group's Month 6 responder rate was:

1. at least 70% *and*
2. statistically superior to the responder rate for the "no-treatment" control

The primary endpoint was based upon the average of 2 blinded Evaluating Investigators' assessments of overall mid-face volume deficit. The MFVDS is a 6-point photometric scale that has been independently validated for use in assessing the degree of mid-face volume deficit in males and females, where a 1-point change was shown to be clinically different.

Both criteria for the primary endpoint were met:

- **85.6% of subjects in the Treatment Group were responders ($p < 0.0001$) *and***
- **the responder rate for the Treatment Group was significantly greater ($p < 0.0001$) than the responder rate for the Control Group (a difference of 46.7 percentage points) at Month 6**

Subjects used daily diaries to report any treatment site responses experienced during the first 30 days after any study treatment. These treatment responses were as expected with implantation of an HA filler. The most frequently reported responses were tenderness (92.1% of subjects), swelling (85.7% of subjects), and firmness (82.3% of subjects). These

treatment responses were typically rated as mild to moderate in severity (80.7% of subjects) and lasted 2 weeks or less for the majority (55.4%) of subjects.

Any treatment response that was ongoing at the end of the 30-day diary was automatically recorded as an adverse event (AE) by the Treating Investigator. AEs could also be reported at any time by subjects or Treating Investigators. The most frequent device-related AEs following treatment were injection site mass (i.e., lumps and bumps, 18.9% of subjects) and injection site induration (i.e., firmness, 14.1% of subjects). Device-related AEs were typically mild to moderate in severity (87.7% of events).

There were no unexpected histological results or unanticipated adverse device effects. One subject died due to a stroke one year after treatment, and the death was considered to be unrelated to the device or procedure. Eleven treated subjects experienced 16 serious adverse events (SAEs); 3 of the 16 were related to the device. The 3 device-related SAEs were reported in 2 subjects, and included: 1) lumps at injection sites that were treated with medication (hyaluronidase) and resolved with sequelae of a scar at the biopsy site, 2) an inflammatory reaction under the eye that was treated with medication and resolved, and 3) nodularity in the cheek that was treated with medication and resolved.

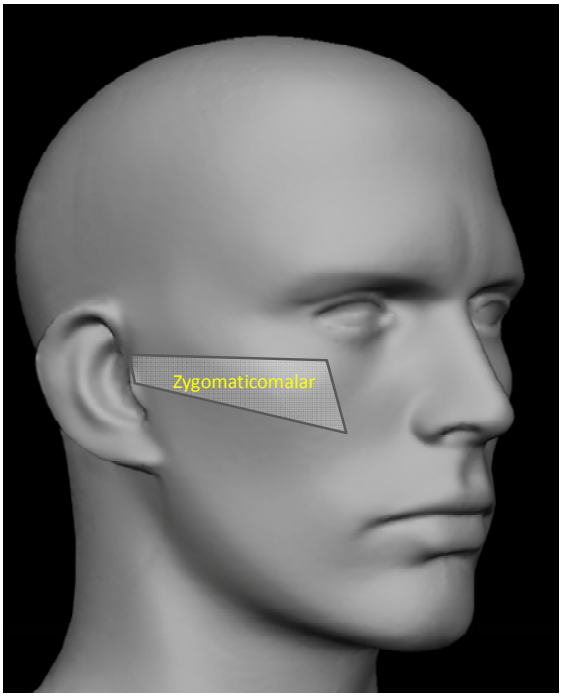
Based on preclinical data, extensive clinical experience outside the US, and clinical data generated from the VOLUMA-002 trial proving to be consistent with what has been observed with global clinical experience, the effectiveness and safety of VOLUMA™ XC have been demonstrated, with the product meeting the pre-specified effectiveness criteria while maintaining an acceptable safety profile. This briefing book describes the appropriateness of VOLUMA™ XC for correction of mid-face volume deficit and details the results of the VOLUMA-002 clinical study.

6. CLINICAL NEED FOR MID-FACIAL VOLUMIZING

Mid-face volume loss is one of the changes that takes place in varying degrees as people age. As the population of Americans seeking the aesthetic, psychological, and social benefits of cosmetic procedures has increased significantly over the last decade, treatment of age-related volume loss represents a growing need in the field of cosmetic medicine.

As is evidenced by 14.6 million cosmetic procedures performed in 2012,[3] which represents a 98% increase since 2000, cosmetic procedures have become more socially accepted, and facial rejuvenation is more than a trivial indulgence. For many, looking young and vibrant has become an important aspect of their career development, earning potential, social interaction, and self-esteem.[4] The youthful face is characterized by a round, full mid-face across the cheek and malar area with prominent cheekbones.[5-9] Although gender, ethnic, and cultural differences must also be considered,[10] the zygomaticomalar complex has been described as the "hallmark of youth" (shown in Figure 2 below).[11] Universally, the mid-facial striated muscles, combined with the skin and subdermal fat, create an anterior convexity from the lower eyelid onto the cheeks, forming a smooth S-shape when viewed from an oblique angle.[8,12]

Figure 2. Zygomaticomalar Complex



Surgical options to treat volume loss in the mid-face include mid-face lift, cheek implants, and lower lid blepharoplasty with fat transposition.[13] However, surgery requires significant time for recovery and exposes the patient to the inherent risks of general anesthesia. Rejuvenation from a pear-shaped to a heart-shaped face should fundamentally involve the process of volume redistribution,[12] with an emphasis on "push" filling (i.e., volumizing) instead of "pull" surgery (i.e., face-lifting) — the new paradigm for aesthetic medicine.[5]

Autologous fat transfer is one filling or volumizing option.[14-18] However, it requires an additional, invasive procedure to harvest the fat, which adds to the risks of this type of treatment. Additionally, patients with little fat available for harvest may not be good candidates for the procedure. The technique for fat transfer is meticulous,[14] but the results are unpredictable due to variable fat cell survival, which may lead to insufficient duration of correction.

The key to minimally invasive rejuvenation of the mid-facial area is volume restoration through re-inflation and re-contouring with injectable dermal fillers.[10] Dermal fillers act by taking up space under and thereby pushing against the skin, providing volume and smoothing the surface. Appropriate volumetric augmentation of the malar area (i.e., the malar bone and zygomatic arch) produces the greatest aesthetic and volumetric change in the contour of the cheek, maximizes the projection of the zygomaticomalar eminence, and accentuates the lateral cheekbone, creating a high, arched appearance.[19] Injection of fillers inferiorly and laterally to the lateral canthus have been reported to make the malar area fuller, lifting the upper cheek skin and restoring the desirable shape of the face.[6]

There are currently no FDA-approved treatments for patients with age-related mid-face volume deficit. As detailed in Section 7, two injectable dermal fillers are currently FDA-approved in the US for volumization of the mid-face, but only in patients with HIV-associated lipoatrophy: Radiesse® (calcium hydroxylapatite particles suspended in a gel carrier consisting primarily of water and glycerin) and Sculptra® (poly-L-lactic acid). Radiesse® achieves its volumizing effect by occupying space in the injection site. The mechanism of action of Sculptra® involves creating a 'scaffold' which promotes the formation of new collagen by the body, rather than by directly replacing lost volume.

HA has emerged as an ideal compound for cosmetic and restorative augmentation of the face, with a history of safe and effective use in the correction of facial wrinkles and folds in the United States beginning in 2003. Due to its mechanism of action (directly replacing lost volume), HA-based dermal fillers provide instant results, allowing the patient and physician to achieve the desired effect during treatment. HA-based dermal fillers are chemically

crosslinked to increase persistence in the body and are naturally broken down over time, providing temporary effects that last up to 12 months or sometimes longer, without the risks associated with surgery or permanent fillers.[10]

Numerous publications have described the use of HA-based dermal fillers for mid-face volumizing.[5,6,8,10,11,17,20-30] Literature suggests HA-based dermal fillers are the "ideal sculptural facial rejuvenation agents, providing a more natural and youthful countenance with greater safety and convenience for the aesthetic subject."[5] Despite the documented use of HA fillers for mid-face augmentation, there are currently no HA fillers approved in the US for this indication.

With the paradigm of facial rejuvenation focusing on restoring the features of a youthful face through volumization, there is a need for safe and effective treatment options for correction of mid-face volume loss for patients seeking treatment of this facial region. While recent advancements in medicine have produced an array of non-surgical, minimally invasive cosmetic treatments for wrinkle correction, the current treatment options for cheek augmentation for the general aging population are limited to plastic surgery and autologous fat transfers. Based on experience with the members of the approved JUVÉDERM® family of HA-based dermal fillers, and with patient needs and expectations in mind, Allergan designed VOLUMA™ XC specifically to be a mid-face dermal filler. Patients may want to look younger and feel more confident but with only a subtle change in appearance that does not suggest a facial treatment was performed. Therefore, Allergan conducted VOLUMA-002, a pivotal clinical study to assess the safety and effectiveness of VOLUMA™ XC as a minimally-invasive option for those desiring age-related mid-face volume restoration.

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7. DERMAL FILLER REGULATORY HISTORY

Various types of dermal filler materials have been approved by the FDA including absorbable, biodegradable biologic materials such as collagen and HA, absorbable synthetic materials (including poly-L-lactic acid and calcium hydroxylapatite), and a nonabsorbable material (polymethylmethacrylate microspheres). Below is a chronological list of the key FDA approvals organized by type of dermal filler material.

- Collagen
  - Zyderm® /Zyplast® (bovine collagen) were approved under PMA P800022 in 1981/1985 (respectively) for use in the dermis for correction of contour deficiencies of this soft tissue
  - Fibrel® (bovine collagen) was approved under PMA P850053 in 1988 for the correction of depressed cutaneous scars
  - CosmoDerm® (recombinant human collagen) was approved under PMA P800022 in 2003 for injection into the superficial papillary dermis for correction of soft tissue contour deficiencies
  - CosmoPlast® (recombinant human collagen) was approved under PMA P800022 in 2003 for injection into the mid to deep dermis for correction of soft tissue contour deficiencies, such as wrinkles and acne scars
  - Evolence® (porcine collagen) was approved under PMA P070013 in 2008 for the correction of moderate to deep facial wrinkles and folds
- HA
  - Restylane® was approved under PMA P020023 in 2003 for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds
  - Hylaform®/Captique®/Prevelle® (avian-derived HA) were approved under PMA P030032 in 2004/2004/2008 (respectively) for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds
  - JUVÉDERM®, including JUVÉDERM® Ultra and JUVÉDERM® Ultra Plus, was approved under PMA P050047 in 2006 for use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds
  - Elevess™ (HA with lidocaine) was approved under PMA P050033 in 2006 for use in mid to deep dermis for correction of moderate to severe facial wrinkles and folds
  - The addition of 0.3% lidocaine hydrochloride into the JUVÉDERM® Ultra and JUVÉDERM® Ultra Plus formulations (named JUVÉDERM® Ultra XC

and JUVÉDERM® Ultra Plus XC, respectively) was approved under PMA P050047 in 2010
    - The addition of 0.3% lidocaine hydrochloride into Restylane® (named Restylane®-L) was approved under PMA P040024 in 2010
    - Restylane® was approved under PMA P040024 in 2011 for lip augmentation
    - Belotero Balance® was approved under PMA P090016 in 2011 for injection into facial tissue to smooth wrinkles and folds
- Poly-L-Lactic Acid (PLLA)
    - Sculptra® was approved under PMA P030050 in 2004 for restoration and/or correction of the signs of facial fat loss (facial lipoatrophy) in people with HIV
- Polymethylmethacrylate (PMMA) Beads
    - Artefill® was approved under PMA P020012 in 2006 for use in the facial tissue around the mouth
- Calcium Hydroxylapatite
    - Radiesse® was approved under PMA P050037 in 2006 for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with HIV
    - Radiesse® was approved under PMA P050052 in 2006 for subdermal implantation for correction of moderate to severe facial wrinkles and folds

As described in the list above, dermal filler devices were, in general, approved for injection into the mid to deep dermis for the correction of moderate to severe facial wrinkles and folds. Within the past 9 years, however, the FDA has approved additional dermal filler indications that reflect the focus on facial volume loss. These indications include restoration and/or correction of signs of facial fat loss (lipoatrophy) in patients with HIV (i.e., Sculptra® and Radiesse®) and submucosal implantation for lip augmentation (Restylane®).

Similarly focusing on facial volume loss, the impetus for designing VOLUMA™ XC was to provide physicians with a product that could volumize the mid-face. In 2005, Juvéderm® VOLUMA (without lidocaine) was CE marked and then introduced into the European market (including over 30 countries). Juvéderm® VOLUMA has now been registered in 40 countries in Europe (including the EU), 11 countries in the Middle East, 10 countries in the Asia Pacific region, 6 countries in Latin America, and Canada. In 2009, VOLUMA™ XC was CE marked and introduced into the European market. VOLUMA™ XC has now been registered in 38 countries in Europe (including the EU), 9 countries in the Asia Pacific region, 7 countries in Latin America, 7 countries in the Middle East, and Canada. The product specifications of Juvéderm® VOLUMA and VOLUMA™ XC are identical with the exception

of lidocaine (VOLUMA™ XC contains 0.3% w/w lidocaine hydrochloride) and are both indicated to restore volume to the face.

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8. DEVICE DESCRIPTION

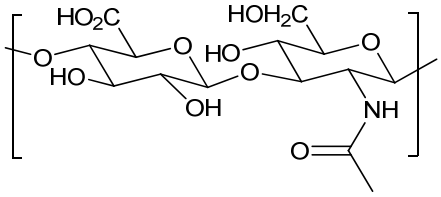
VOLUMA™ XC is a viscoelastic, sterile, non-pyrogenic, non-cytotoxic, clear, colorless, and biodegradable crosslinked HA hydrogel in a physiological buffer, which contains 0.3% lidocaine to reduce pain on injection.

HA is a naturally occurring linear polysaccharide and belongs to the family of structurally similar polysaccharides known as glycosaminoglycans. HA is a major component of the extracellular matrix and is found in most human tissues. This biopolymer serves important biological functions, including assisting with cell migration in the extracellular matrix, contributing to wound healing, and providing protection of structural interfaces.[31] HA is well-known for its lubricious properties and is found in the synovial fluid of joints and the vitreous body of the eye.

HA-based biomaterials have demonstrated a wide range of efficacious uses within the biomedical industry, including ophthalmic, orthopedic, and dermatologic use as a viscoelastic supplement, wound dressings to prevent post-surgical adhesion, and for soft-tissue augmentation, respectively.

The chemical structure of HA is shown in Figure 3. It is comprised of a repeating disaccharide of D-glucuronic acid and *N*-acetyl-D-glucosamine linked by β-1,4-glycosidic bonds. Due to the carboxylic acid present on the D-glucuronic acid, under physiologic conditions, HA is anionic in nature.

Figure 3. Hyaluronic Acid



HA solutions are highly viscoelastic, meaning that they demonstrate both viscous and elastic behavior when undergoing deformation.[32] The viscoelastic nature of HA is attributed to both inter- and intra-molecular hydrogen bonding. These interactions are primarily responsible for the high solubility and retention of water in HA. Therefore, HA is extremely hygroscopic and in aqueous solutions forms a 3-dimensional hydrated network. It has been reported that 1 gram of HA can bind up to 6 L of water.[33] Taking advantage of HA's ability to bind large amounts of water and its inherent viscoelastic properties, HA-based biomaterials have

demonstrated excellent use as dermal fillers, as evidenced by the numerous FDA-approved HA-based dermal fillers.

The HA in VOLUMA™ XC is obtained by bacterial fermentation using *Streptococcus equi.* This non-animal origin reduces the risk of developing an immunological response to exogenous animal proteins. During fermentation, the bacteria secrete HA. After fermentation, bacterial growth is stopped by heat treatment, and the bacteria are removed by filtration. The HA fibers are then purified to meet the purity specifications set forth in the European Pharmacopeia for sodium hyaluronate (EP Monograph 1472).

Degradation of HA is rapid in vivo, and unstabilized (i.e., uncrosslinked) HA is readily cleared from the body, either enzymatically or by oxygen derived free radical degradation.[35] Therefore, the polysaccharide must be stabilized through chemical crosslinking. Crosslinking decreases the rate of degradation and therefore improves HA's persistence locally at the site of injection.[36] It creates a robust network, and in addition to reducing the rate of degradation, it allows for the opportunity to fine-tune the desired physicochemical properties.[32]

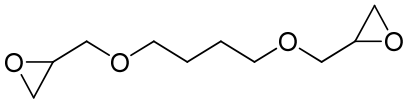
Several methods of crosslinking have been described in the literature.[37] Generally, each of these methods forms a chemical bond between the crosslinking agent and HA, thereby forming a stable gel matrix.

The HA dermal fillers currently approved by FDA use 3 different crosslinking agents:

(1) Divinyl sulfone – used for crosslinking of Hylaform®, Captique®, and Prevelle® (P030032)
(2) Biscarbodiimide – used for crosslinking of Elevess® (P050033)
(3) 1,4 Butanediol diglycidyl ether (BDDE) – used for crosslinking of JUVÉDERM® 30, Ultra, Ultra Plus, Ultra XC, and Ultra Plus XC (P050047); Restylane® and Perlane® (P040024); and Belotero® Balance (P090016)

VOLUMA™ XC is crosslinked using BDDE. The chemical structure of BDDE is shown in Figure 4. Crosslinking is performed in an alkaline solution, and subsequent to the crosslinking reaction, unreacted BDDE is removed from the gel matrix via dialysis.

Figure 4. Chemical Structure of BDDE



In addition, lidocaine hydrochloride is mixed into the gel during homogenization to a final concentration of 0.3% w/w.

Lidocaine is the most widely used local anesthetic, with 50 years in the market; it has been extensively used in dentistry and in various specialties of medicine such as urology, ophthalmology, and dermatology. Lidocaine has also been used in the formulation of collagen-based dermal fillers such as Zyderm®, Zyplast®, CosmoDerm®, and CosmoPlast® as well as the more recently approved HA-based dermal fillers such as JUVÉDERM® Ultra XC, JUVÉDERM® Ultra Plus XC, Elevess®, Prevelle Silk®, Restylane-L®, Perlane-L®, and the PMMA microsphere formulation Artefill®. It is well established in the literature that patients feel less pain during injection of filler products containing lidocaine compared to those without lidocaine.[38-43] All of the aforementioned filler formulations provide the same final lidocaine concentration (0.3% w/w).

The FDA-approved family of JUVÉDERM® formulations includes JUVÉDERM® Ultra, JUVÉDERM® Ultra Plus, JUVÉDERM® Ultra XC, and JUVÉDERM® Ultra Plus XC. Evident within this family, slight differences in formulation impart different rheological properties that prove specific to a particular use while retaining similar physical and chemical properties to other approved members of the line. Thus, despite these minor differences in composition, utilization of identical components and a manufacturing paradigm that has already been approved for the JUVÉDERM® line of dermal fillers strongly suggests that VOLUMA™ XC will be safe upon injection. This was confirmed by pre-clinical biocompatibility testing (described in Section 9). The table below shows a composition comparison of VOLUMA™ XC to approved JUVÉDERM® formulations (Table 1).

Table 1. Comparison of VOLUMA™ XC to the FDA-approved family of JUVÉDERM® formulations

	JUVÉDERM®		
	Ultra, Ultra Plus	**Ultra XC, Ultra Plus XC**	**VOLUMA™ XC**
[HA]	24 mg/mL	24 mg/mL	20 mg/mL
HA Molecular Weight	high	high	low and high
Crosslinker	BDDE	BDDE	BDDE
Concentration of Added Crosslinker	more[a]	more[a]	less
Lidocaine Content	-	0.3%	0.3%
Indication	Injection into the mid-to-deep dermis for the correction of moderate to severe facial wrinkles and folds (such as nasolabial folds)		Deep (dermal/subcutaneous and/or submuscular/supraperiosteal) implantation to restore lost volume in the mid-face for aesthetic improvement

[a] The formulations of JUVÉDERM® Ultra, Ultra Plus, Ultra XC, and Ultra Plus XC are proprietary. All are higher in added BDDE concentration than VOLUMA™ XC, although the Ultra and Ultra Plus formulations contain different concentrations of added BDDE.

Each product's unique chemical composition imparts an overall level of cohesivity and gel hardness (G') that contribute to degrees of lift and injectability. For example, JUVÉDERM® Ultra Plus XC has a cohesivity and gel hardness of approximately 90 gmf and 200 Pa, respectively, making the gel suitable for injection via a smaller diameter needle but appropriate for amelioration of wrinkles and folds following injection to the mid to deep dermis. In contrast, VOLUMA™ XC has a lower cohesivity but higher gel hardness (40 gmf and 300 Pa, respectively), resulting in a more viscous solution. These properties make VOLUMA™ XC appropriate for deeper injection in the skin, at the deep dermal/subcutaneous level and submuscular/supraperiosteal level, and, thus, allow for higher lift of tissue and volume restoration, while still being injected via a small diameter needle.

The final VOLUMA™ XC product is a viscoelastic, sterile, non-pyrogenic, non-cytotoxic, clear, colorless, aénd biodegradable crosslinked derivative of the HA polymer and contains 0.3% lidocaine to reduce pain on injection. Like other approved members of the JUVÉDERM® family, VOLUMA™ XC is provided prefilled in a USP Class VI 1.0 mL cyclicolefin copolymer (COC) syringe and due to the specific rheological properties of the gel, can be used with 25G x 1" or 27G x ½" needles.

9. PRE-CLINICAL TESTING

VOLUMA™ XC is a dermal filler and based on ISO 10993-1 is considered an implantable material in contact with tissue and bone for greater than 30 days. All appropriate biocompatibility testing was performed in conformance to Good Laboratory Practices (GLPs) per 21 CFR 58. In each test the final product concentrations were evaluated, and, where applicable, comparable or higher than the expected clinical doses were utilized.

The following biocompatibility studies were conducted on the VOLUMA™ XC gel implant:

1. Cytotoxicity
2. Dermal Sensitization
3. Acute Systemic Toxicity
4. Subchronic Toxicity
5. Muscle Implantation:
    - 4-Week Muscle Implantation
    - 12-Week Muscle Implantation
6. Intracutaneous Reactivity
7. Genotoxicity:
    - Bacterial Reverse Mutation
    - Chromosomal Aberration
    - Micronucleus Study
8. Pyrogenicity

In addition to the standard tests listed above, an additional intracutaneous reactivity evaluation was performed including a histological assessment to evaluate the skin reaction and inflammatory response, as well as an endotoxin evaluation. The existing data and history of safe use for HA dermal fillers crosslinked with BDDE, including the JUVÉDERM® filler family, was applied to VOLUMA™ XC.

Table 2 briefly summarizes the results of the biocompatibility testing sponsored by Allergan.

Results of the testing demonstrated that VOLUMA™ XC is non-cytotoxic, a non-irritant, non-toxic, non-sensitizing, non-genotoxic, non-pyrogenic, and well tolerated. Furthermore, these biocompatibility results demonstrated that VOLUMA™ XC was in compliance with ISO standards as well as Allergan's internal standards for product qualification.

Table 2. Summary of Biocompatibility Testing

Test	Description	Result
Cytotoxicity – negligible cytotoxicity		
ISO Cell Culture Agar Overlay	Test substances added to L929 cells[a] for 24 hours	No visible signs of cytotoxicity or cell lysis
ISO Elution Method	Test substances extracted with growth media for 24 hours to 2 mg/mL and then placed on L929 cells[a] for 48 hours	Signs of toxicity determined to be procedural artifact[b]
Dermal Sensitization - non-sensitizing		
Maximization Assay (guinea pigs)	2 induction phases with test substances followed by a challenge phase and scored for irritation or sensitization	No signs of dermal sensitization
Acute Systemic Toxicity – not systemically toxic		
Acute Systemic Toxicity	A single dose of test substance injected intraperitoneally with monitoring over 7 days	Not systemically toxic
Subchronic Toxicity – non-toxic		
13 Week Subchronic Toxicity (rat)	Intradermal injection with test substances and monitoring over 13 weeks followed by histological processing	No mortalities or signs of toxicity. No effects on hematologic or clinical chemistry parameters
Muscle Implantation – non-irritant		
4-Week Implantation (rabbit)	4- week muscle implantation of test substances	No macroscopic or microscopic signs of irritation.
12-Week Implantation (rabbit)	12-week muscle implantation of test substances	No macroscopic or microscopic signs of irritation
Intracutaneous Reactivity – non-irritant		
72 Hour Direct Administration (rabbit)[c]	Intracutaneous injection sites graded over 72 hours	Increase in reactivity observed compared to control articles[c]
14-Day Direct Administration with Histological Assessment[d]	Test substances injected into rabbits via intracutaneous route.[d] Injection sites graded over 14 days. Injection sites collected at end of experiment for histology	Slight erythema observed compared to saline though similar to VOLUMA™ (without lidocaine) and Juvéderm Ultra Plus XC controls. All samples trended towards resolution. Microscopic evaluation showed no evidence of tissue edema. Slightly more polymorphonucleocytes and macrophages observed compared to VOLUMA™ (without lidocaine) and Juvéderm Ultra Plus XC

Test	Description	Result
Genotoxicity – non-mutagenic, non-genotoxic		
Bacterial Reverse Mutation	*S. typhimurium* and *E. coli* reverse mutation standard plate incorporation study	Non-inhibitory to growth of strains. Non-mutagenic
Micronucleus (mice)	Intraperitoneal injection with test articles. On Day 4, blood collected and erythrocytes evaluated for presence of micronuclei	No evidence of cellular toxicity, no increase in number of micronucleated reticulocytes
Chromosomal Aberration	CHO cells exposed to test articles	No difference in number of aberrant cells
Pyrogenicity – non-pyrogenic		
USP Pyrogen Study	Rabbits intravensouly injected with extracted test substances. Body temperatures recorded over 3 hours.	No temperature increases observed
Bacterial Endotoxin		
Colorimetric Titration with Lysate Amoebocytes Limulus (EP 2.6.14 and USP <85>)	Colorimetric titration with Lysat Ameobocytes Limulus (LAL)	Meets specification (< 5 EU/syringe)

[a] L929 cells are a mouse fibroblast cell line. In these experiments, cells were grown to confluence in MEM.
[b] The anionic nature of concentrated HA may have led to absorption of essential serum proteins present in MEM growth medium, which also may have led to the cytotoxic result. A third party toxicologist also determined the results to be procedural artifact due to test article concentration being 2x higher than the ISO 10993-12 recommended concentration.
[c] Saline was used as control
[d] Saline, JUVÉDERM® Ultra Plus XC, and VOLUMA™ (without lidocaine) were used as controls

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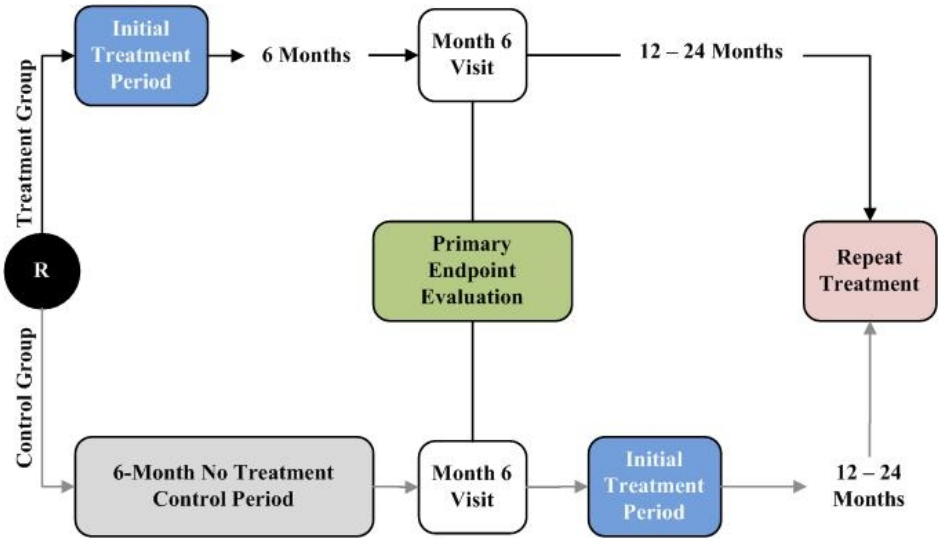
10. VOLUMA-002 CLINICAL STUDY DESIGN

The pivotal clinical study for VOLUMA™ XC, protocol VOLUMA-002, was first approved by FDA on July 24, 2009. This study was designed to evaluate the safety and effectiveness of VOLUMA™ XC for the treatment of age-related mid-face volume deficit in healthy subjects (Figure 5).

Figure 5. VOLUMA-002 Clinical Study Design



Enrolled subjects exhibited moderate to severe age-related mid-face volume deficit. Under the study design, subjects were randomized to either the treatment group, who received treatment with VOLUMA™ XC, or to the "no-treatment" control group, where treatment was delayed until after the primary 6-month follow-up period. Delayed treatment of the control group was included to create an incentive for subjects randomized to the "no treatment" control group to remain in the study. Subjects were followed for up to 24 months after treatment with VOLUMA™ XC and returned to the investigational site at regular intervals throughout the study for safety and effectiveness evaluations. At the end of the follow-up period, an optional repeat treatment with scheduled follow-up was offered to all subjects.

The primary effectiveness endpoints of this study were evaluated at Month 6. To prove effectiveness of VOLUMA™ XC:

1) at least 70% of treatment group subjects had to demonstrate improvement in overall volume deficit (reduction by ≥ 1 grade on the MFVDS compared to pre-treatment) at 6 months, as assessed by the average of both Evaluating Investigator overall MFVDS assessments *and*

2) the responder rate of the treatment group had to be statistically superior to the responder rate for the "no-treatment" control group at Month 6

In addition to presentation and discussion of the primary effectiveness endpoint, the data presented in this briefing document include safety and effectiveness data obtained through 24 months for the treatment group, limited safety and effectiveness data through 18 months post-treatment for the control group, and early safety data for subjects in the treatment group who have undergone repeat treatment.

10.1 Overview of Pivotal Study Design

10.1.1 Enrollment

VOLUMA-002 is an ongoing, multicenter, single-blinded, randomized, "no-treatment" control study. The study was approved for enrollment of up to 315 subjects with moderate to severe age-related mid-face volume deficit, as determined using the Mid-Face Volume Deficit Scale (described in Section 10.2.1). Study enrollment included 30 non-randomized "run-in" subjects and 285 randomized subjects. The "run-in" subjects consisted of the first 2 subjects enrolled at each site. They were not randomized but were treated in order to allow each Treating Investigator 2 practice cases to gain experience with injection characteristics of VOLUMA™ XC and to allow Treating and Evaluating Investigators, as well as clinical research staff, to gain practice in the study-specific procedures, including performing assessments.

Within the randomization group, up to 240 subjects were to receive treatment with VOLUMA™ XC and at least 45 subjects were to be assigned to the "no-treatment" control group, where treatment would be delayed until after the primary 6-month follow-up period.

Similar to other facial filler studies, the study design established enrollment targets for each of a series of demographic subgroups. A target of 40 subjects was identified for the subgroups defined by gender (female/male), race (Caucasian, Hispanic, African-American, Asian), and 6 geographic regions; and a target of 48 was identified for each of 3 Fitzpatrick skin type subgroups (I/II, III/IV, and V/VI, defined in Section 10.1.4). Note that the size of the control group was driven by the statistical power needed for the primary endpoint analysis, and only the size of the treatment group was increased to accommodate these subgroup enrollment targets.

10.1.2 Treatment

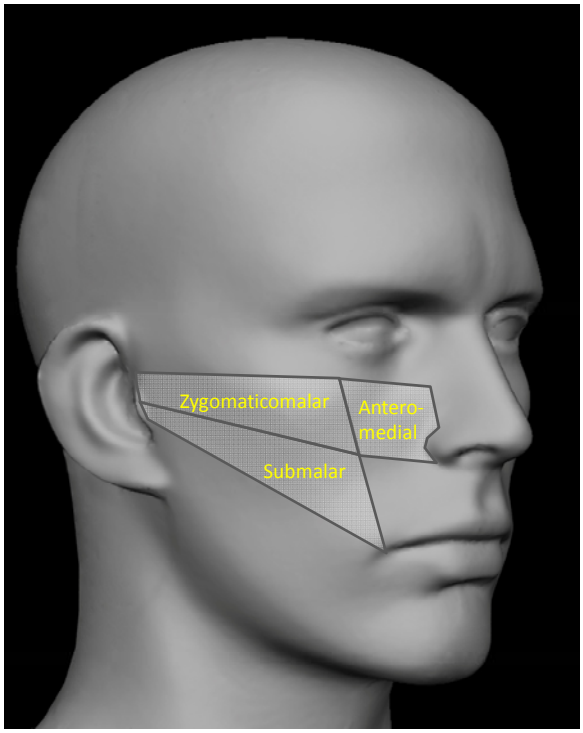
The initial treatment period involved up to 2 treatment sessions (initial and touch-up) performed by the Treating Investigator to correct volume deficit in the mid-face, specifically in the zygomaticomalar region, anteromedial cheek, and/or submalar region (regions shown in Figure 6). Treatment of the tear troughs, nasojugal folds, nasal sidewall, nasolabial folds, and upper lip were not permitted during the course of the study.

At the initial treatment session, the Treating Investigator discussed the treatment goals with the subject and then determined the appropriate treatment area and appropriate volume of VOLUMA™ XC to be injected (based on his/her clinical experience, though not to exceed 12 mL for both the initial and touch-up treatment combined). VOLUMA™ XC was to be injected into the subcutaneous and/or supraperiosteal planes of dermal tissue using injection techniques deemed suitable by the Treating Investigator, including tunneling, fanning, serial puncture, ferning, or crosshatching in an antegrade or retrograde manner.

Each subject was to also receive a subdermal depot injection of VOLUMA™ XC in the medial aspect of the upper inner arm or behind the ear during the first treatment session. The goal of the depot injection was to target a minimum of 18 biopsies over the course of the study from volunteers to obtain histological data as well as be able to biopsy the depot injection site in any subject who presented with severe inflammatory symptoms in the treatment area of depot area over the course of the study.

Subjects returned approximately 30 days after initial (first) treatment. The Treating Investigator evaluated whether volume augmentation of the mid-face had been optimized. If deemed necessary and the subject's allotment of VOLUMA™ XC (12 mL) had not been exhausted, a touch-up treatment was performed.

Figure 6. Mid-Face Regions Treated



Subjects were seen for follow-up at 3, 6, 9, 12, 15, 18, and 24 months after the their last treatment (initial or touch-up, if performed). However, if subjects returned to baseline between Months 12 and 24 based on their MFVDS score, they were offered an optional, complimentary repeat treatment at their next visit. All other subjects were offered the optional, complimentary repeat treatment at their Month 24 visit. The repeat treatment was to be performed no later than 3 months after the end of the extended follow-up period (as described in the section below). At the repeat treatment, the Treating Investigator determined the appropriate volume of VOLUMA™ XC to be injected (though not to exceed 12 mL) in the zygomaticomalar region, anteromedial cheek, and/or submalar region.

10.1.3 Follow-up

Follow-up during the VOLUMA-002 study consisted of the primary safety and effectiveness follow-up period, the extended follow-up period, and follow-up after repeat treatment. All subjects were evaluated at quarterly intervals, and applicable safety and effectiveness evaluations were performed. Only Treating Investigators performed safety evaluations. Two blinded Evaluating Investigators performed a range of effectiveness evaluations. To maintain study blinding, the Evaluating Investigators were not present during the safety evaluations, and subjects were instructed not to divulge their randomization assignments to the Evaluating Investigators.

Table 3 defines each study phase and follow-up schedule. Primary effectiveness endpoints were evaluated at Month 6. Subject follow-up prior to optional repeat treatment was to last up to 24 months (for subjects randomized to treatment) or 30 months (for subjects randomized to control). Data from the visits shown in red were not yet available at the time of submission to the FDA and, thus, those results are not discussed herein.

Table 3. Follow-Up Schedule

Primary Safety and Effectiveness Period									
Treatment Group	Month 1	Month 3	Month 6[c]						
Control Group[a]	Month 1	Month 3	Month 6[c]						
Extended Follow-up Period									
Treatment Group				Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Control Group[b]	Month 1	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24
Follow-up After Optional Repeat Treatment									
Treatment Group	Month 1	Month 3	Month 6	Month 9	Month 12				
Control Group	Month 1	Month 3	Month 6	Month 9	Month 12				

Red indicates data not available at the time of FDA submission
[a] No treatment
[b] After treatment
[c] Primary endpoint assessment

Primary Safety and Effectiveness Period

During the primary follow-up period, both treatment and control group subjects attended office visits at 1, 3, and 6 months. Month 6 marked the end of the primary follow-up period.

Extended Follow-up Period

Treatment group subjects continued to be followed for an extended follow-up period, which constituted the follow-up time after Month 6 and up to Month 24, or until any visit after Month 12 when the average score of the Evaluating Investigators' live assessments of the subject's zygomaticomalar region, anteromedial cheek, submalar region, and overall Mid-face Volume Deficit Scale (MFVDS) returned to or was worse than the pre-treatment level.

Control subjects received treatment after completion of the 6-month primary follow-up period, and similar to the treatment group, attended office visits at 1, 3, and 6 months as well continuing follow-up through Month 24, or until any visit after Month 12 when the average score of the Evaluating Investigators' live assessments of the subject's zygomaticomalar

region, anteromedial cheek, submalar region, and overall MFVDS returned to or was worse than the pre-treatment level.

Follow-up After Repeat Treatment

At the end of the extended follow-up period, an optional repeat treatment was offered to all subjects (at subject and Treating Investigator convenience, but no later than 3 months after the end of the extended follow-up period), with a subsequent office visit at Month 1 and telephone or office visits at Months 3, 6, 9, and 12 after repeat treatment.

To check safety of treatment, subjects were contacted by telephone or email on Day 3 following any treatment (initial, touch-up, or repeat).

10.1.4 Discussion of Study Design

The design of VOLUMA-002, agreed upon by Allergan and the FDA, contained several elements meant to ensure that the pivotal clinical study would appropriately characterize the effectiveness and safety profile of VOLUMA™ XC for treatment of age-related mid-face volume deficit in healthy subjects.

"No-treatment" control group

The use of a concurrent "no-treatment" control group within this study was necessary because there are no products approved by the FDA for the proposed indication to serve as a control. This type of control group was considered the most appropriate type of control, and was recommended by the FDA in order to understand the effectiveness of VOLUMA™ XC. By using a "no-treatment" control group the effectiveness of the product could be more fully evaluated than if a control group had not been utilized. The "no-treatment" control group did not receive treatment but did follow the same visit schedule and underwent the same effectiveness evaluations by blinded Evaluating Investigators as the treatment group for the first 6 months of the study. Delayed treatment following the Month 6 evaluations was incorporated into the control arm to provide incentive for subjects randomized to the control group to participate and remain in the study.

Fitzpatrick Skin Types

The safety and effectiveness of other members of the JUVÉDERM® family in darker skin phototypes has been demonstrated previously, including JUVÉDERM® Ultra and Ultra Plus following injection in the nasolabial folds.[44,45] However, in order to ensure evaluation of the safety and effectiveness of VOLUMA™ XC in all skin phototypes, FDA required that a minimum number of subjects representing the skin phototypes be enrolled in the VOLUMA-002 clinical study. The Fitzpatrick Skin Phototype scale is a recognized scale which

classifies skin color based on genetic disposition and reaction to sun exposure (Table 4). Based on the classification scale, minimum enrollment targets of 48 subjects representing Fitzpatrick skin types I and II, III and IV, and V and VI were set for subgroup safety and effectiveness analyses.

Table 4. Fitzpatrick Skin Phototype Scale

Phototype	Genetic Disposition			Reaction to Sun Exposure
	Skin Color	Hair Color	Eye Color	
I	white, very fair	red, blonde	blue	always burns, never tans
II	white, fair	red, blonde	blue, hazel, green	usually burns, tans with difficulty
III	cream white, fair	any	any	can mildly burn, gradually tans
IV	brown, olive	any	any	rarely burns, tans with ease
V	dark brown	any	any	very rarely burns, tans very easily
VI	black	any	any	never burns, tans very easily

Run-in subjects

The first 2 subjects enrolled at each site were not randomized. These 2 run-in subjects were treated at each site to allow each Treating Investigator 2 practice cases to gain experience with the injection characteristics of VOLUMA™ XC and to allow Treating and Evaluating Investigators as well as each site's clinical research staff to gain practice in the study-specific procedures, including performing assessments. The run-in subjects followed the same follow-up schedule and assessments as the treatment group subjects.

Sample Size

To demonstrate statistical superiority of the treatment group over the control group (with >99% power for a 2-sided 2-group Fisher's exact test at the 0.025 significance level) as well as assuming responder rates in the treatment group as 90% and control group as less than 40% at Month 6, a sample size of 36 control subjects and 216 treatment group subjects was deemed adequate. However, to allow for 20% attrition in the control group and 10% attrition in the treatment group, the number of randomized subjects was set at 45 control group subjects and 240 treatment group subjects (i.e., 5.3:1 treatment to control ratio). This treatment group size provided >99% power with a 2-sided exact binomial test at the 0.025 level to demonstrate that the responder rate in the treatment group was significantly greater than 70%. The seemingly large treatment group size compared to control group size was set to achieve adequate power for subgroup analyses. Enrollment targets were set at ≥ 40 subjects within subgroups by various covariates including gender, race, geographical region, treatment site, treatment plane, and treatment technique. Enrollment targets were set at ≥ 48 subjects for each of the 3 Fitzpatrick skin type subgroups (I/II, III/IV, V/VI).

Investigator Evaluations

Based on recommendations from the FDA, 2 blinded Evaluating Investigators were used at each site rather than a single Evaluating Investigator, in order to further enhance reliability. Results were obtained by averaging both Evaluating Investigator's effectiveness rating scores. The Evaluating Investigators performed their assessments independently through live observation of the subjects.

Treatment administration and safety evaluations were performed only by the Treating Investigator, and during such procedures and evaluations, Evaluating Investigators were not present.

10.1.5 Selection of Study Population

For enrollment into the study, the Treating Investigator ensured that each subject met all study inclusion criteria and none of the exclusion criteria. Listed below are key inclusion and exclusion criteria; the complete listing can be found in the study protocol included in the panel pack.

Inclusion Criteria

- Was male or female, 35-65 years of age
- Had zygomaticomalar region, anteromedial cheek, submalar region, and/or overall mid-facial volume deficit assessed by the Treating Investigator as Grade 3 (Moderate), 4 (Significant), or 5 (Severe) on the photometric Mid-Face Volume Deficit Scale (MFVDS)
- Desired cheek augmentation to correct age-related volume deficit in the mid-face, i.e., zygomaticomalar region, anteromedial cheek, and/or submalar region, as recommended by the Treating Investigator
- Accepted the obligation not to receive any other facial procedures or treatments affecting facial volume deficit at any time during the study

Exclusion Criteria

- Had undergone cosmetic facial plastic surgery (with the exception of rhinoplasty more than 2 years prior to enrollment), tissue grafting, or tissue augmentation with silicone, fat, or other permanent, or semi-permanent dermal fillers or was planning to undergo any of these procedures at any time during the study
- Had undergone temporary facial dermal filler injections with HA-based fillers within 12 months, porcine-based collagen fillers within 24 months, or neuromodulator injections, mesotherapy, or resurfacing (laser, photomodulation, intense pulsed light, radio frequency, dermabrasion, chemical peel, or other ablative or non-ablative procedures) within 6 months prior to entry in the study or was planning to undergo any of these procedures at any time during the study
- Had very thin skin in the mid-facial region, tendency to accumulate fluid in the lower eyelids, or large infraorbital fat pads, i.e., significant convexity or projection from the infraorbital fat pads
- Had 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 HIV-related disease

10.2 Effectiveness Measures and Analyses

10.2.1 Primary Effectiveness Measure and Analysis

The primary effectiveness measurement was based on the blinded, independent Evaluating Investigators' live assessments of the subject's overall mid-face volume deficit on the validated 6-point Mid-Face Volume Deficit Scale (MFVDS). The scale grade descriptions are provided in Table 5 and a portion of the photographic guide is provided in Figure 7. The entire MFVDS is provided in Appendix 1.

Table 5. Mid-Face Volume Deficit Scale Wording

Score	Grade	Description
5	Severe	• Wasting • Severe concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Severe tear troughs and/or nasolabial folds • Significant nasojugal folds and/or prejowl sulcus • Significant prominence of bony landmarks • Significant visibility of underlying musculature
4	Significant	• Significant concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Significant tear troughs and/or nasolabial folds • Moderate nasojugal folds and/or prejowl sulcus • Moderate prominence of bony landmarks • Moderate visibility of musculature
3	Moderate	• Moderate concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Moderate tear troughs and/or nasolabial folds • Mild nasojugal folds and/or prejowl sulcus • Mild prominence of bony landmarks • Mild visibility of musculature
2	Mild	• Mild concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Mild tear troughs and/or nasolabial folds
1	Minimal	• Flattening in the zygomaticomalar region, anteromedial cheek, and/or submalar region
0	None	• Moon face • Fullness (convexity) in the zygomaticomalar region, anteromedial cheek, and/or submalar region

Figure 7. Mid-Face Volume Deficit Scale Example Photos

Score	0	1	2	3	4	5
Grade	None Convexity	Minimal Flattening	Mild Concavity	Moderate Concavity	Significant Concavity	Severe Wasting

At each investigational site, 2 Evaluating Investigators separately assessed the subject's overall volume deficit based on the MFVDS at baseline and at all follow-up visits. For analysis, the 2 Evaluating Investigator's MFVDS scores were averaged (e.g., if, at baseline,

one Evaluating Investigator assigned an MFVDS score of 3 and the other assigned a score of 4, the average MFVDS score of 3.5 was used as the subject's baseline MFVDS score).

The primary effectiveness analysis was based on the percent of "responders" at Month 6. To be considered a "responder," the average of the 2 blinded, independent Evaluating Investigators' assessments of the subject's overall mid-face volume deficit at Month 6 had to be improved (reduced) by ≥ 1 grade compared with the average of the Evaluating Investigator pre-treatment assessments. The MFVDS scores were based on the Evaluating Investigators' live assessments of the subject.

VOLUMA™ XC was considered to be clinically effective if at least 70% of treatment group subjects were responders at Month 6, determined by a 2-sided exact binomial test at the 0.025 significance level, *and* if the responder rate for the treatment group subjects was statistically superior to the responder rate for the "no-treatment" control group at Month 6, using a 2-sided, 2-group, Fisher's exact test at the 0.025 significance level. As a conservative approach, these analyses were adjusted for multiplicity so that the conclusions could be interpreted independently.

10.2.2 Secondary Effectiveness Measurements and Analyses

At each follow-up visit, the Evaluating Investigators used the MFVDS to independently perform live assessment of the subject's mid-face volume deficit for each of the 3 treatment areas (zygomaticomalar region, anteromedial cheek, and/or submalar region). Following the MFVDS assessments, the Evaluating Investigators then independently assessed the subject's level of aesthetic improvement using the 5-point Global Aesthetic Improvement Scale (GAIS; shown in Table 6), by comparing the live subject with the subject's pre-treatment digital image.

Table 6. 5-Point Global Aesthetic Improvement Scale

Score	Grade	Description
2	Much Improved	Marked improvement in appearance
1	Improved	Improvement in appearance, but a touch-up or retreatment is indicated
0	No Change	The appearance is essentially the same as the original condition
-1	Worse	The appearance is worse than the original condition
-2	Much Worse	The appearance is much worse than the original condition

The secondary effectiveness analyses included the responder rate based on GAIS (with a 98.75% confidence interval) and responder rates (with 98.75% confidence intervals) in each mid-face region based on MFVDS for the treatment group at 6 months. For all analyses, the average scores of 2 Evaluating Investigators were used. A subject was a responder on GAIS

if the average score of 2 Evaluating Investigators was ≥ 1, indicating appearance that was Improved or Much Improved, and a responder on MFVDS for each mid-face region if the average score of 2 Evaluating Investigators was ≥ 1 grade improvement since baseline in that mid-face region.

A statistical multiplicity adjustment was applied to the width of the confidence intervals of responder rate by applying Bonferroni correction to alpha.

10.2.3 Additional Effectiveness Measurements and Analyses

Other effectiveness measures included assessing Other Aesthetic Features of the Mid-Face (OAFM) and the severity of the subject's nasolabial folds (NLFs) using the NLF Severity Scale (NLFS). The OAFM is an 11-point scale (range, 0-10) used to assess symmetry, proportion, and shape of the mid-face. NLFs are assessed because volumizing the mid-face may lift the tissue above the NLF and reduce its severity. The Grade descriptions for the validated, 5-point NLFS are provided in Table 7. Prior to treatment and at all follow-up visits, the Evaluating Investigators independently examined the subject's NLFs (using the NLFS) and examined the mid-face (using the OAFM) from multiple angles, in repose and in animation, for other aesthetic features such as symmetry, proportion, and shape. At Month 6 after treatment, the Evaluating Investigators independently guessed the subject's randomization assignment (i.e., treated or not treated), and recorded the reasons for their guess. Note that the *Treating Investigator* did not do any effectiveness assessments post-treatment.

Table 7. 5-Point NLF Severity Scale

Score	Severity Descriptions	
4	Extreme	Very deep wrinkle, redundant fold (overlapping skin)
3	Severe	Deep wrinkle, well-defined edges (but not overlapping)
2	Moderate	Moderately deep wrinkle
1	Mild	Shallow, just perceptible wrinkle
0	None	No wrinkle

Prior to treatment, subjects set treatment goals and independently assessed their overall MFVDS, NLFS, and level of satisfaction with the 3 mid-facial treatment areas and adjacent non-treatment areas. At all follow-up visits, subjects completed those assessments as well as noting whether treatment goals had been met. Additional subject outcome measures included GAIS, qualitative satisfaction questions regarding the look and feel of the mid-face (LAFM, 11-point scale from 0 to 10 assessing subjects' level of satisfaction with their cheeks while relaxed and in motion), self-perception of age (SPA, multiple choice whether subjects look their age, younger, or older and number of years younger/older, if applicable), and the facial

appearance prior to treatment and at 1, 6, 12, 18, and 24 months post-treatment. Note that control group subjects completed these assessments only after treatment and not during the "no-treatment" follow-up period.

Volume changes of the right and left cheeks were calculated by Canfield Scientific from 3D digital imaging recorded at pre-treatment and post-treatment visits at Months 1, 6, 12, 18, and 24. For control subjects, only Month 1 and Month 6 volume changes in the primary follow-up period and Month 12 post-treatment volume changes were calculated.

For follow-up data after 6 months, a survival analysis was performed using Kaplan-Meier estimates to determine the duration of effect of VOLUMA™ XC based on the timepoint when the average of the 2 blinded Evaluating Investigators' assessments of the subject's MFVDS (overall or by region) returned to or were worse than the averages of the respective pre-treatment scores.

Table 8 describes each endpoint including how and when it was evaluated. All assessments were compared to data collected at baseline.

Table 8. Endpoints Evaluated

ENDPOINT	DESCRIPTION	EVALUATOR(S)	TIMEPOINT
Primary	70% responder rate based on live assessment of subject's overall MFVDS score	Blinded EI (average of both independent scores)	Month 6
Primary	Superiority over control based on live assessment of subject's overall MFVDS score	Blinded EI (average of both independent scores)	Month 6
Secondary	GAIS responder rate based on live subject vs. pre-treatment digital image	Blinded EI (average of both independent scores)	Month 6
Secondary	Responder rates of MFVDS by facial sub-region based on live assessment of subject	Blinded EI (average of both independent scores)	Month 6
Secondary	Kaplan-Meier estimate of duration of effect of product	Blinded EI (average of both independent scores)	All timepoints
Additional	Live assessment of overall MFVDS	TI[a], Blinded EI (average of both independent scores), Subject[b]	All timepoints
Additional	GAIS based on live assessment of subject vs. pre-treatment digital image	Blinded EI (average of both independent scores), Subject[b]	All timepoints
Additional	NLF severity	TI[a], Blinded EI (average of both independent scores), Subject[b]	All timepoints
Additional	Other Aesthetic Features of the Mid-Face Area	TI[a], Blinded EI (average of both independent scores)	All timepoints
Additional	Guess of subject's randomization assignment (based on MFVDS score)	Blinded EI	Month 6
Additional	3D imaging volume change	3D Digital Imaging calculations by Canfield	Treatment Group: Months 1, 6, 12, 18, 24 Control Group: Months 1 and 6 during "no – treatment", and Month 12 post-treatment
Additional	Level of satisfaction with mid-facial sub-regions	Subject[b]	All timepoints
Additional	Self-Perception of Age	Subject[b]	Months 1, 6, 12, 18, 24
Additional	Facial Appearance Evaluation	Subject[b]	Months 1, 6, 12, 18, 24
Additional	Look and Feel of the Mid-face	Subject[b]	Months 1, 6, 12, 18, 24

EI = Evaluating Investigator; TI = Treating Investigator
[a] TI performed assessment only at screening visit
[b] Control group subjects completed these assessments only after treatment

10.3 Safety Measurements

The presence, location (zygomaticomalar region, anteromedial cheek, and/or submalar region), severity, and duration of common treatment site responses (CTRs) and any adverse events (AEs) were assessed after each treatment by a subject diary for 30 days, by telephone/email follow-up with the Treating Investigator at 3 days, by office visits at 30 days, and by discussion of the subject's observations and the Treating Investigator's personal observation of the subject at multiple scheduled timepoints throughout the study.

CTRs were obtained from subject diaries. Each diary page contained a table listing 9 common treatment site responses that could be expected after this type of procedure. The subject was instructed to mark the severity (from none to severe) of any symptom experienced for each of the 3 treatment regions.

Definitions for the classification of severity (either as CTR or AE) are shown below:

- Mild: symptoms are barely noticeable or do not make the subject uncomfortable. The AE/CTR does not influence performance or functioning. Prescription drugs are not ordinarily needed for relief of symptom(s).
- Moderate: symptoms are of sufficient severity to make the subject uncomfortable. Performance of daily activities is influenced. Treatment of symptom(s) with prescription drugs or therapies may be needed.
- Severe: Symptoms are of sufficient severity to cause the subject severe discomfort. Performance of daily activities is compromised. Treatment for symptom(s) with prescription drugs or therapies may be needed.

Figure 8 below shows a sample page of the diary.

Figure 8. Subject Diary

COMMON TREATMENT RESPONSE (CTR)*	Anteromedial Cheek (between the nose and cheekbone)				Submalar Region (below cheekbone)				Zygomaticomalar Region (over cheekbone)			
	[redacted]											
	Severity											
If no CTRs are present in any treatment area, right or left, check NONE ☐	Right				Left				Right			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Redness												
Pain												
Tenderness (to Touch)												
Firmness												
Swelling												
Lumps/Bumps												
Bruising												
Itching												
Discoloration (not Redness or Bruising)												
Other (specify): _____												

COMMON TREATMENT RESPONSE (CTR)*	Zygomaticomalar Region (over cheekbone)							
	Severity							
If no CTRs are present in any treatment area, right or left, check NONE ☐	Left				Right			
	None	Mild	Moderate	Severe	None	Mild	Moderate	Severe
Redness								
Pain								
Tenderness (to Touch)								
Firmness								
Swelling								
Lumps/Bumps								
Bruising								
Itching								
Discoloration (not Redness or Bruising)								
Other (specify): _____								

AEs were those identified by the Treating Investigator as well as all CTRs that were ongoing at the end of the 30-day diary. To maintain the study blinding, the Evaluating Investigators were not present during the time of the safety evaluations.

Depot injections were deposited behind the ear or in the medial aspect of the inner upper arm of subjects in order to assess whether overt reactions occurred away from the targeted injection areas. Histological evaluation was planned for approximately 18 volunteer subjects, with a target of 2 biopsy specimens per timepoint as well as for any subject with severe inflammatory symptoms. The biopsy visit for each volunteer was randomly assigned to 1 of the 9 study follow-up visits (Month 1 through Month 24).

10.4 Analysis Population

10.4.1 Main Analyses

Effectiveness analyses were performed on the mITT population as described in the study protocol, comprised of all subjects who were randomized to receive the treatment and were treated (the treatment group) and subjects who were randomized to no-treatment (the control group). Subjects who were randomized to treatment but discontinued before the treatment

did not provide any post-baseline effectiveness data or any safety data related to treatment, and, therefore, were not included in the mITT population.

All effectiveness analyses were performed without data imputation using an observed case analysis (i.e., only subjects who completed the visit within the analysis window were included in the analysis for that timepoint). As described in the study protocol, a sensitivity analysis was performed where the primary effectiveness analysis was repeated on the mITT population using various imputation techniques to determine the sensitivity of the study conclusion to missing assessments at Month 6. Additionally, the primary effectiveness analysis was repeated on the per protocol (PP) population, which included all mITT subjects who were not considered to be major protocol violators, in order to determine the sensitivity of the study's conclusions to deviations. All demographic and baseline information was summarized for the mITT population.

Safety analyses were performed on all mITT subjects who were treated in the study. Analyses for run-in subjects were done separately, as specified in the study protocol.

10.4.2 Subgroup Analyses

Pre-specified subgroup analyses were conducted for the primary effectiveness endpoints (i.e., responder rate for the treatment group based on the overall MFVDS). These included stratification by baseline volume deficit as assessed by the Treating Investigator, gender, ethnicity, Fitzpatrick skin type, investigational site, geographical location of investigational site, injection plane at initial or touch-up treatment, injection technique at initial or touch-up treatment, and total volume injected at initial and touch-up treatment combined. Within each subgroup the responder rate and the 95% confidence interval were provided. For volume of product injected, the subgroups were defined based on median injection volume.

In order to identify subgroup variables that may affect the primary outcome, a multiple logistic regression was performed as an exploratory analysis, with responder rate based on overall MFVDS as the dependent variable and the following subgroup variables as independent variables:

- Baseline overall mid-face volume deficit
- Gender
- Race
- Fitzpatrick skin type
- Investigational site
- Geographical location

- Subcutaneous plane of injection
- Supraperiosteal plane of injection
- Injection technique as tunneling
- Injection technique as fanning
- Injection technique as antegrade
- Injection technique as retrograde
- Other injection technique (includes serial puncture, ferning, and crosshatching)
- Volume injected

Volume injected (mL) was included as a continuous variable in the model. Plane of injection and injection technique variables were included as dichotomous variables, where 1 indicates use of that plane (or technique) at initial or touch-up treatment and 0 indicates otherwise. All other variables were categorical.

All variables were included in the model in a single step, and significance of the coefficients was reported. The variable was considered significant if the corresponding p-value was less than 0.10. Significance of a variable implies that the responder rates in the strata of the subgroup variable differ significantly, which indicates that the subgroup variable affects the responder rate in the presence of other subgroup variables. For dichotomous and continuous variables, the coefficients and odds ratio estimates were also calculated.

Subgroup analyses for safety endpoints (incidence rate of a CTR at any injection site and also by injection site) included stratification by investigational site, volume of product injected, injection plane, and injection technique. Incidence rates and their 95% confidence intervals were calculated within each subgroup for each treatment area.

To determine the impact of stratification factor on the incidence rate of a CTR, a planned exploratory analysis involving a multiple logistic regression with incidence rate of a CTR as the dependent variable and the subgroup variables as independent variables was employed separately for each treatment area.

A post-hoc subgroup analysis for incidence of device-related adverse events was performed in a similar manner with covariates of gender, race, Fitzpatrick skin phototype, investigational site, injection plane and technique, and volume injected.

Subgroup analyses for the control group were not performed since the number of control group subjects in some of the subgroups was less than 5. Furthermore, the purpose of the

control group was not to identify a difference between the treatment and control group within a subgroup, but rather to validate the effectiveness of the product in the entire study population.

10.5 Appropriateness of Measurements

10.5.1 MFVDS

Standardized facial lipoatrophy/volume loss scales and patient-reported outcomes (PRO) measures are key to evaluating the effectiveness of volume restoration in a reliable and reproducible way. In order to measure treatment of facial lipoatrophy, defined as a "loss of facial fat due to aging, trauma, or diseases, manifested by flattening or indentation of normally convex contours," a 6-point classification system (range, 0-5) was developed and validated based on 3 criteria: contour, bony prominence, and the visibility of musculature.[46]

Using the facial lipoatrophy scale as a guideline, Allergan developed the 6-point photometric MFVDS. Allergan recognizes that patients may want to undergo subtle mid-face volume deficit correction without the suggestion that a facial treatment was performed. Therefore, in developing the MFVDS, an instrument that would be applicable to subtle changes for the most discriminating patient and physician was required so that the spectrum of small but important changes as well as aggressive changes would be possible. Thus, the range of grades (from Grade 0 "None" to Grade 5 "Severe") was intended to represent the full spectrum of mid-face volume deficit. To determine the level of inter- and intra-rater agreement with use, and thereby validate the scale, Allergan held a meeting with 9 aesthetic physicians who independently rated digital 3D images and live subjects who exhibited volume deficit characteristics of each of the 6 grades on the scale. Evaluators rated the images and live subjects twice in 2 rating sessions spaced at least 2 hours apart. Inter- and intra- rater agreement was at least substantial for both rounds of evaluation, with the exception of the Round 2 inter-rater agreement, which was moderate.

However, because the interval between reviews was approximately 2 hours, FDA recommended that the validation be repeated with a 2-week interval between assessments. It was also recommended that the difference in grades associated with clinically significant differences be established. Finally, it was requested that the mid-face be subdivided into specific treatment areas based on different anatomical aspects and treatment algorithms, and that the MFVDS be validated for use with these facial sub-regions.

As a result, the MFVDS was revised (Table 5, Figure 7) and re-validated. Unique from the original MFVDS, the revised scale identifies discrete mid-facial sub-regions that are

volumizing treatment areas, i.e., the zygomaticomalar region, anteromedial cheek, and submalar region (Figure 6) and describes each grade of volume deficit in detail.

A total of 61 physicians participated in scale validation, which included a web-based training teleconference and 2 rounds of independent online test sessions separated by 14 days. During each test session, physicians used the MFVDS to rate 76 subjects' 3D images. Inter-rater agreement (agreement between raters) and average intra-rater agreement for raters (agreement between Round 1 and Round 2) were substantial (i.e., ≥ 0.60, the minimum acceptable level of agreement per the protocol) for the overall mid-face as well as for all mid-facial sub-regions, and a 1-point difference in scale scores was determined to be clinically significant. The scale validation summary detailing the procedures and analyses is included in Appendix 2.

Table 9 shows a comparison of inter-rater agreement at both rounds during the initial validation study and the re-validation study.

Table 9. MFVDS Scale Validation: Inter-Rater Agreement

	Region	Inter-Rater Round 1 ICC	Inter-Rater Round 2 ICC	Intra-Rater Weighted Kappa
Initial Validation[a]				
Digital 3D Images	Overall Mid-Face	0.77	0.80	0.87
Live Subjects	Overall Mid-Face	0.63	0.50	0.74
Re-Validation[b]				
Digital 3D Images	Overall Mid-Face	0.73	0.73	0.83
Digital 3D Images	Anteromedial Cheek	0.67	0.67	0.80
Digital 3D Images	Submalar	0.67	0.65	0.79
Digital 3D Images	Zygomaticomalar	0.64	0.65	0.78

ICC = Intra-Class Correlation
[a] 9 participants rating images and subjects2 hours apart using the original MFVDS scale
[b] 61 participants rating images 2 weeks apart using a revised MFVDS scale

The re-validation study of the MFVDS was also used to train and qualify potential investigators for the VOLUMA-002 clinical study. Once satisfactory validation results were obtained from the first 50 raters, the clinical trial was initiated. As specified in the VOLUMA-002 study protocol, all investigators had to demonstrate satisfactory agreement scores before they could start evaluations. Data from Round 1 and Round 2 for the 61 raters who participated in the revised scale validation showed acceptable agreement scores and 45 of the 61 raters continued as study investigators in the VOLUMA-002 clinical study with 15 as Treating Investigators and 30 as Evaluating Investigators. Among these, there were 24 physicians who had either lower intra-rater agreement or lower pair-wise agreement (i..e, <.0.60) with ≥ 5 raters . These physicians were asked to complete a third round of ratings to

provide more experience with the scale. After the third round, the physicians showed improvement in agreement scores. As such, all study investigators were deemed adequately trained to start the MFVDS evaluations at their investigational sites. The remaining 15 raters from the validation study also met all qualifications for use of the MFVDS (i.e., showed substantial agreement scores), but did not participate in the clinical study because they were at investigational sites at which the protocol was not initiated.

10.5.2 GAIS, NLFS, and OAFM

GAIS is a commonly used (although not validated) measure of patient satisfaction in dermal filler studies.[47,48] The GAIS is a relative scale rather than an absolute scale: the evaluator grades the overall improvement by comparing the appearance of the live subject at follow-up against the appearance before treatment (using baseline photographs).[49]

The NLFS was the primary scale for other JUVÉDERM® pivotal studies examining dermal fillers for nasolabial folds,[50-52] and the scale underwent validation prior to use in these studies.[53]

The Other Aesthetic Features of the Mid-Face (OAFM) scale was patterned after the Facial Lines Outcomes (FLO-11) and Look and Feel (LAF) questionnaires. The FLO-11 questionnaire uses an 11-point Likert scale (0 = not at all, 5 = somewhat, and 10 = very much) to assess patients' level of concern about their upper facial lines during the previous 7-day period. In a recent study of JUVÉDERM® Ultra Injectable Gel, adaptations of the FLO-11 (i.e., LAF, Other Aesthetic Features, and Function and Sensation questionnaires) demonstrated dramatic improvements without significant change in function and sensation as assessed by subjects treated for aesthetic enhancement of the lips and perioral area (data on file).

10.5.3 Patient Reported Outcomes

Patient reported outcome (PRO) instruments have become important assessments in facial studies; since nonsurgical cosmetic procedures are voluntary, effectiveness of the results are primarily measured by patient satisfaction with the outcome.[54] Three PRO instruments were utilized in this study.

The Self Perception of Age questionnaire is relevant to a subject's treatment goal, and is a very simple to administer PRO. The SPA measure was previously used in studies demonstrating that Botox® Cosmetic or concurrent Botox® Cosmetic/HA filler treatment made subjects think they looked younger than their current age.[55,56]

Similar to the OAFM scale, the Look and Feel of the Mid-Face (LAFM) was also patterned after the FLO-11 and the LAF questionnaires.

The Facial Appearance Evaluation (FAE) was patterned after Alsarraf's validated instruments, developed for specific cosmetic procedures: facelift, rhinoplasty, blepharoplasty, and skin resurfacing, but includes additional items to explore the relation of facial appearance to gender, ethnic, and cultural aspects. Alsarraf reported on 4 PROs, each of which was validated with specific procedures, and included items that measure physical, mental, and social elements. The PROs used a 5-point Likert scale format for each of the 6 items, and those items are very similar across the 4 procedure-specific instruments.[57]

10.5.4 3D Imagery Volume Calculations

Objective measures of facial volume were obtained using standardized, three-dimensional (3D), digital photographic images. Objective measures of the change in facial volume were calculated by overlaying the pre- and post-treatment photos and calculating the difference in the 3D digital images. There is no assessment of actual 3D volume at baseline or at a follow-up visit; only the *change* in volume since baseline is provided.

Digital photography has recently been utilized as a tool for detecting changes in facial topography[58-60] and has been shown to be reproducible and reliable.[61] At the first visit, each subject bit on a sheet of warm dental wax to form a mold of the inside of the mouth, which was used at each subsequent visit for consistent positioning of the teeth and jaw during image capture. The volume change calculations were performed by Canfield Scientific using validated software.

11. VOLUMA-002 CLINICAL STUDY RESULTS

11.1 Subject Disposition

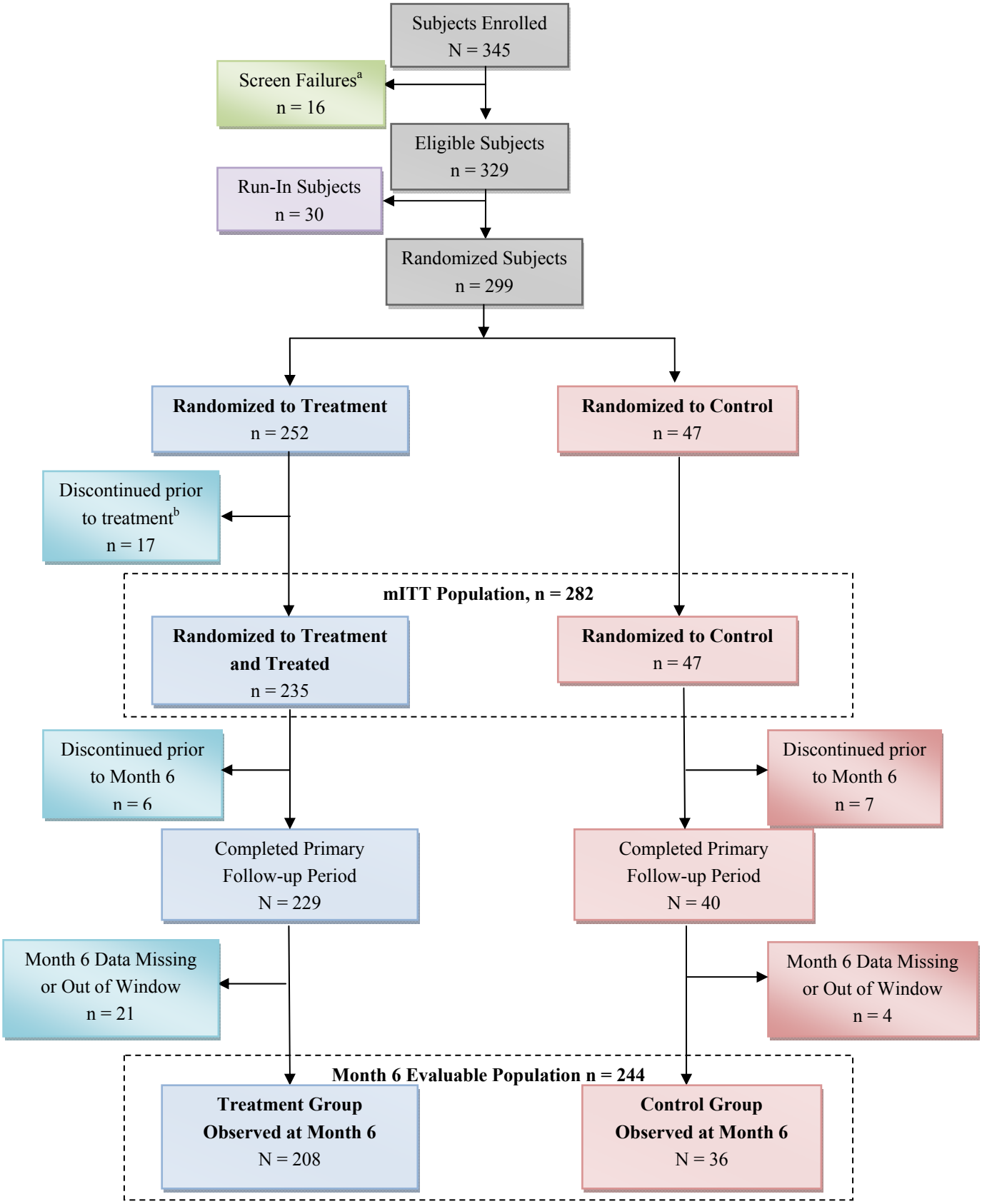
11.1.1 Primary Safety and Effectiveness Period

Subject disposition is presented in Figure 9. Enrollment was defined as the subject signing the IRB-approved consent form. A total of 345 subjects were enrolled in the study. Among these, 16 were screen failures, 30 were run-in subjects, and 17 discontinued prior to treatment. This led to a total of 282 subjects in the mITT population, of which 235 (83.3%) were randomized to the treatment group and continued to treatment, and 47 (16.7%) were randomized to the control group. The initial treatment period occurred between August 26, 2009 and June 17, 2010.

Overall subject visit compliance through the primary follow-up period (Month 6) for both treatment and control groups was high, with 97.4% (229/235) of treatment group subjects and 85.1% (40/47) of control group subjects completing the Month 6 visit. A total of 208 treatment group subjects and 36 control group subjects were evaluable at Month 6 for the primary endpoint assessment.

Overall, 270 subjects were randomized and treated in this study. This included 238 subjects treated at the onset of the study, including 235 randomized to the treatment group and 3 subjects in the control group treated in error; these errors are listed among the major protocol deviations (Section 11.3). The remaining 32 subjects were randomized to the control group and were not treated until after completing their “no-treatment” follow-up period.

Figure 9. Subject Disposition, mITT, and Month 6 Evaluable Populations



[a] Primary reason for screen failure was ineligibility (13 of 16 subjects)
[b] Primary reason for discontinuation prior to treatment was withdrawn consent (11 of 17 subjects)

11.1.2 Extended Follow-up Period

Three-fourths (74.0%, 174/235) of the treatment group completed the extended follow-up period by either remaining in the study until the post-treatment Month 24 visit (162 subjects) or stopping the follow-up earlier than Month 24 due to loss of correction of mid-face volume deficit in all treatment areas, as allowed by the protocol (12 subjects). Sixty-one subjects (26.0%) discontinued the study during the extended follow-up period primarily due to loss to follow-up (34.4%, 21/61) or withdrawal of consent (36.1%, 22/61).

As described above, 3 subjects randomized to the control group received treatment in error at the onset of the study, and 2 of these subjects completed the extended follow-up period. Of the remaining 44 control group subjects, 32 (68.1%) were treated after completing the primary blinded follow-up period, and, at the time of submission to FDA, 26 of the 32 (81.3%) have completed the post-treatment follow-up through Month 15. For those control subjects who discontinued, the primary reasons were loss to follow-up or withdrawn consent.

The compliance rates through Month 24 for treatment group subjects and Month 15 for control group subjects are noteworthy given that VOLUMA-002 clinical protocol prohibits any concurrent aesthetic procedures during the course of the study.

11.1.3 Repeat Treatment and Follow-up

Subjects who completed the extended follow-up were offered repeat treatment. At the time of submission to the FDA, 125 of the 187 mITT (66.8%) subjects who were offered repeat treatment have received treatment. As control subjects are currently completing the extended follow-up period, they had not yet been offered repeat treatment.

11.2 Subject and Treatment Characteristics

11.2.1 Subject Demographics

Subjects were primarily female (80.1%) with a median age at study entry of 55 years (range, 35-65). Fifty-eight percent were of Caucasian descent, and Fitzpatrick skin type enrollment targets were met. Demographics were similar for the treatment and control groups. Table 10 presents subject demographics for the mITT population.

Table 10. Subject Demographics: mITT

Characteristic		mITT (N = 282) % (n/N)	Treatment Group (N = 235) % (n/N)	Control Group (N = 47) % (n/N)
Gender				
	Female	80.1% (226/282)	80.4% (189/235)	78.7% (37/47)
	Male	19.9% (56/282)	19.6% (46/235)	21.3% (10/47)
Age (years)				
	Mean	54.4	54.4	54.7
	Standard Deviation	6.98	7.18	5.95
	Median	55.0	56.0	55.0
	Range (Min, Max)	(35, 65)	(35, 65)	(35, 65)
Race				
	Caucasian	58.5% (165/282)	58.3% (137/235)	59.6% (28/47)
	Hispanic	13.8% (39/282)	14.9% (35/235)	8.5% (4/47)
	African-American	19.9% (56/282)	18.7% (44/235)	25.5% (12/47)
	Asian	4.3% (12/282)	3.8% (9/235)	6.4% (3/47)
	Other[a]	3.5% (10/282)	4.3% (10/235)	0.0% (0/47)
Fitzpatrick Skin Type				
	I	2.8% (8/282)	2.6% (6/235)	4.3% (2/47)
	II	25.5% (72/282)	26.4% (62/235)	21.3% (10/47)
	III	27.7% (78/282)	28.5% (67/235)	23.4% (11/47)
	IV	20.2% (57/282)	18.3% (43/235)	29.8% (14/47)
	V	18.8% (53/282)	18.7% (44/235)	19.1% (9/47)
	VI	5.0% (14/282)	5.5% (13/235)	2.1% (1/47)
Geographical Location				
	Northeast (NE)	18.4% (52/282)	17.9% (42/235)	21.3% (10/47)
	Southeast (SE)	27.7% (78/282)	28.5% (67/235)	23.4% (11/47)
	Midwest (MW)	11.0% (31/282)	10.6% (25/235)	12.8% (6/47)
	Northwest (NW)	13.5% (38/282)	12.8% (30/235)	17.0% (8/47)
	Southwest (SW)	17.7% (50/282)	18.7% (44/235)	12.8% (6/47)
	Canada	11.7% (33/282)	11.5% (27/235)	12.8% (6/47)
Investigational Site (Geographical Region)				
	F0701(SW)	6.0% (17/282)	6.8% (16/235)	2.1% (1/47)
	F0702 (SW)	5.3% (15/282)	5.1% (12/235)	6.4% (3/47)
	F0703 (NW)	4.6% (13/282)	4.3% (10/235)	6.4% (3/47)
	F0704 (NE)	7.8% (22/282)	7.7% (18/235)	8.5% (4/47)
	F0705 (NW)	8.9% (25/282)	8.5% (20/235)	10.6% (5/47)
	F0706 (NE)	7.1% (20/282)	7.2% (17/235)	6.4% (3/47)
	F0707 (MW)	3.5% (10/282)	3.4% (8/235)	4.3% (2/47)
	F0708 (SE)	11.3% (32/282)	11.9% (28/235)	8.5% (4/47)
	F0709 (NE)	3.5% (10/282)	3.0% (7/235)	6.4% (3/47)
	F0710 (SE)	8.5% (24/282)	8.9% (21/235)	6.4% (3/47)
	F0711 (MW)	7.4% (21/282)	7.2% (17/235)	8.5% (4/47)
	F0712 (SW)	6.4% (18/282)	6.8% (16/235)	4.3% (2/47)
	F0713 (Canada)	5.3% (15/282)	5.1% (12/235)	6.4% (3/47)
	F0714 (Canada)	6.4% (18/282)	6.4% (15/235)	6.4% (3/47)
	F0715 (SE)	7.8% (22/282)	7.7% (18/235)	8.5% (4/47)

[a] Other races include American Indian (Cherokee), Indian + Caucasian, Native American (2 subjects), Asian/African American, Black Hispanic, Black/Indian/Caucasian, Persian, Dominican Republic/Italian, and Arabic

Table 11 provides the Treating Investigator's baseline assessment of the subject's mid-face volume deficit (where a score of 0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = significant, and 5 = severe). Most subjects had either moderate (51.5% and 51.1% for the treatment and control group, respectively) or significant (41.7% and 44.7%, respectively) volume deficit in their overall mid-face.

Table 11. Subject MFVDS Baseline Characteristics

	None (0)	Minimal (1)	Mild (2)	Moderate (3)	Significant (4)	Severe (5)
	%	%	%	%	%	%
Treatment Group (N=235)						
Overall Mid-Face	0.0%	0.4%	2.6%	**51.5%**	**41.7%**	**3.8%**
Zygomaticomalar Region	0.0%	2.6%	13.6%	45.5%	35.3%	3.0%
Anteromedial Cheek	0.0%	0.9%	5.1%	45.1%	42.6%	6.4%
Submalar Region	0.0%	4.7%	14.0%	43.0%	31.9%	6.4%
Control Group (N=47)						
Overall Mid-Face	0.0%	2.1%	0.0%	**51.1%**	**44.7%**	**2.1%**
Zygomaticomalar Region	0.0%	6.4%	8.5%	44.7%	38.3%	2.1%
Anteromedial Cheek	0.0%	0.0%	2.1%	42.6%	51.1%	4.3%
Submalar Region	2.1%	4.3%	4.3%	57.4%	27.7%	4.3%

11.2.2 Treatment Administration

Of the 270 treated mITT subjects, 221 subjects (81.9%) also had touch-up treatment because it was deemed necessary by the Treating Investigator. At the time of submission to the FDA, 125 subjects (46.3%) had undergone repeat treatment. All treatment administration characteristics (anesthesia, plane of injection, injection techniques, needle sizes) were similar for initial, touch-up, and repeat treatment. The only exception was volume injected; much smaller volumes were used at touch-up as well as at repeat treatment compared to volumes injected at initial treatment.

Anesthesia

Anesthesia was administered to 179 of the 270 treated mITT subjects (66.3%) in preparation for their initial treatment, and many subjects had more than one type of anesthesia during initial treatment. Methods of administering anesthesia are described in Table 12.

Table 12. Types of Anesthesia Used During Initial Treatment

Type of Anesthesia	Initial Treatment % (n/N)
Topical Agent	77.1% (138/179)
Ice	55.3% (99/179)
Nerve Block	15.6% (28/179)
Local Anesthesia	15.1% (27/179)

Treatment Sites

Initial treatment was performed in the 3 mid-facial treatment sites with roughly equal frequency, and the majority of subjects received treatment in all 3 areas (Table 13). Touch-up and repeat treatment was performed least often in the submalar region.

Table 13. Treatment Sites

Treatment Region	Initial Treatment % (n/N)	Touch-Up Treatment % (n/N)	Repeat Treatment % (n/N)
Zygomaticomalar	96.7% (261/270)	81.4% (180/221)	88.0% (110/125)
Anteromedial	95.6% (258/270)	77.8% (172/221)	84.0% (105/125)
Submalar	93.0% (251/270)	62.4% (138/221)	66.4% (83/125)

Injection Volumes

The volume injected for treated mITT subjects is shown in Table 14. Subjects received a mean volume of 6.79 mL for intial and touch-up treatments combined.

Table 14. Volume Injected for Treated mITT Subjects

	Initial Treatment (N = 270)	Touch-up Treatment (N = 221)	Initial & Touch-up Combined[a] (N = 270)	Repeat Treatment (N = 125)
Median	4.8 mL	1.9 mL	6.6 mL	2.0 mL
Mean	5.2 mL	2.0 mL	6.8 mL	2.6 mL
Standard Deviation	2.5 mL	1.3 mL	3.0 mL	2.0 mL
Range (Min, Max)	(1.0 mL, 12.0 mL)	(0.1 mL, 7.0 mL)	(1.2 mL, 13.9 mL)	(0.2 mL, 12.0 mL)

[a] Not all subjects received *both* initial and touch-up treatment

On average, subjects with a higher mid-face volume deficit at baseline received higher volumes, as expected. Subjects with a moderate baseline MFVDS score had median volume of 5.2 mL, whereas subjects with “significant” or “severe” deficit had a median volume of 7.9 mL and 8.5 mL, respectively.

Planes of Injection

For initial treatment, the majority of subjects were treated using a combination of subcutaneous and supraperiosteal injections (85.9% overall, 232/270) except for the submalar region, where the majority of injections were only subcutaneous injections (72.4%, 181/250).

Injection Technique

Multiple injection techniques were used for the majority of mITT subjects, with 70% of subjects receiving at least 4 techniques, and no differences between those treated in the primary and extended follow-up periods. Injection techniques included tunneling, fanning, and serial puncture at approximately equal rates (77.4%, 75.2%, and 75.2%, respectively), with some crosshatching (48.1%) and minimal ferning (4.1%).

Needle Size

At initial treatment 50.0% of subjects were injected with a 27 G x ½" UTW (135/270) needle and 48.5% of subjects with a 25 G x 1" UTW (131/270), with a small number of other needles used (primarily 25 G x 5/8"). Touch-up treatment and repeat treatment needle usage was similar.

Massage

Gentle (44.1%, 119/270) to moderate (33.3%, 90/270) massage after injection was frequently used and facilitated with topical gel in 55.6% of subjects (150/270). During touch-up and repeat treatment massage was similar though topical gel was slightly less common.

Pain

Subjects assessed pain of injection on an 11-point scale, where 0 is no pain and 10 is the worst pain imaginable. Mean pain scores were generally low at all treatments: initial (3.0), touch-up (2.5), and repeat (2.1) treatments.

Biopsy

A total of 211 subjects received a mean 0.1 mL depot injection either behind their ear or in the medial aspect of the upper inner arm for potential later biopsy. Among these subjects, 36 were randomized for biopsy at 1 of the follow-up visits, 21 subjects underwent the biopsy, and their histopathology results are provided in Section 12.5. Fifteen subjects did not undergo the biopsy because they either missed the biopsy visit or exited the study prior to the visit (6 subjects), withdrew consent for biopsy or declined the biopsy (5 subjects), the site forgot to do the biopsy which was noted as a protocol deviation (2 subjects), or the depot site could not be located at the time of biopsy (2 subjects).

11.3 Protocol Deviations

Protocol deviations that would be likely to confound the primary effectiveness measurement were considered major protocol deviations. Twenty-five randomized subjects had 27 major protocol deviations. Two of the 25 subjects were randomized to treatment but discontinued the study before actually receiving treatment, resulting in 23 mITT subjects who were excluded from the PP population. Table 15 summarizes the major deviations for the 25 subjects. Notably, in no instance was the Evaluating Investigators' blind broken.

Table 15. Major Protocol Deviations (Treatment and Control Subjects)

Subject	Visit	Deviation Description	Detail
Treatment Group			
[redacted]	Screening	Inclusion/Exclusion	Intense pulsed light occurred within washout period
	Screening	Baseline Assessment Error	Subject ineligible due to MFVDS score <3 as assessed by the Treating Investigator
	Screening	Baseline Assessment Error	Subject ineligible due to MFVDS score <3 as assessed by the Treating Investigator
	Screening	Baseline Assessment Error	Subject ineligible due to MFVDS score <3 as assessed by the Treating Investigator (subject was randomized but was never treated)
	Screening	Baseline Assessment Error	Subject ineligible due to MFVDS score <3 as assessed by the Treating Investigator
	Initial Treatment	Inclusion/Exclusion	Subjects had facelift had 10 years ago
	Initial Treatment	Inclusion/Exclusion	Subject had JUVÉDERM® injected in the NLF within the washout period
	Initial Treatment	Inclusion/Exclusion	Subject had cosmetic history of semi-permanent filler (Sculptra®)
	Initial Treatment	Inclusion/Exclusion	Subject had blepharoplasty surgery
	Initial Treatment	Inclusion/Exclusion	Subject had cosmetic history of semi-permanent filler (Radiesse®)
	Initial Treatment	Inclusion/Exclusion	Subject had eyelid lift
	Initial Treatment	Inclusion/Exclusion	History of laser hair removal (upper lip) within washout period
	Initial Treatment	Inclusion/Exclusion	Subject had cosmetic procedure of Botox® injection in glabellar area within the washout period
	Initial Treatment	Inclusion/Exclusion	Subject had cosmetic procedure of Botox® injection in glabellar area within the washout period
	Initial Treatment	Prohibited Treatment or Procedure	Laser was used for bruising 1 day following study treatment
	Initial	Prohibited Treatment or	Subject had VBeam (pulsed-dye laser) 1

Subject	Visit	Deviation Description	Detail
	Treatment	Procedure	day following study treatment
	Touch-up Treatment	Treatment Error	Total volume injected at Initial and Touch-up treatment combined exceeds 12 mL (13.9 mL total)
	Month 1	Prohibited Treatment or Procedure	Treated with hyaluronidase for lumps/bumps
	Unscheduled Post-Month 1	Prohibited Treatment or Procedure	Treated with hyaluronidase for overcorrection
	Month 3	Prohibited Treatment or Procedure	Subject had permanent lip and eye liner procedure
	Month 6	Prohibited Treatment or Procedure	Subject received prohibited concomitant medication of Botox® injection in glabellar area
Control Group			
	Screening	Baseline Assessment Error	Subject ineligible due to MFVDS score <3 as assessed by the Treating Investigator
	Initial Treatment	Treatment Error	Control subject treated with study product
	Initial Treatment	Inclusion/Exclusion	Subject had cosmetic procedure of Botox® injection in glabellar area within washout period
	Initial Treatment	Treatment Error	Control subject treated with study product
	Initial Treatment	Treatment Error	Control subject treated with study product
	Touch-up Treatment	Prohibited Treatment or Procedure	Treated with hyaluronidase for reduction of lumps/bumps

11.4 EFFECTIVENESS RESULTS

Results for the treatment group through Month 24 are discussed in the sections below. Results from the control group during the primary blinded follow-up period (i.e., prior to treatment) and extended follow-up period (i.e., after treatment) up to the Month 12 visit are also discussed. Complete 18-month data for the control group were not available at the time of data submission to the Agency.

11.4.1 Primary Effectiveness Results

Both primary effectiveness criteria of the study were met. More than 70% ($p < 0.0001$) of subjects in the treatment group were responders at Month 6 (85.6% improved by ≥ 1 grade compared with their pre-treatment assessment), and the responder rate for the treatment group was significantly greater ($p < 0.0001$) than the responder rate for the control group (a difference of 46.7 percentage points) at Month 6 (Figure 10 and Table 16). The primary effectiveness analysis was performed on the mITT population without data imputation (i.e., the analysis included only those mITT subjects with an MFVDS assessment within the

Month 6 analysis window), as planned in the study protocol. The analysis was based on the "as-randomized" assignment and, thus, the control group responder rate includes assessment for 2 control group subjects who were treated in error at the start of the study and provided a Month 6 assessment. The third control group subject treated in error did not provide data within the Month 6 analysis window.

Figure 10. Primary Endpoint Analysis

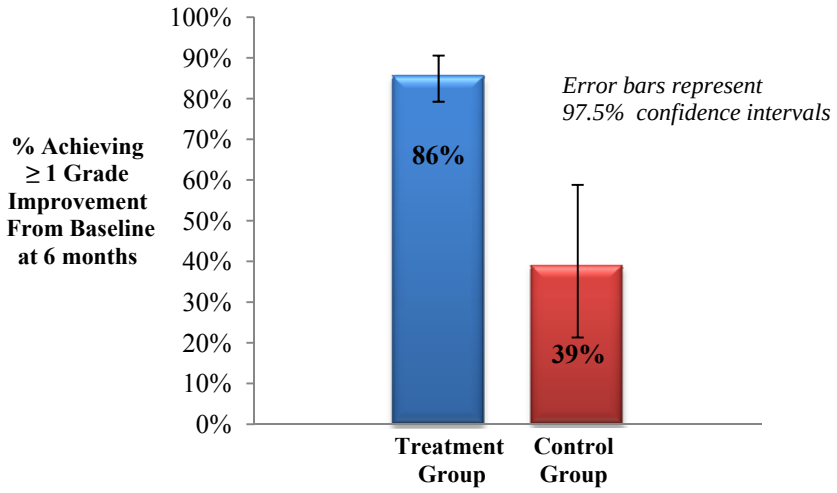


Table 16. Primary Effectiveness Analysis (mITT Population)

	Responder Rate at Month 6[a]	97.5% CI	p-value
Treatment Group	85.6% (178/208)	(79.24%, 90.59%)	<0.0001[b]
Control Group[c]	38.9% (14/36)	(21.33%, 58.82%)	
Difference in Responder Rates (Treatment rate - Control rate)	46.7%		<0.0001[d]

[a] Five subjects attended the Month 6 visit but did not have the MFVDS assessment completed and are not included in this table
[b] p-value corresponding to the exact binomial test to demonstrate that responder rate for the treatment group is greater than 70%, where responder rate is the percent of subjects with at least 1-point improvement since baseline based on the average of the 2 EIs' assessments of the subject's overall mid-face volume deficit
[c] Includes 2 subjects who were treated in error and evaluable at Month 6
[d] p-value corresponding to the 2-sided 2-group Fisher's exact test to demonstrate that responder rate for the treatment group is superior to that of the control group

The observed control group response was anticipated in the VOLUMA-002 study protocol, with as much as a 40% control response as a possible outcome for a control of this type in an aesthetic outcome study using a subjective visual scale to measure the primary effectiveness endpoint. The 39% Month 6 responder rate observed in the control group is not unusually high in the context of other studies of facial aesthetic treatments. For example, the US pivotal study of Restylane® for lip augmentation (P040024/S051) yielded a responder rate of

37% in the "no-treatment" control group at 6 months. Similarly, the 2 US pivotal studies for LAVIV for the correction of facial wrinkles and folds (BL 125348/0) showed responder rates of 36% and 48% for the sham control group subjects at 6 months.

The primary endpoint analysis is based on subjects' randomized assignment (under an intent-to-treat principle) and, as such, the Month 6 control group mITT responder rate of 39% includes 2 control subjects treated in error and providing Month 6 data. When these and all other major protocol deviations are excluded in the Per Protocol (PP) analysis, the responder rate of the treatment group remains essentially unchanged while the responder rate of the control group decreases to 29% (Table 17).

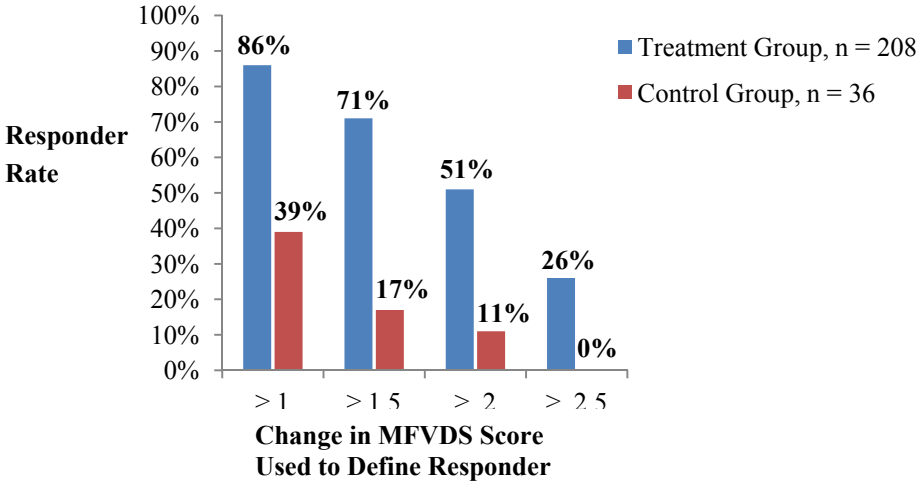
Table 17. Month 6 MFVDS Responder Rates (PP Population)

	Responder Rate at Month 6	97.5% CI	p-value
Treatment Group	87.0% (168/193)	(80.65%, 91.96%)	<0.0001[a]
Control Group	29.0% (9/31)	(12.69%, 50.58%)	
Difference in Responder Rates (Treatment rate - Control rate)	58.0%		<0.0001[b]

[a] p-value corresponding to the exact binomial test to demonstrate that responder rate for the treatment group is at least 70%, where responder rate is the percent of subjects with at least 1 point improvement since baseline based on the average of the 2 Evaluating Investigators' assessments of the subject's overall mid-face volume deficit
[b] p-value corresponding to the 2-sided 2-group Fisher's exact test to demonstrate that responder rate for the treatment group is superior to that of the control group

In VOLUMA-002, Evaluating Investigators performed a live visual assessment of the subject to score their mid-face volume deficit using the MFVDS; they were blinded to randomization assignment and did not compare the subject's appearance to a baseline photo. As discussed in Section 10.1.4, a 40% responder rate was assumed in the calculation of statistical power for the primary endpoint criteria that the responder rate in the treatment group must be statistically significantly greater than that of the control group. Prior to the clinical trial, a 1-point difference in MFVDS scale scores was established as clinically different. However, only 15% of subjects had exactly a 1-point improvement. As seen in Figure 11, if a larger MFVDS improvement is used to define responders, a substantial response rate is still seen in the treatment group, while the control group rate drops dramatically. This result suggests that the responder rate in the control group may be due, in part, to variability in the subjective MFVDS ratings among the Evaluating Investigators. The impact of subjectivity can be further reduced by classifying the subject as a responder only if the MFVDS ratings of *both* Evaluating Investigators showed a 1-pt or greater improvement. When this analysis was performed, the control rate dropped by two-thirds (from 39% to 14%), while the treatment group rate remained high at 76%.

Figure 11. Responder Rate at Month 6 for Various MFVDS Improvements



Sensitivity Analysis for Imputation of Missing Data

Although the primary effectiveness analysis was performed on observed cases as planned in the protocol, to understand the impact of missing observations on the primary effectiveness analysis, the analysis was repeated with various imputation scenarios for missing data. These scenarios included best case (i.e., all missing subjects in the treatment group imputed as responders and all missing subjects in the control group imputed as non-responders), all subjects with missing data imputed as responders, half missing data as responders, all missing as non-responders, and worst case (i.e., all missing treatment as non-responders, and all missing control as responders). Further, a tipping point analysis was also performed in which all combinations of imputing missing treatment and control subjects as responders or non-responders were applied. A tipping point analysis identifies all scenarios (including the ones identified above) which result in the change in the study conclusion (i.e., insignificance of at least 1 of the primary endpoints).

The imputation analyses confirm that the primary effectiveness result is robust and largely insensitive to the method of imputation. In the treatment group, 27 subjects had missing observations at Month 6, whereas in the control group, 11 subjects had missing observations. For the endpoint that > 70% of the treatment group will be responders, a tipping point was observed only when ≥ 25 out of 27 subjects with missing data were imputed as non-responders. Considering that the observed responder rate in the treatment group was 86%, this imputation scenario seems unlikely.

For the comparison of treatment to control group responder rates, all scenarios demonstrated significance, and no tipping point was found that could eliminate significance. Even under the worst case scenario, the difference in responder rates was still significant (22.6%, $p = 0.0025$).

Table 18 shows the difference in responder rates of treatment and control group and confidence intervals for the difference under the various data imputation scenarios.

Table 18. Difference in Treatment and Control Group MFVDS Responder Rates at Month 6 with Data Imputation Scenarios

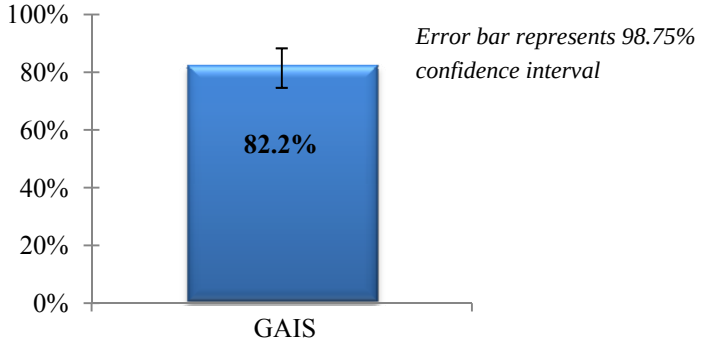
Imputation Scenario	Difference (Treatment – Control)	97.5% CI
Observed Cases; N = 244	46.7%	27.7, 65.7
Best case: All missing Treatment as success All missing Control as failure[a]	57.4%	41.7, 73.2
All missing as success[a]	34.0%	17.0, 51.1
Half of missing as failure[a]	39.1%	22.0, 56.3
All missing as failure[a]	46.0%	29.8, 62.2
Worst Case: All missing Treatment as failure All missing Control as success	22.6%	5.1, 40.0

[a] n= 282 for imputation scenarios with results for 27 Treatment subjects and 11 Control subjects imputed

11.4.2 Secondary Effectiveness Results

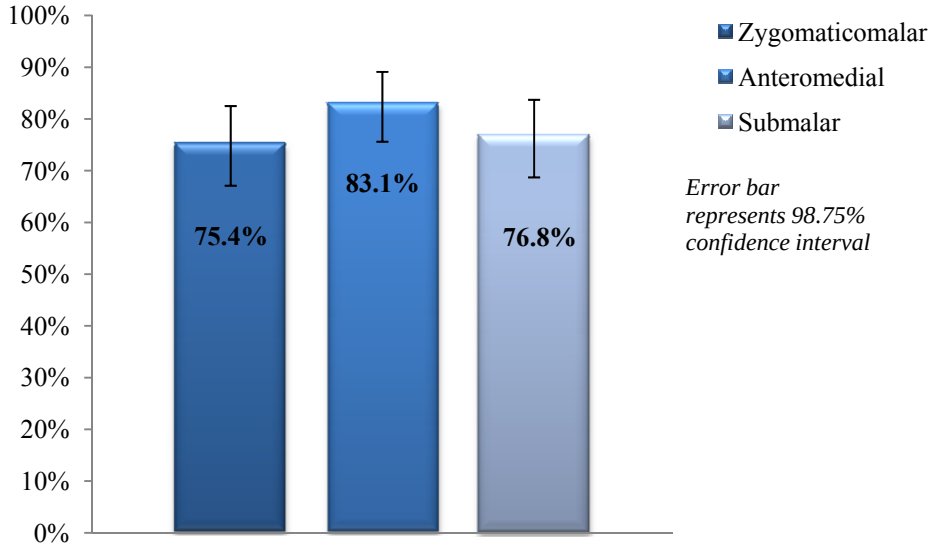
The GAIS responder rate for the treatment group as assessed by Evaluating Investigators at Month 6 was 82.2% (171/208) (Figure 12). This demonstrates that the vast majority of treatment group subjects were considered to have improvement in their facial appearance compared to baseline photographs.

Figure 12. GAIS Responder Rate at Month 6



The Month 6 responder rate for the improvement in volume deficit for each mid-facial region was 75.5% (157/208) for the zygomaticomalar region, 83.2% (173/208) for the anteromedial cheek region, and 76.9% (160/208) for the submalar region (Figure 13) demonstrating that each region was improved for most subjects.

Figure 13. MFVDS Responder Rates by Mid-Face Region at Month 6



11.4.3 Effectiveness Beyond Month 6 using MFVDS and GAIS

Effectiveness Results Beyond Month 6 using MFVDS

The overall MFVDS responder rate for the treatment group through Month 24 and the responder rates for the control group through Month 18 (after delayed treatment) are provided in Table 19. At Month 24, 67.1% of treatment group subjects (112/167) had a 1 point or greater improvement in their overall MFVDS since baseline, as determined by the average of the 2 blinded Evaluating Investigators. In the control group after treatment, a 73.1% responder rate (19/26) was observed at Month 12.

Table 19. MFVDS Responder Rates through Month 24

	N	Responder Rate % (n/N)
Treatment Group		
Month 1	205	87.3% (179/205)
Month 3	214	85.5% (183/214)
Month 6	208	85.6% (178/208)
Month 9	209	86.6% (181/209)
Month 12	203	85.2% (173/203)
Month 18[a]	179	71.5% (128/179)

Month 24[a]	167	67.1% (112/167)
Control Group		
Primary Follow-up Period (no treatment)		
Month 1	38	28.9% (11/38)
Month 3	35	37.1% (13/35)
Month 6	36	38.9% (14/36)
Extended Follow-up Period (after treatment)		
Month 1	25	96.0% (24/25)
Month 3	29	86.2% (25/29)
Month 6	29	82.8% (24/29)
Month 9	29	82.8% (24/29)
Month 12	26	73.1% (19/26)
Month 18[a]	21	61.9% (13/21)

[a] Subjects who lost correction at earlier visits and exited the extended follow-up period are counted as non-responders at these visits

Effectiveness Results Beyond Month 6 Using GAIS

The GAIS responder rate for the treatment group through Month 24 and control group through Month 12 are provided in Table 20. At Month 24, the GAIS responder rate for the treatment group was 69.7% (n=155), compared to 78.3% (n=203) at Month 12. The GAIS responder rates for the control groups after treatment were similar.

Table 20. GAIS Responder Rates through Month 24

	n/N	Percent
Treatment Group		
Month 1	176/205	85.9%
Month 3	180/214	84.1%
Month 6	171/208	82.2%
Month 9	171/210	81.4%
Month 12	159/203	78.3%
Month 18[1]	119/175	68.0%
Month 24[1]	108/155	69.7%
Control Group (after treatment)		
Month 1	23/25	92.0%
Month 3	25/29	86.2%
Month 6	23/29	79.3%
Month 9	21/29	72.4%
Month 12	20/26	76.9%
Month 18	16/19	84.2%

Effectiveness Results Beyond Month 6 Using MFVDS by Facial Region

At Month 24, the responder rates in the zygomaticomalar, anteromedial cheek, and submalar region for the treatment group were 58.1%, 68.3%, and 56.9%, respectively. The responder rates for the control group at Month 12 after treatment were 46.2%, 76.9%, and 61.5%, respectively in the 3 regions.

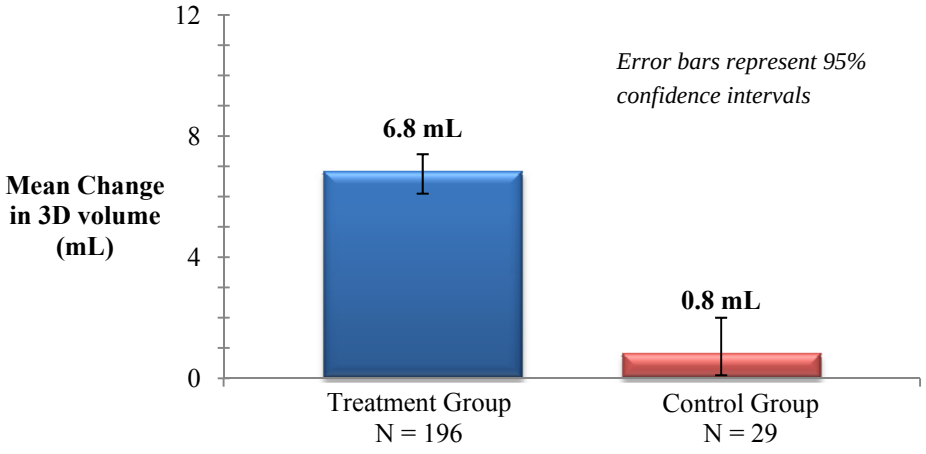
11.4.4 Additional Effectiveness

Most of the additional effectiveness measures showed an improvement from baseline to after treatment followed by a gradual decline after Month 12. This section details the effectiveness at Month 6 for the treatment group. Control group subjects showed similar improvements as the treatment group after receiving treatment.

Quantitative 3D Volume Change

The non-subjective assessment of volume changes calculated from the 3D digital images confirms the results from the scale assessments. Digital imaging showed clear evidence of changes in facial volume after treatment with VOLUMA™ XC. Mean volume in the face calculated from the 3D digital images for the treatment group increased since baseline by 6.8 mL at Month 6 whereas the control group's mid-facial volume before treatment was essentially unchanged from baseline (an increase of 0.8 mL). These objective measurements reinforce the results of subjective assessments by blinded Evaluating Investigators that volume deficit and facial appearance had improved (Figure 14) and correlates with the mean volume used at initial treatment (6.8 mL, Table 14).

Figure 14. 3D Imaging Calculation of Mid-Face Volume Change from Baseline to Month 6



Nasolabial Fold Severity

Although subjects did not receive treatment in the NLFs, NLF severity improved from baseline for some subjects. Thirty-two percent of treatment group subjects had a 1-point or greater improvement on the NLF severity scale at Month 6.

Aesthetic Features of the Mid-Face Area

The Evaluating Investigators' overall satisfaction with the subject's aesthetic features in repose and in animation was provided on a scale of 0 (not at all satisfied) to 10 (very much satisfied). Only 9.4% of treatment group subjects in repose were classified as satisfied at baseline (i.e., EIs provided a score of 7-10) compared to 68.8% at Month 6.

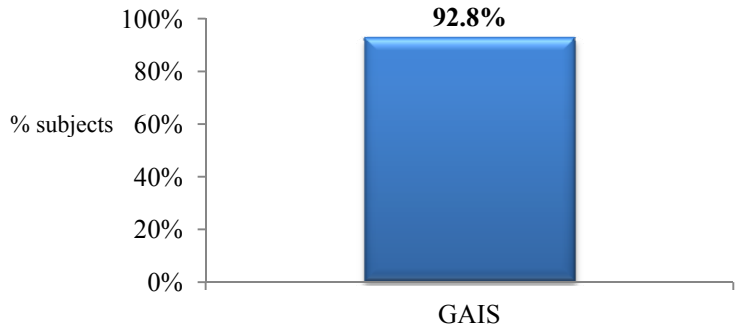
Scores for satisfaction in animation were slightly higher than those for in repose. For the treatment group, 14.5% of subjects were in the 7-10 range at baseline, increasing to 79.1% at Month 6.

11.4.5 Subject Self-Assessments

As described in Section 10.2.3, prior to treatment and at follow-up visits, subjects performed a number of self-assessments. Results at Month 6 are detailed below for the treatment group. Control group subjects showed similar results at Month 6 post-treatment.

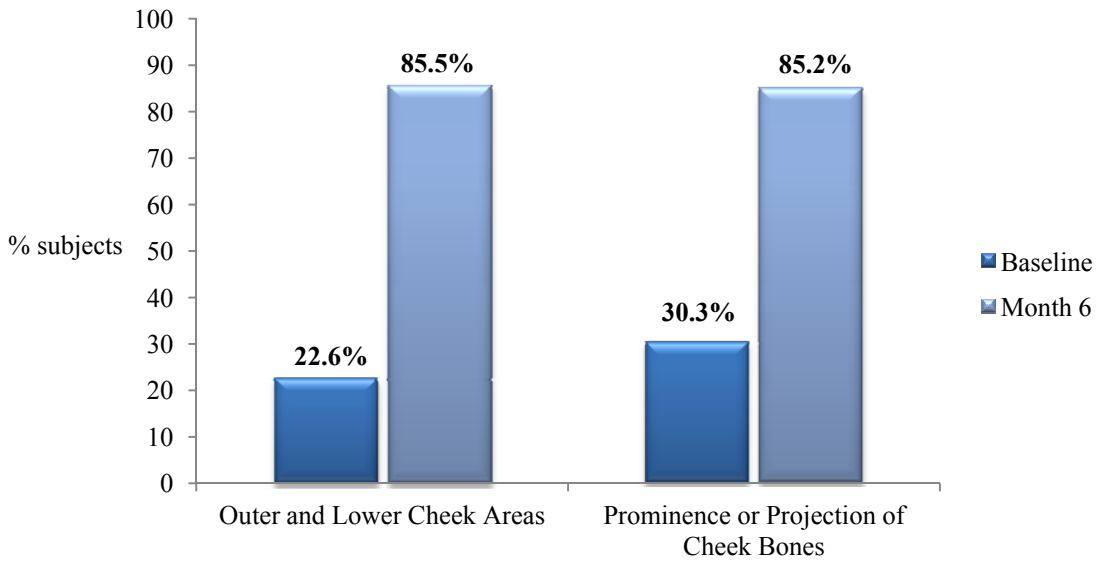
- Subject evaluation of mid-face volume deficit *after treatment*: Over half of subjects improved 1 point or more on the MFVDS scale at Month 6 (58.0%).
- GAIS assessment 6 months after treatment: 92.8% of treatment group subjects rated themselves as improved or much improved (Figure 15). This high responder rate is consistent with EI assessments of subjects on the GAIS, where 82.2% of subjects were rated as improved or much improved by the blinded EIs. (Figure 12, Section 11.4.2).

Figure 15. Subject GAIS Assessment



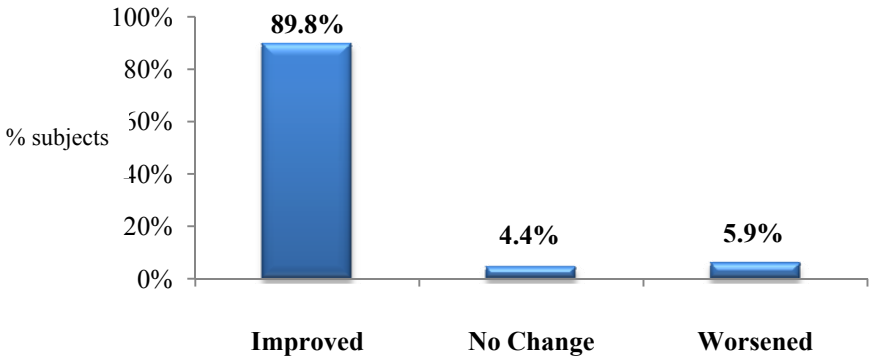
- Subject satisfaction with appearance of the 5 mid-facial areas (outer and lower cheeks, prominence or projection of cheek bones, sides of nose, tear troughs, and NLFs): improved at Month 6 compared to baseline (Figure 16).

Figure 16. Subject Satisfaction with Mid-Face Regions



- Self-perception of age: At Month 6, 72% of treatment group subjects rated themselves as looking younger; on average subjects thought they looked 5 years younger
- Facial Appearance Evaluation: At Month 6, 90% of subjects reported improvement in satisfaction scores since baseline (Figure 17).

Figure 17. Satisfaction with Facial Appearance Since Baseline



- Look and Feel of the Mid-Face: Improvement for 4 of the 9 categories (cheeks made the subject look older, sad, tired, and unattractive). In the other 5 categories, subjects

noted at both baseline and Month 6 that their cheeks did not feel hard, lumpy or grainy, or unnatural, and did not look uneven or unnatural. There was an improvement in satisfaction with the look and feel of the face after treatment followed by a gradual decline over time

11.4.6 Subgroup Analysis

As discussed in Section 10.4.1, the MFVDS responder rates at Month 6 for the treatment group were summarized for subgroups defined by gender, race, Fitzpatrick skin type, baseline volume deficit, plane of injection, injection technique, injection volume, geographical region, and investigational site. Table 21 summarizes the MFVDS responder rates at Months 6, 12, and 24 to show responder rate trend over time. The MFVDS responder rate at Month 6 for the majority of subgroups is generally similar to the overall mITT results.

Table 21. Subgroup Effectiveness Analyses for Treatment Group

Subgroup (N[a])	Overall MFVDS Responder Rate		
	Month 6 %	Month 12 %	Month 24 %
Gender			
Female (169)	84.0	84.8	66.4
Male (39)	92.3	87.2	69.7
Race			
Caucasian (124)	91.9	88.1	70.7
Hispanic (29)	93.1	90.3	64.0
African-American (38)	63.2	77.1	53.6
Asian (7)	100	88.9	100
Other (10)	60.0	60.0	55.6
Fitzpatrick Skin Type			
I (6)	100	100	60.0
II (58)	93.1	85.5	73.8
III (57)	89.5	93.2	70.8
IV (36)	88.9	88.9	70.6
V (41)	63.4	65.8	48.4
VI (10)	90.0	90.0	71.4
Baseline Volume Deficit			
Moderate (103)	76.7	80.8	61.7
Significant (90)	96.7	90.9	73.7
Severe (8)	100	100	83.3
Plane of Injection			
Subcutaneous (205)	86.8	85.2	67.5
Supraperiosteal (191)	84.8	85.3	66.3
Injection Technique			
Retrograde Direction (164)	82.9	83.1	66.9
Antegrade Direction (113)	94.7	92.1	75.5
Tunneling (169)	87.0	85.3	69.5
Fanning (162)	86.4	85.4	70.5
Other (195)	85.1	84.7	68.4
Injection Volume			
≤ 6.5 mL (100)	74.0	77.0	57.0
> 6.5 mL (108)	96.3	93.2	76.1
Geographical Region			
Northeast (40)	62.5	69.4	65.4
Southeast (59)	84.7	78.9	62.7
Midwest (23)	87.0	100	50.0
Northwest (27)	96.3	89.3	78.9
Southwest (37)	97.3	94.7	75.0
Canada (22)	95.5	91.7	69.6
Investigational Site			
F0701 (14)	100	92.3	58.3
F0702 (12)	100	100	90.9
F0703 (8)	87.5	80.0	83.3
F0704 (17)	94.1	88.2	100
F0705 (19)	100	94.4	76.9
F0706 (16)	12.5	25.0	10.0

Subgroup (N[a])	Overall MFVDS Responder Rate		
	Month 6 %	Month 12 %	Month 24 %
F0707 (7)	57.1	100	33.3
F0708 (21)	90.5	81.8	71.4
F0709 (7)	100	100	NR[b]
F0710 (21)	71.4	68.4	25.0
F0711 (16)	100	100	53.8
F0712 (11)	90.9	92.9	77.8
F0713 (12)	91.7	91.7	45.5
F0714 (10)	100	91.7	91.7
F0715 (17)	94.1	87.5	92.9

[a] n's shown are for subjects in the subgroup who provided a Month 6 assessment

The potential impact of demographic, baseline, or treatment administration characteristics on effectiveness was analyzed using multiple logistic regression with responder rate as the dependent variable and the covariates as the independent variables. In this analysis, the p-value for each covariate tests the hypothesis that the responder rate for the treatment group is equal for all strata of that covariate in the presence of all other covariates in the multivariate model. Significance of a variable at the 10% level implies that the covariate may predict the responder rate (i.e., responder rates differ among the strata of that covariate). Logistic regression analysis revealed that baseline volume deficit, skin type, geographical location, volume injected, and injecting the device in an antegrade manner were the only significant covariates relating to responder rates. Subjects with significant or severe baseline deficit were more likely to be responders than those with moderate baseline deficit, possibly due to having a greater margin for improvement from baseline. Those treated with higher injection volumes yielded more responders than those treated with lower injection volumes. Subjects in the northeast region and subjects of skin type V had lower responder rates compared to other regions or other skin types. A higher responder rate was also observed among subjects injected in an antegrade manner compared to those subjects who were not injected in that manner (Table 22).

Table 22. Month 6 Multivariate Subgroup Effectiveness Analyses for Treatment Group

Subgroup	p-value[a]
Gender (Female vs. Male)	0.1043
Race (Overall)	0.2582
Fitzpatrick Skin Phototype (Overall)	0.0483
Baseline Volume Deficit[b] (Overall)	0.0615
Investigational Site (Overall)	0.6685
Geographical Location (Overall)	0.0095
Plane of Injection[c]	
Supraperiosteal (Yes vs. No)	0.7435
Injection Technique[c]	
Tunneling (Yes vs. No)	0.1002
Fanning (Yes vs. No)	0.8310
Other[d] (Yes vs. No)	0.3330
Retrograde Direction (Yes vs. No)	0.5742
Antegrade Direction (Yes vs. No)	0.0375
Volume Injected[e] (mL)	0.0034

[a] p-value tests the hypothesis that the responder rate for the treatment group is equal for all strata of the subgroup variable, with all other subgroup variables in the multivariate model
[b] Treating Investigator's assessment of overall mid-face volume deficit at baseline
[c] Plane of injection or injection technique at an treatment area at initial or touch-up treatment. Subcutaneous plane of injection (Yes vs. No) is not included in the model since almost all subjects except 3 have used that plane of injection and hence the variable does not include enough variation to allow convergence of the model.
[d] Other includes serial puncture, ferning, and crosshatching
[e] Total volume injected at initial and touch-up treatment combined

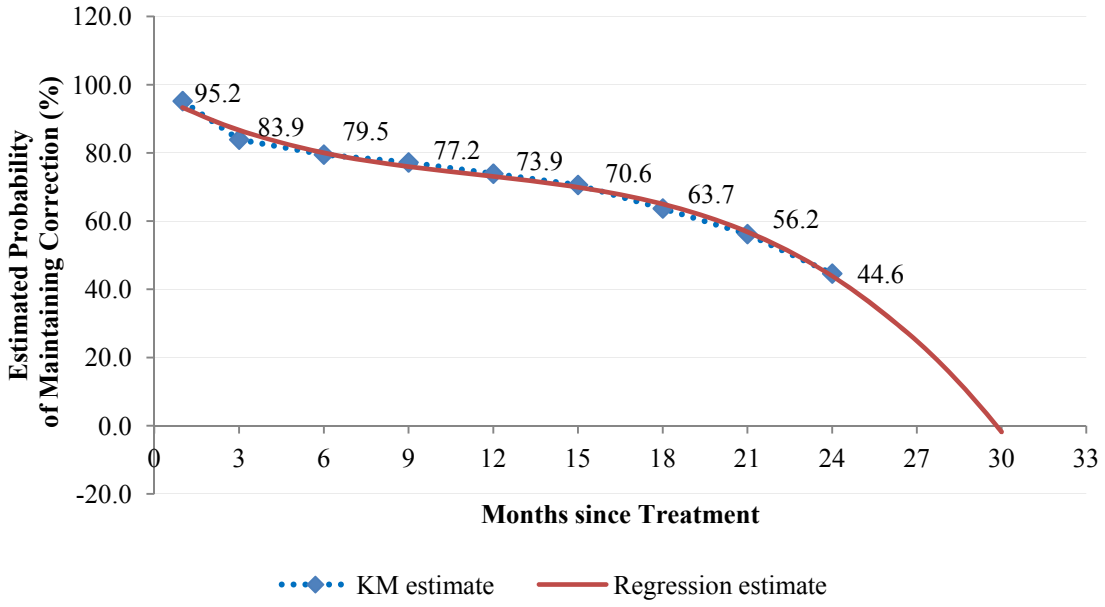
11.5 Duration of Effect

Figure 18 depicts the duration of effect of the product for the treatment group over time. As some subjects discontinued from the study or received re-treatment prior to establishing the timepoint at which correction was lost, duration of effect was determined using Kaplan-Meier estimates of the probability of retaining at least a 1-point improvement in overall MFVDS since baseline, as determined by the average of the 2 blinded Evaluating Investigators. This analysis is more conservative than the responder rate analysis because it is based on the first timepoint when a subject loses correction and also takes into account subjects with early discontinuations from the study.

The points in Figure 18 are the Kaplan-Meier estimates of the probability of maintaining the correction in mid-face volume deficit at each timepoint. More than half of treated subjects (56.2%) are estimated to maintain a duration of effect through Month 21, decreasing to 44.6% at Month 24. To predict the duration of volumizing effect VOLUMA™ XC after Month 24, a third-order polynomial was fit to the data through Month 24 using "Months since Treatment" as the explanatory variable and "Estimated Probability of Maintaining Correction" as the response variable. The solid curve based on the polynomial model is an

excellent fit to the estimated values ($R^2 = 0.99$). Extrapolating the curve past Month 24 predicts a zero responder rate at almost 30 months.

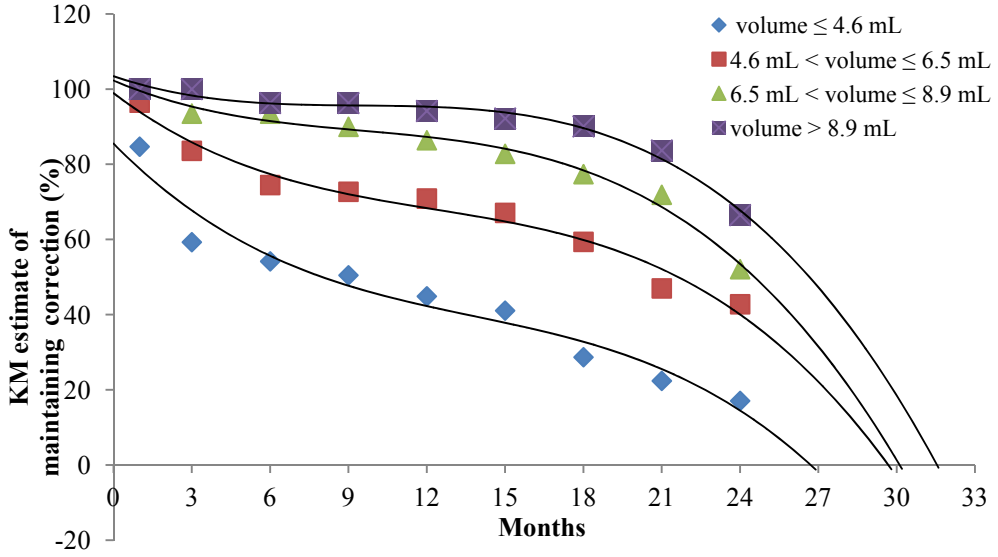
Figure 18. Duration of Volumizing Effect



To evaluate the possible relationship between volume injected and duration of effect, separate polynomial functions were fit to 4 subgroups of subjects, defined by the quartiles of volume injected. There appeared to be a relationship between volume injected and treatment duration such that higher injection volumes were correlated with a longer duration of effect.

Figure 19 shows the duration of effect for 4 volume categories, divided by quartiles of injection volume for the treatment group.

Figure 19. Duration of Volumizing Effect by Volume Injection



11.6 Safety Results

Safety evaluation was performed for all treated mITT subjects, including treatment group subjects as well as the control group subjects who were treated in error at the beginning of the study or treated according to the protocol after completion of the 6-month "no-treatment" phase of the study. Thus, safety results are based on data from 270 subjects including 235 in the initial treatment group, 3 from the control group who were treated in error at study onset, and 32 subjects from the control group who crossed over to treatment after the Month 6 evaluation per the protocol. Additionally, safety results from 125 subjects who received repeat treatment and contributed safety data at the time of submission to FDA are discussed.

CTRs were identified by the subject during his or her daily observation of the treatment sites and recording of events for 30 days after any treatment and by telephone or email follow-up with the Treating Investigator 3 days following each treatment. Adverse events were those identified by the Treating Investigator via both observation of the subject as well as those CTRs which were ongoing at the end of the 30-day subject safety diary.

CTRs and adverse events are discussed below.

11.6.1 Common Treatment Responses

Among the 270 treated subjects, 265 (98.1%) completed 30-day diaries. Of these, 260 (98.1%) reported at least 1 CTR. The most frequently reported CTRs were tenderness, swelling, and firmness. Most CTRs were reported as mild or moderate (80.7% of CTRs) in

severity. Table 23 summarizes CTRs reported following initial and touch-up treatment (if performed). Overall, the duration of any CTR was 2 weeks or less for 55.4% of subjects following initial treatment and 80.4% of subjects following touch-up treatment (Table 24).

Table 23. Common Treatment Site Responses by Maximum Severity

		Severity[a]		
CTR[b]	% (n/N)	Mild % (n/N)	Moderate % (n/N)	Severe % (n/N)
Initial Treatment (N = 265)[c]				
Any CTR	98.1% (260/265)	21.5% (56/260)	59.2% (154/260)	19.2% (50/260)
Tenderness	92.1% (244/265)	46.3% (113/244)	50.0% (122/244)	3.7% (9/244)
Swelling	85.7% (227/265)	46.7% (106/227)	43.6% (99/227)	9.7% (22/227)
Firmness	82.3% (218/265)	37.6% (82/218)	54.6% (119/218)	7.8% (17/218)
Lumps/Bumps	81.1% (215/265)	41.4% (89/215)	48.8% (105/215)	9.8% (21/215)
Bruising	77.7% (206/265)	37.4% (77/206)	51.5% (106/206)	11.2% (23/206)
Pain	66.4% (176/265)	59.1% (104/176)	38.6% (68/176)	2.3% (4/176)
Redness	66.0% (175/265)	60.0% (105/175)	36.0% (63/175)	4.0% (7/175)
Discoloration	41.1% (109/265)	62.4% (68/109)	27.5% (30/109)	10.1% (11/109)
Itching	38.5% (102/265)	70.6% (72/102)	18.6% (19/102)	10.8% (11/102)
Other	12.5% (33/265)	51.5% (17/33)	30.3% (10/33)	18.2% (6/33)
Touch-up Treatment (N = 212)[c]				
Any CTR	91.5% (194/212)	48.5% (94/194)	41.2% (80/194)	10.3% (20/194)
Tenderness	73.6% (156/212)	62.2% (97/156)	32.1% (50/156)	5.8% (9/156)
Swelling	64.2% (136/212)	58.8% (80/136)	36.8% (50/136)	4.4% (6/136)
Lumps/Bumps	54.7% (116/212)	65.5% (76/116)	30.2% (35/116)	4.3% (5/116)
Bruising	54.2% (115/212)	60.0% (69/115)	33.0% (38/115)	7.0% (8/115)
Firmness	52.8% (112/212)	60.7% (68/112)	34.8% (39/112)	4.5% (5/112)
Pain	45.3% (96/212)	70.8% (68/96)	25.0% (24/96)	4.2% (4/96)
Redness	45.3% (96/212)	76.0% (73/96)	21.9% (21/96)	2.1% (2/96)
Discoloration	21.7% (46/212)	69.6% (32/46)	17.4% (8/46)	13.0% (6/46)
Itching	21.2% (45/212)	80.0% (36/45)	13.3% (6/45)	6.7% (3/45)
Other	4.7% (10/212)	40.0% (4/10)	50.0% (5/10)	10.0% (1/10)

[a] Maximum reported severity in the diary. The denominator for percentages by severity is the number of subjects with the corresponding CTR.
[b] CTRs are listed in decreasing order of frequency of occurrence
[c] N denotes number of subjects who recorded entries in their diaries after treatment

Table 24. Common Treatment Site Responses by Maximum Duration

		Duration[a]				
		1-3 Days	4-7 Days	8-14 Days	15-30 Days	>30 Days
CTR[b]	% (n/N)	% (n)	% (n)	% (n)	% (n)	% (n)
Initial Treatment (N = 265)[c]						
Any CTR	98.1% (260/265)	8.1% (21)	22.7% (59)	24.6% (64)	24.6% (64)	20.0% (52)
Tenderness	92.1% (244/265)	29.9% (73)	30.7% (75)	27.9% (68)	8.6% (21)	2.9% (7)
Swelling	85.7% (227/265)	41.0% (93)	33.0% (75)	17.6% (40)	5.3% (12)	3.1% (7)
Firmness	82.3% (218/265)	26.6% (58)	29.8% (65)	20.2% (44)	11.0% (24)	12.4% (27)
Lumps/Bumps	81.1% (215/265)	21.4% (46)	22.3% (48)	22.3% (48)	18.1% (39)	15.8% (34)
Bruising	77.7% (206/265)	24.8% (51)	30.6% (63)	29.6% (61)	14.6% (30)	0.5% (1)
Pain	66.4% (176/265)	56.3% (99)	31.3% (55)	9.7% (17)	2.8% (5)	0
Redness	66.0% (175/265)	59.4% (104)	28.0% (49)	8.6% (15)	2.3% (4)	1.7% (3)
Discoloration	41.1% (109/265)	64.2% (70)	19.3% (21)	6.4% (7)	5.5% (6)	4.6% (5)
Itching	38.5% (102/265)	81.4% (83)	16.7% (17)	2.0% (2)	0	0
Other	12.5% (33/265)	66.7% (22)	15.2% (5)	3.0% (1)	12.1% (4)	3.0% (1)
Touch-up Treatment (N = 212)[c]						
Any CTR	91.5% (194/212)	20.6% (40)	32.5% (63)	27.3% (53)	12.9% (25)	6.7% (13)
Tenderness	73.6% (156/212)	39.1% (61)	34.0% (53)	21.2% (33)	4.5% (7)	1.3% (2)
Swelling	64.2% (136/212)	41.2% (56)	42.6% (58)	12.5% (17)	1.5% (2)	2.2% (3)
Lumps/Bumps	54.7% (116/212)	37.1% (43)	28.4% (33)	16.4% (19)	12.1% (14)	6.0% (7)
Bruising	54.2% (115/212)	28.7% (33)	39.1% (45)	25.2% (29)	6.1% (7)	0.9% (1)
Firmness	52.8% (112/212)	37.5% (42)	33.9% (38)	16.1% (18)	9.8% (11)	2.7% (3)
Redness	45.3% (96/212)	62.5% (60)	27.1% (26)	8.3% (8)	2.1% (2)	0
Pain	45.3% (96/212)	62.5% (60)	24.0% (23)	12.5% (12)	0	1.0% (1)
Discoloration	21.7% (46/212)	69.6% (32)	15.2% (7)	13.0% (6)	0	2.2% (1)
Itching	21.2% (45/212)	88.9% (40)	4.4% (2)	4.4% (2)	0	2.2% (1)
Other	4.7% (10/212)	50.0% (5)	20.0% (2)	10.0% (1)	10.0% (1)	10.0% (1)

[a] Maximum reported successive occurrence of a CTR. Denominator for percentages by duration is the number of subjects with corresponding CTR.
[b] CTRs are listed in decreasing order of frequency of occurrence
[c] N denotes number of subjects who recorded entries in their diaries after the treatment

To provide context to reported CTRs, Table 25 shows the diary reports of common responses from the VOLUMA-002 study and those reported in the pivotal study for JUVÉDERM® Ultra Plus. There are similarities with regards to CTRs reported by subjects following initial treatment with VOLUMA™ XC and those reported by subjects who received JUVÉDERM® Ultra Plus under the JD-ZZ-001 clinical study for correction of moderate to severe nasolabial folds (administered via mid to deep dermal injection), which was approved by FDA in 2006. The most common CTRs reported by subjects for JUVÉDERM® Ultra Plus via the initial treatment diary were redness, firmness, and swelling (Table 25). For JUVÉDERM® Ultra Plus, the majority of these CTRs were mild or moderate in severity and lasted 7 days or less.

Table 25. Common Treatment Site Responses with JUVÉDERM® Ultra Plus (JD-ZZ-001 Study) vs. VOLUMA™ XC

CTR[a]	VOLUMA™ XC % (n/N)	95% CI	JUVÉDERM Ultra Plus % (n/N)	95% CI
Any CTR	98.1%	(95.65%, 99.38%)	97.1%	(92.74%, 99.20%)
Tenderness	92.1%	(88.14%, 95.03%)	81.9%	(74.43%, 87.92%)
Swelling	85.7%	(80.85%, 89.65%)	82.6%	(75.24%, 88.53%)
Firmness	82.3%	(77.12%, 86.67%)	86.2%	(79.34%, 91.50%)
Lumps/Bumps	81.1%	(75.89%, 85.66%)	79.0%	(71.23%, 85.45%)
Bruising	77.7%	(72.24%, 82.60%)	53.6%	(44.94%, 62.15%)
Pain	66.4%	(60.38%, 72.08%)	71.0%	(62.69%, 78.42%)
Redness	66.0%	(59.99%, 71.72%)	87.7%	(81.01%, 92.66%)
Discoloration	41.1%	(35.15%, 47.32%)	31.2%	(23.55%, 39.59%)
Itching	38.5%	(32.60%, 44.64%)	28.3%	(20.93%, 36.55%)

[a] VOLUMA™ XC CTRs were reported via a 30-day diary; JUVÉDERM® Ultra Plus CTRs were reported via a 14-day diary

The incidence of redness appears higher in subjects treated with JUVÉDERM® Ultra Plus, and the incidence of bruising appears higher with VOLUMA™ XC, as can be seen from non-overlapping confidence intervals. However, the median injection volume used at initial treatment to treat a single nasolabial fold with JUVÉDERM® Ultra Plus in the JD-ZZ-001 Study was 1.6 mL compared to 4.8 mL used for initial treatment in the VOLUMA-002 study to treat mid-face volume deficit. Furthermore, the diary used in the VOLUMA-002 study lasted 30 days compared to the 14-day diaries used in the JD-ZZ-001 study. When analyses were performed on 14-day dairy data for subjects receiving ≤ 3.2 mL of VOLUMA™ XC, none of the CTRs reported in the VOLUMA-002 trials have a significantly higher incidence compared to the JD-ZZ-001 study, and severity and duration statistics are comparable. Thus, for comparable volumes, both products have a similar CTR profile.

11.6.2 Adverse Events

AEs consisted of events that were either unrelated or related to the device or treatment. A subject may have multiple AEs with each attributed to a different cause, severity, action taken, duration, or resolution. Thus, the totals for subjects in the individual categories may not match the total number of subjects with AEs.

AEs that result in death, life-threatening injury or illness, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, or jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above are deemed serious adverse events (SAEs).

AEs Unrelated to the Device or Treatment

The most frequently reported adverse events determined to be unrelated to the device or treatment were nasopharyngitis and headache (5 subjects each).

SAEs Unrelated to the Device or Treatment

Ten subjects had unrelated SAEs, as described in Table 26.

Table 26. Serious Adverse Events Unrelated to the Device or Treatment

Subject	SAE Verbatim Term	Date Started/ Ended	Reason Serious	Action Taken	Outcome
[redacted]	Basal cell carcinoma left lower leg	7/13/10-7/13/10	Medical or surgical intervention	Other: Surgically Removed	Resolved
	Basal cell carcinoma right posterior lower leg	11/30/10-12/9/10	Medical or surgical intervention	Other: Surgically Removed	Resolved
	Basal cell carcinoma left anterior lower leg	11/30/10-12/9/10	Medical or surgical intervention	Other: Surgically Removed	Resolved
	Basal cell carcinoma left calf	9/28/10-9/28/10	Medical or surgical intervention	Other: Surgically Removed	Resolved
	Left humerus fracture	1/17/10-1/22/10	Medical or surgical intervention	Mediation/Non-drug therapy: open reduction left upper arm; internal fixation left upper arm	Resolved
	Carcinoid tumor to the lung, right lower lobe	10/7/10-12/1/10 Hospital Dates 12/1/10-12/5/10	Hospitalization	Medication/ Hospitalization/ Other: Surgical removal of carcinoid tumor to right lower lobe	Resolved
	Malignant thyroid	6/30/10-9/14/10 Hospital Dates 9/14/10-9/15/10	Medical or surgical intervention	Medication/ Hospitalization/Non-drug therapy: thyroidectomy, ultrasound, radioactive iodine	Resolved
	Torn meniscus in right knee[a]	8/6/10-9/15/10	Medical or surgical intervention	Other: Outpatient arthroscopic repair	Resolved
	Recurrent basal cell carcinoma	3/17/11-5/16/11	Medical or surgical intervention	Other: Mohs surgery	Resolved

Subject	SAE Verbatim Term	Date Started/ Ended	Reason Serious	Action Taken	Outcome
[redacted]	Appendicitis	4/25/10-4/26/10	Medical or surgical intervention	Hospitalization/ Non-drug therapy: Appendectomy	Resolved with Sequelae: pain
[redacted]	Posterior ischemic optic neuropathy right eye[a]	1/27/11–Ongoing	Persistent or Significant Disability	Other: Subject went to PCP, Neuro Opthalmol., Opthalmol.	Ongoing
[redacted]	Left optic neuropathy[a]	6/3/11-Ongoing	Persistent or Significant Disability	None	Ongoing
[redacted]	Stroke[b]	3/7/11-3/20/11 Admitted 3/7/11	Death	None	Death
[redacted]	Squamous cell skin cancer-chest[c]	10/29/10-11/16/10	Medical or surgical intervention	Non-drug therapy: Outpatient Mohs surgical excision	Resolved
[redacted]	Squamous cell skin cancer – upper chest	9/9/11-11/1/11	Medical or surgical intervention	Medication/ Non-drug therapy: Biopsy	Resolved

Occurred in a 60-year-old woman who developed inferior field vision loss 7 months after her last treatment. Specialists diagnosed the event as an optic nerve stroke
[b] Occurred in a 65-year-old male one year after last treatment
[c] These unrelated SAEs occurred in control subjects before treatment

AEs Related to the Device or Treatment

AEs at the injection site were enumerated based on each specific event at each specific injection site. If a subject had the same AE at multiple injection sites, a separate event was counted for each injection site (e.g., if the subject reported swelling at the right and left zygomaticomalar region and the right and left anteromedial cheek, there were a corresponding total of 4 events and 1 unique event). Among the 270 treated mITT subjects, 88 subjects (32.6%) reported 627 AEs (174 unique) related to the device or injection after initial or touch-up treatment. Of these subjects, 87 experienced an AE at the injection site.

As shown in the Table 27 below, device-related AEs reported in greater than 5% of subjects all occurred at the injection site and included firmness, feeling lumps/bumps, swelling, or pain. Most AEs (94%) resolved without treatment. Only 5% of the AEs required medication or non-drug therapy (hyaluronidase injection, biopsy, V-beam, aspiration) as a treatment, and 1% of AEs were resolved following treatment with ice or a facial massage.

Except for 2 subjects, device-related AEs were resolved for all subjects. One subject reported mild ongoing swelling at the time of submission, which was later reported to be

resolved. The other subject reported mild ongoing firmness; however, she reported that she was satisfied with her treatment outcome.

Table 27. Device-Related Adverse Events

System Organ Class/ Preferred Term[a]	Subjects % (n/N)	Events % (n/N[b])
One or More Adverse Event	32.6% (88/270)	100.0% (627/627)
General disorders and administration site conditions	32.2% (87/270)	99.5% (624/627)
Injection site mass	18.9% (51/270)	27.4% (172/627)
Injection site induration	14.1% (38/270)	31.6% (198/627)
Injection site swelling	7.0% (19/270)	12.0% (75/627)
Injection site pain	5.9% (16/270)	10.0% (63/627)
Injection site hematoma	3.7% (10/270)	5.3% (33/627)
Injection site discoloration	2.2% (6/270)	3.2% (20/627)
Injection site erythema	1.9% (5/270)	2.6% (16/627)
Injection site reaction	1.5% (4/270)	3.8% (24/627)
Injection site hypertrophy	0.7% (2/270)	1.1% (7/627)
Injection site nodule	0.7% (2/270)	0.6% (4/627)
Inflammation	0.4% (1/270)	0.2% (1/627)
Injection site anesthesia	0.4% (1/270)	1.0% (6/627)
Injection site dryness	0.4% (1/270)	0.3% (2/627)
Injection site erosion	0.4% (1/270)	0.3% (2/627)
Mass	0.4% (1/270)	0.2% (1/627)
Eye disorders	0.4% (1/270)	0.2% (1/627)
Iritis	0.4% (1/270)	0.2% (1/627)
Injury, poisoning and procedural complications	0.4% (1/270)	0.2% (1/627)
Contusion	0.4% (1/270)	0.2% (1/627)
Nervous system disorders	0.4% (1/270)	0.2% (1/627)
Syncope	0.4% (1/270)	0.2% (1/627)

[a] If a subject had the same AE at multiple injection sites, a separate event is counted for each injection site (e.g., swelling reported at both the right and left zygomaticomalar regions would count as 2 events of swelling).

The majority of device-related AEs (76%) resolved by 60 days, with a mean duration of 50 days. The duration of AEs was on average greater than that of CTRs (which lasted 2 weeks or less for the majority of subjects) because all CTRs that were ongoing at the end of the 30-day diary were classified as adverse events.

Most AEs were mild (44%) or moderate (44%) in severity, and most did not require treatment. Three AEs classified as moderate in severity did require medication, as shown in Table 28.

Table 28. Device-related Adverse Events Reported as Moderate and Requiring Treatment

Subject	Adverse Event	Duration (Days)	Days from Last Treatment Before Onset	Outcome	Action Taken
[redacted]	Lumps/Bumps	37	1	Resolved without sequelae	Hyaluronidase
	Lumps/Bumps/Overcorrection	131	1	Resolved without sequelae	Hyaluronidase
	Ache	27	0	Resolved without sequelae	Tylenol 3

Twelve subjects had 20 unique device-related AEs with a severe rating. The majority of severe AEs (87%) did not require treatment. Three events in 2 subjects required treatment and were the only device-related SAEs reported in the study, as detailed in the section below.

SAEs Related to the Device or Treatment

There were 3 SAEs occurring in 2 subjects determined to be related to the device or treatment (Table 29). The related SAEs included lumps at injection sites (treated with hyaluronidase and resolved with sequelae of a scar from the biopsy site after subcision), a delayed inflammatory reaction under the eye (treated with hyaluronidase and resolved), and delayed nodularity in the cheek (treated with hyaluronidase and resolved). The treatments employed were according to recommendations outlined by the American Society for Dermatologic Surgery (ASDS). Theses device-related SAEs all began within 8 months of the last initial treatment injection (initial or touch-up).

Table 29. Serious Adverse Events Related to the Device or Treatment

Subject	SAE Verbatim Term	Duration (Days)	Reason Serious	Action Taken	Outcome
[redacted]	Lumps of face left and right cheek regions at injection sites	250	Medical Intervention	Antibiotics, Anti-inflammatory steroids, Hyaluronidase	Resolved with Sequelae: Scar from biopsy site
	Inflammatory reaction under left eye	70	Persistent Disability and Medical Intervention	Medication: Hyaluronidase	Resolved
	Nodularity on right cheek	49	Medical Intervention	Medication: Hyaluronidase	Resolved

11.6.3 Subgroup Analyses of Device-Related Adverse Events

The potential impact of demographic, baseline, or treatment administration characteristics on safety was analyzed using multiple logistic regression with incidence rate of device-related AEs as the dependent variable and the covariates as the independent variables. In this analysis, the p-value for each covariate tests the hypothesis that the incidence rate of a device-related adverse event is equal for all strata of that covariate in the presence of all other covariates in the multivariate model. Significance of a variable at the 10% level implies that the covariate has an effect on the incidence rate (i.e., incidence rates differ among the strata of that covariate). As Table 30 below shows, in addition to volume injected, gender appeared to have a significant impact on the incidence rate with a lower incidence of device-related adverse events among males compared to females.

Table 30. Multivariate Analysis of Device-Related Adverse Events

Subgroup	p-value[a]
Gender (Female vs. Male)	0.0682
Race (Overall)	0.2893
Fitzpatrick Skin Phototype (Overall)	0.8978
Baseline Volume Deficit[b](Overall)	0.4161
Investigational Site (Overall)	0.3204
Plane of Injection[c]	
Supraperiosteal (Yes vs. No)	0.8644
Injection Technique[c]	
Tunneling (Yes vs. No)	0.5794
Fanning (Yes vs. No)	0.4660
Serial Puncture (Yes vs. No)	0.8047
Cross-hatching (Yes vs. No)	0.9073
Ferning (Yes vs. No)	0.7883
Retrograde Direction (Yes vs. No)	0.8524
Antegrade Direction (Yes vs. No)	0.9740
Volume Injected[d] (mL)	0.0091

[a] p-value tests the hypothesis that the incidence rate of all device related AEs is equal for all strata of the subgroup variable, with all other subgroup variables in the multivariate model
[b] Treating Investigator's assessment of overall mid-face volume deficit at baseline
[c] Plane of injection or injection technique at initial or touch-up treatment
[d] Total volume injected at initial and touch-up treatment combined

11.6.4 Common Treatment Site Responses and Adverse Events After Repeat Treatment

As of November 30, 2012, 125 subjects have received repeat treatment. Of these 125 mITT subjects, 120 subjects completed their 30-day diary after repeat treatment. As reported via subject diary, the severity of CTRs was similar between initial and repeat treatment, though the incidence and duration of events were reduced after repeat treatment (Table 31 and Table 32).

Table 31. Common Treatment Site Responses after Repeat Treatment by Maximum Severity

		Severity[a]		
CTR[b]	**% (n/N)**	**Mild % (n/N)**	**Moderate % (n/N)**	**Severe % (n/N)**
Repeat Treatment (N = 120)[c]				
Any CTR	90.0% (108/120)	35.2% (38/108)	50.0% (54/108)	14.8% (16/108)
Tenderness	75.0% (90/120)	53.3% (48/90)	42.2% (38/90)	4.4% (4/90)
Swelling	65.8% (79/120)	49.4 (39/79)	48.1% (38/79)	2.5% (2/79)
Firmness	68.3% (82/120)	46.3% (38/82)	51.2% (42/82)	2.4% (2/82)
Lumps/Bumps	60.0% (72/120)	51.4% (37/72)	43.1% (31/72)	5.6% (4/72)
Bruising	60.0% (72/120)	52.8% (38/72)	33.3% (24/72)	13.9% (10/72)
Pain	55.8% (67/120)	62.7% (42/67)	32.8% (22/67)	4.5% (3/67)
Redness	54.2% (65/120)	60.0% (39/65)	36.9% (24/65)	3.1% (2/65)
Discoloration	23.3% (28/120)	75.0% (21/28)	25.0% (7/28)	0.0% (0/28)
Itching	32.5% (39/120)	79.5% (31/39)	20.5% (8/39)	0.0% (0/36)
Other	7.5% (9/120)	77.8% (7/9)	22.0% (2/9)	0.0% (0/9)

[a] Maximum reported severity in the diary. The denominator for percentages by severity is the number of subjects with the corresponding CTR.
[b] CTRs are listed in decreasing order of frequency of occurrence
[c] N denotes number of subjects who recorded entries in their diaries after treatment

Table 32. Common Treatment Site Responses after Repeat Treatment by Duration

		Duration[a]				
		1-3 Days	4-7 Days	8-14 Days	15-30 Days	>30 Days
CTR[b]	% (n/N)	% (n)	% (n)	% (n)	% (n)	% (n)
Repeat Treatment (N = 120)[c]						
Any CTR	90.0% (108/120)	20.4% (22/108)	32.4% (35/108)	21.3% (23/108)	20.4% (22/108)	5.6% (6/108)
Tenderness	75.0% (90/120)	40.0% (36/90)	35.6% (32/90)	11.1% (10/90)	12.2% (11/90)	1.1% (1/90)
Swelling	65.8% (79/120)	64.6% (51/79)	21.5% (17/79)	7.6% (6/79)	5.1% (4/79)	1.3% (1/79)
Firmness	68.3% (82/120)	28.0% (23/82)	36.6% (30/82)	18.3% (15/82)	12.2% (10/82)	4.9% (4/82)
Lumps/Bumps	60.0% (72/120)	41.7% (30/72)	29.2% (21/72)	11.1% (8/72)	12.5% (9/72)	5.6% (4/72)
Bruising	60.0% (72/120)	38.9% (28/72)	34.7% (25/72)	18.1% (13/72)	8.3% (6/72)	0.0% (0/72)
Pain	55.8% (67/120)	64.2% (43/67)	23.9% (16/67)	10.4% (7/67)	1.5% (1/67)	0.0% (0/67)
Redness	54.2% (65/120)	56.9% (37/65)	30.8% (20/65)	9.2% (6/65)	3.1% (2/65)	0.0% (0/65)
Discoloration	23.3% (28/120)	85.7% (24/28)	3.6% (1/28)	3.6% (1/28)	7.1% (2/28)	0.0% (0/28)
Itching	32.5% (39/120)	82.1% (32/39)	15.4% (6/39)	2.6% (1/39)	0.0% (0/39)	0.0% (0/39)
Other	7.5% (9/120)	77.8% (7/9)	11.1% (1/9)	0.0% (0/9)	11.1% (1/9)	0.0% (0/9)

Of the 125 subjects who have received repeat treatment at time of submission to the FDA, subjects experienced 45 AEs related to the device or treatment. These AEs were either mild (40.0%, 18/45) or moderate (60.0%, 27/45) in severity. None of the AEs required any action and all AEs resolved without sequelae. Subjects are now being followed through 12 months after repeat treatment as part of Allergan's Post-Approval Plan (see Section 12 below).

11.7 Histopathology Results

A board-certified dermatopathologist evaluated each hematoxylin and eosin stained slide from each biopsy sample individually. In addition, a colloidal iron stain and a digested colloidal iron stain were performed to demonstrate carboxylated and sulfated mucopolysaccharides and glycoproteins.

The slide evaluation included all skin compartments from the epidermis to the subcutaneous tissue. The epidermis was measured with an ocular micrometer for the thinnest and the thickest regions. The epidermis was checked for necrosis, ulceration, and inflammation. The dermis and subcutaneous tissue were evaluated for fibrosis, inflammation, and implant material.

Inflammatory cells were subcategorized as neutrophils, lymphocytes, histiocytes, giant cells, eosinophils, or plasma cells. Vessels, nerves and adnexal structures, and any abnormality in

the various compartments were noted. Due to being a negatively charged glycosaminoglycan, the implant material stained blue in the hematoxylin and eosin sections, was positive for colloidal iron, and absent in the after digestion by hyaluronidase for the digested colloidal iron stain. These qualities were utilized to determine the presence or absence of implant material.

Twenty-one biopsies were obtained throughout the study, with at least 1 biopsy taken approximately every 3 months. In all samples, lymphocytes and histiocytes were observed with scant or mild inflammation present in all but one. Fibrosis was observed in 16 of the 21 biopsies.

However, the implant was absent in two-thirds of the samples (66.7%, 14/21). This absence of material at time of biopsy may be due to the small size of the depot injection and biological differences in the tissue between the face and tissue behind the ear (the latter site contained the depot injection, performed at the initial treatment visit). Of the 7 tissue samples noted to have the implant present, nearly all noted that none of the observed inflammation or fibrosis were in proximity to or associated with the implant (2 reports did not contain this level of detail about either inflammation or fibrosis).

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12. POST-APPROVAL PLANS

In review of the PMA application for VOLUMA™ XC, FDA expressed interest in understanding long-term safety after repeat treatment. Though CTR results and preliminary AE data are presented herein, longer term safety data collection is ongoing. Following FDA approval of VOLUMA™ XC, Allergan intends to continue to evaluate the safety of repeat treatment with VOLUMA™ XC in subjects who received treatment under VOLUMA-002. Post-approval study VOLUMA-003 is a statistical analysis protocol of safety data collected under VOLUMA-002 through 12 months after repeat treatment. Subjects who receive repeat treatment return for follow-up visits at Day 3 and Months 1, 3, 6, 9, and 12. The proposed post-approval study protocol focuses on the safety of repeat treatment and, thus, will test the hypothesis that the incidence of device-related AEs after repeat treatment is not more than the incidence rate with a 5% margin for the device-related AEs after initial/touch-up treatment.

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13. PRODUCT EXPERIENCE WITH VOLUMA™

13.1 POST-APPROVAL STUDIES WORLD-WIDE

Allergan conducted an open label, post-approval study (VOL-AP01) in Australia to evaluating the safety and effectiveness of VOLUMA™ (without lidocaine) in 103 subjects with moderate to significant mid-face volume deficit.[62] Overall results of the study were consistent with results of the US pivotal study, VOLUMA-002. In this study, the majority of enrolled subjects presented with moderate to significant volume deficiency in the mid-face at baseline. Treatment with the study product was administered in 1 or 2 sessions over the initial 4-week period of the study.

Based on the MFVDS, clinically relevant correction in 96% of subjects was observed when independently evaluated by investigators at the first post-treatment visit (Week 8), coupled with nearly 100% of Investigators and 98% of subjects grading subjects to be responders on the GAIS. At Month 18, this clinically relevant improvement was maintained in 81.7% of subjects, based on investigators assessment on the MFVDS. There was a high degree of consistency in the evaluation of a clinically meaningful correction during the study, as measured independently by both the Investigator and subject using the GAIS. Furthermore, subjects indicated a high level of satisfaction with the treatment outcome when evaluated at each scheduled clinic visit, including at the end of the study. The majority of treatment-related adverse events were transient. The most commonly reported events were injection site bruising and swelling of mild to moderate severity.

13.2 SUMMARY OF RELEVANT LITERATURE

A review of the literature pertaining to mid-face volume loss and the various treatment options, including Juvéderm VOLUMA™ (without Lidocaine), is provided in Appendix 3. VOLUMA™ XC contains 0.3% of lidocaine in the formulation, which is added to reduce pain during injection. While the literature identified in this section describes the use of a Juvéderm VOLUMA™ formulation that does not contain lidocaine, all other product specifications are identical, and thus, results are applicable to VOLUMA™ XC.

Five different publications were identified which studied Juvéderm VOLUMA™ in subjects with mid-face volume loss. The results of these studies are presented in Table 33. The literature supports the use of Juvéderm VOLUMA™ in individuals with mid-face volume loss as evidenced by these findings:

- Juvéderm VOLUMA™ yielded significant improvement in mid-face volume and appearance across a variety of scales

- Juvéderm VOLUMA™ was well-tolerated by subjects, with no unique serious safety issues compared to currently marketed HA dermal fillers. The most commonly reported adverse events were bruising, pain and swelling upon injection

Table 33. Summary of Juvéderm VOLUMA™ Use in Published Literature

Study Author Year	Subject Population	Follow Up	Effectiveness	Safety (Number of Reports)
Bechara 2008[21]	21 HIV subjects with facial lipoatrophy	9 months	100% (21/21) of subjects were much improved or very much improved at 9 months	Mild erythema (8) Swelling (4) Bruising (4)
		12 months	76.2% (16/21) of subjects were much improved or very much improved at 12 months	
Raspaldo 2008[a,30]	102 subjects	1 month	99% (101/102) of subjects were rated as improved, much improved, or very much improved at 1 month	Overcorrection (4) Bruising (3) Swelling (1) Hypersensitivity (1)
		6-18 months	99% (100/101) of subjects were rated as improved, much improved, or very much improved at 6-18 months	
Hoffmann 2009[b,47]	70 subjects	2 weeks	Mean volume loss declined from 3.7 to 2.1 ($p < 0.001$) on 5-point scale 76% (53/70) of subjects rated themselves and 88% (60/68) of physicians rated subjects very much or much improved	Bruising (7) Pain and bruising (4) Swelling (3) Bruising and swelling (3) Pain and swelling (2) Pain (2) Bruising and bleeding (1) Infection and swelling (1) Not specified (1)
Cattin 2010[c,63]	60 subjects	18 months	Single injection technique at the subdermal level and above the muscle reduced bruising and swelling and increased subject comfort (observational)	Small needle mark at entry point
Fischer 2010[c,64]	84 subjects treated with Restylane SubQ <2 years previously	Unspecified	75% of physicians found Juvéderm VOLUMA™ fairly or very easy to inject 84.5% of physicians found Juvéderm VOLUMA™ easy to sculpt/massage 98% of subjects and physicians rated effect as improved	Bruising (4) Swelling (2) AE not specified (1)

[a] Study sponsored by Allergan
[b] Allergan provided product for the study but no other financial assistance was provided
[c] Allergan provided manuscript editorial assistance

13.3 POST-MARKET SURVEILLANCE DATA ON VOLUMA™ XC

As part of Allergan's commitment to monitor the safety of its products in commercial use, Allergan has collected post-market surveillance data for both patient-related complaints and device-related complaints on VOLUMA™ XC since its commercialization outside of the US. Juvedérm VOLUMA™ (without lidocaine) received the CE Mark in 2005, and VOLUMA™ XC received CE mark in 2009. As of December 31, 2012, more than 520,000 syringes of Juvéderm VOLUMA™ formulations (with and without lidocaine) have been distributed worldwide.

Patient-related and device-related complaints for VOLUMA™ and VOLUMA™ XC reported in 5 or more patients from Allergan's post-market surveillance program are summarized in Table 34 and Table 35. These tables include reports collected globally from all sources including scientific journals and voluntary reports. The reported rate is the number of events divided by the number of devices distributed.

As shown in Table 34, all patient-related events occurred with a frequency of less than 0.1%; the most prevalent reports were swelling/edema, inflammatory reaction, nodule, pain, and redness/rash. Reported interventions for these events included medications (antibiotics, steroids, anti-inflammatory medication, antihistamines, and hyaluronidase injection), ice application, massage, and needle aspiration.

Infections were associated with other symptoms including pain, induration, erythema, edema, ecchymosis, nodule, paresthesia, skin discoloration, displacement, and headache, and some events were treated with antibiotics. Headaches were typically described as transient sinus headaches.

The most frequent device-related complaints were accidental spillage and needle disengagement, with both complaints occurring at rates less than 0.2% (Table 35).

The events observed under post-market surveillance spanning an 8-year history of use, are consistent with those for other dermal fillers, with no unique safety signals, and support safe use of the device.

Table 34. Worldwide Reported Medical Events for VOLUMA™ and VOLUMA™ XC Reported from July 1, 2007 through December 31, 2012

	VOLUMA™ and VOLUMA™ XC n[a] = 520,764	
Events[b]	Number of Events[c]	Report Rate
Swelling/Edema	276	0.0530%
Inflammatory Reaction	265	0.0509%
Nodule	207	0.0397%
Pain	130	0.0250%
Redness/Rash	89	0.0171%
Hematoma/Ecchymosis	50	0.0096%
Loss/Lack of Correction	46	0.0088%
Infection	41	0.0079%
Migration of Product/Displacement	36	0.0069%
Discoloration	31	0.0060%
Granuloma	24	0.0046%
Itching	21	0.0040%
Allergic Reaction/Hypersensitivity	18	0.0035%
Abscess	18	0.0035%
Flu-like Symptoms	17	0.0033%
Other	14	0.0027%
Necrosis	9	0.0017%
Numbness/Paresthesia	9	0.0017%
Vision Abnormalities	9	0.0017%
Headache	6	0.0012%
Malaise	6	0.0012%

[a] Total syringes sold
[b] Patient-related and device-related complaints for VOLUMA™ and VOLUMA™ XC reported at a frequency of 5 or more are listed
[c] Some reports included multiple events, so the above numbers do not indicate the number of complaints nor patients involved

Table 35. Worldwide Reported Technical Events for VOLUMA™ and VOLUMA™ XC from July 1, 2007 through December 31, 2012

	VOLUMA™ and VOLUMA™ XC n[a] = 520,764	
Events[b]	Number of Events[c]	Report Rate
Accidental Spillage	975	0.1872%
Needle Disengagement (total)	861	0.1653%
Broken/Damaged/Defective Component	184	0.0353%
Needle Disengagement (partial)	15	0.0029%
Packaging Error	14	0.0027%
Difficult or Impossible to Extrude	11	0.0021%
Consistency of Material Altered	5	0.001%
Void/Air Bubbles	5	0.001%

[a] Total syringes sold
[b] Events reported for VOLUMA™ and VOLUMA™ XC at a frequency of 5 or more are listed
[c] Some reports included multiple events, so the above numbers do not indicate the number of complaints nor patients involved

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14. BENEFIT AND RISK ASSESSMENT

An aesthetic product benefit versus risk is determined by a variety of components including patient outcomes after treatment (assessed by both the physician and the patient), product durability, and product safety. Current treatment options for mid-face volume deficit include invasive surgical procedures such as face lift, cheek implants, and fat transfer, treatment with absorbable synthetic materials, or off-label use of fillers not approved for mid-face volumizing in the general population. The biocompatibility of HA and its resorbability offer a clear advantage to using an non-HA-based product to restore volume deficit. The clinical need to use an effective product to treat mid-face volume deficiencies is clearly demonstrated by the high utilization in today's market of products that have not been approved but are being used off-label for this indication. As products used off-label have not been studied for the proposed indication, controlled, clinical data that would aid in optimal and safe use of these products are not available to clinicians.

VOLUMA™ XC is comprised of the same components and is manufactured in a similar manner to other members of the JUVÉDERM® family of HA-based dermal fillers. The JUVÉDERM® family, including Ultra, Ultra Plus, Ultra XC, and Ultra Plus XC, has a history of safe and effective use in amelioration of lines and wrinkles both in the US and worldwide, as demonstrated both by clinical studies and post-market surveillance. It is the subtle but important differences in formulation that distinguish VOLUMA™ XC from other members of the JUVÉDERM® family and impart properties that make the gel suitable for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face.

The purpose of the VOLUMA-002 clinical trial was to rigorously assess the effectiveness of treatment with VOLUMA™ XC and investigate if these results would be paired with an acceptable safety profile. Assessment of the safety and effectiveness results generated from the VOLUMA-002 clinical trial confirmed what has been observed in over 8 years of global clinical practice worldwide: there is a clinical need for a resorbable product that can provide mid-facial volume enhancement, and VOLUMA™ XC accomplishes this need with an acceptable safety profile and long duration. A favorable benefit/risk assessment was confirmed in the clinical trial; the effectiveness of VOLUMA™ XC was demonstrated consistently across *all* endpoints, and the acceptable safety of the device mirrored what has already been observed through injection of other dermal fillers.

Benefit

The primary effectiveness objective in the VOLUMA-002 clinical study was to show that at 6 months at least 70% of subjects treated with VOLUMA™ XC achieved at least a 1-point improvement on the MFVDS and that the responder rate of the treatment group was statistically superior to the control group, as assessed by averaging the scores of 2 blinded Evaluating Investigators.

Both primary endpoints were achieved:

- **85.6% of subjects in the treatment group were responders ($p < 0.0001$), and**
- **the responder rate for the treatment group was significantly greater ($p < 0.0001$) than the responder rate for the control group (a difference of 46.7%) at Month 6.**

The primary endpoints served to provide quantitative measures of success that are clinically meaningful. Importantly, however, achievement of the primary endpoints was corroborated by the success of all secondary and additional effectiveness endpoints assessed in the VOLUMA-002 clinical trial that investigated overall facial improvement, regional improvement, volumetric change, and subject perspective and satisfaction after treatment.

- The GAIS responder rate for the treatment group as assessed by the blinded Evaluating Investigators at Month 6 was 82.2%, demonstrating that the vast majority of subjects had improvement in their facial appearance
- The mean volume change at Month 6 determined by quantitative 3D volume measurements was 6.8 mL for the treatment group compared to 0.8 mL for the control group
- The responder rate for the improvement in volume deficit for each mid-facial region at Month 6 was 75.5% for the zygomaticomalar region, 83.2% for the anteromedial cheek region, and 76.9% for the submalar region, demonstrating that each region was improved for most subjects
- Subject's self-evaluation of improvement at Month 6 demonstrated that 92.8% rated themselves as improved or much improved on the GAIS assessment
- Subject improvement in satisfaction with facial appearance was 89.8% at Month 6.
- Subject satisfaction with the cheek area was 85.5% at Month 6
- Subject evaluation of restoration in terms of perceived age demonstrated that at Month 6, 72.5% rated themselves as looking younger than their age, with the average for all subjects rating themselves as being 5 years younger than their age

Additionally, one of the most appealing benefits of using HA fillers in general is that they are naturally degraded over time. The resorption profile of VOLUMA XC shows a gradual resorption after 1 year with increased rate of resorption after Month 15. By Month 24, the majority (55.4%) of subjects have lost correction.

Risk

The VOLUMA-002 clinical trial collected safety data from the subjects via subject diaries and adverse events reported by the Treating Investigator at all follow-up visits. During the course of the clinical study, safety outcomes were observed to be consistent with what has been reported with other HA-based dermal fillers:

- The most frequent CTRs were tenderness, swelling, and firmness. CTRs after the initial treatment were generally mild to moderate in severity and lasted 2 weeks or less
- Compared to the initial treatment, CTRs after touch-up or repeat treatment were generally milder in nature and shorter in duration
- There were no unanticipated adverse device events. The most frequent AEs were injection site mass (i.e., lumps/bumps) and injection site induration (i.e., firmness)
- AEs were mostly mild and moderate in severity. In nearly 94.3% of the device-related AEs, no action was taken. Of the remaining AEs, the most common treatment was medication (4.9%)
- The 3 device-related SAEs occurred in 2 subjects approximately 6 months after treatment and were treated according to standard treatment recommendations outlined by the ASDS and subsequently resolved

Importantly, this observed safety profile is not only consistent with the results of pre-clinical biocompatibility testing, but is also consistent with what has been reported through post-market surveillance of VOLUMA™ distributed outside the U.S. since 2005 and with JUVÉDERM® products distributed worldwide since 2003. Over 520,000 syringes of VOLUMA™ and VOLUMA™ XC have been distributed worldwide over the last 8 years. The most common events reported at a rate of approximately 0.05% were swelling/edema, inflammatory reaction, nodule, pain, and redness/rash. The overall distribution of complaints and frequencies were in parallel with the expected groupings of other dermal filler adverse events collected through post-market surveillance.

Risk Management

Allergan has mitigated the risks associated with VOLUMA™ XC injection through a number of mechanisms, including clear physician and patient labeling, a strong product surveillance program, and a post-approval commitment to follow subjects who have undergone complimentary repeat treatment under the VOLUMA-002 protocol.

Allergan believes that VOLUMA™ XC is safe and effective for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face. Thus, the specific indication is clearly stated in both the proposed physician and patient labeling documents. In addition, the physician labeling contains detailed contraindications, precautions, and warnings. Physicians are instructed to obtain the patient's medical history and ensure that prospective patients are suitable for treatment. As with all previously approved Allergan HA-based dermal fillers, treatment instructions are based on global clinical experience and are provided to minimize injection site responses such as bruising, lumps and bumps, and discoloration.

The collection of diary data in the VOLUMA-002 clinical study was compiled and included in the patient labeling to provide patients with specific information of what they could expect upon treatment with VOLUMA™ XC. These 30-day diaries encouraged daily collection of events and their severity after each treatment. As expected, the common treatment site responses collected under the VOLUMA-002 clinical study were similar to what has been anticipated and observed with other dermal fillers, and these are clearly described and tabulated in the physician and patient labeling. The proposed labeling documents also contain adverse events reported in the clinical trial and adverse events received from post-market surveillance. Additionally, patients and physicians are warned that the likelihood of experiencing local treatment responses or adverse events increases with the volume of VOLUMA™ XC injected.

Allergan maintains its commitment to safety by capturing adverse events globally through our vigilant post-market surveillance program. This surveillance program, already utilized for products in the JUVÉDERM® family as well as for VOLUMA™ and VOLUMA™ XC distributed outside the US to date has not uncovered any unique safety signals. As expected, Allergan will continue to monitor post-market utilization of VOLUMA™ XC. Patients are encouraged to contact Allergan for any questions and to report any adverse reactions.

In addition to the high effectiveness of treatment contrasted with a safety profile that is typical of dermal filler treatment, the risk/benefit profile is supported by the majority of

subjects within the repeat treatment window who chose to undergo the optional repeat treatment at the end of their participation in the trial. Results to date suggest that repeat treatment does not pose any additional safety concerns. However, Allergan maintains its commitment to pursuing safety of our dermal filler lines by continuing to follow subjects who receive repeat treatment for 1 year after repeat treatment under post-approval clinical study VOLUMA-002.

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15. CONCLUSION

Restoration of age-related mid-face volume with a resorbable product is an unmet clinical need. VOLUMA™ XC was designed specifically to be a safe and effective device that medical practitioners could use for deep (subcutaneous and/or supraperiosteal) injection for cheek augmentation to correct age-related volume deficit in the mid-face. This outcome was observed in the VOLUMA-002 clinical trial and was corroborated with high subject satisfaction. The safety events reported in the VOLUMA-002 study are reflective both of pre-clinical biocompatibility results as well as the types of safety events that have been reported through global post-market surveillance of VOLUMA™ and other HA-based dermal fillers. In evaluation of all of the data available for VOLUMA™ XC, including favorable pre-clinical biocompatibility, effectiveness in achieving an unmet clinical need, and a safety profile consistent with what has been observed with other dermal fillers, VOLUMA™ XC is a safe and effective device to correct age-related mid-face volume deficit.

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17. APPENDICES

Appendix 1: Mid-Face Volume Deficit Scale

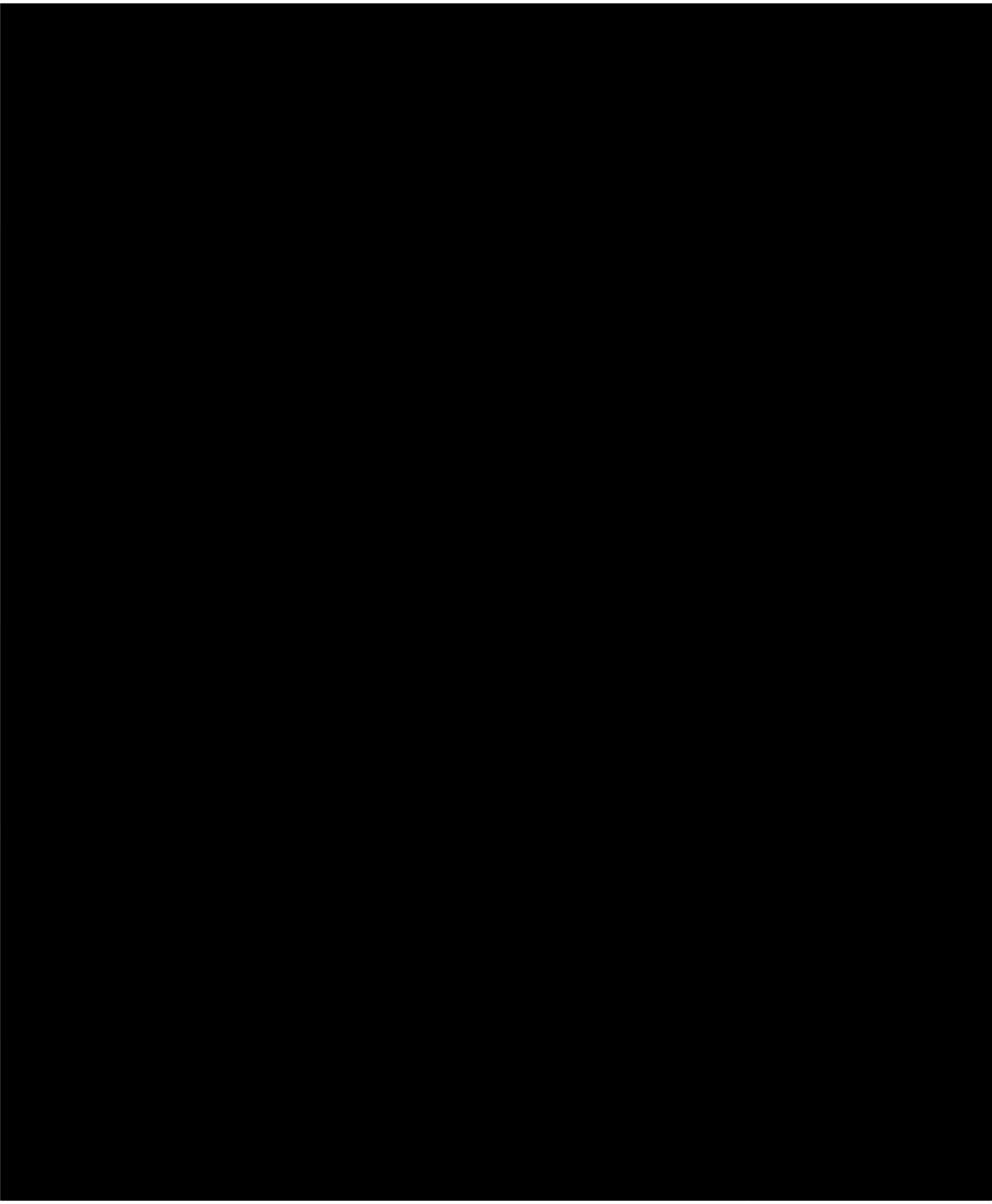
Appendix 2: Summary of the Validation of the Photometric Mid-Face Volume Deficit Scale

Appendix 3: Literature Review

Appendix 1

Mid-Face Volume Deficit Scale (MFVDS)

ALLERGAN Photometric Mid-Face Volume Deficit Scale



0 None	1 Minimal	2 Mild	3 Moderate	4 Significant	5 Severe
• **Moon face** • Fullness (convexity) in the zygomaticomalar region, anteromedial cheek, and/or submalar region	• **Flattening** in the zygomaticomalar region, anteromedial cheek, and/or submalar region	• **Mild concavity** in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Mild **tear troughs and/or nasolabial folds**	• **Moderate concavity** in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Moderate tear troughs and/or nasolabial folds • Mild **nasojugal folds and/or prejowl sulcus** • Mild prominence of bony landmarks • Mild visibility of musculature	• **Significant concavity** in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Significant tear troughs and/or nasolabial folds • Moderate nasojugal folds and/or prejowl sulcus • Moderate prominence of bony landmarks • Moderate visibility of musculature	• **Wasting** • Severe concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Severe tear troughs and/or nasolabial folds • Significant nasojugal folds and/or prejowl sulcus • Significant prominence of bony landmarks • Significant visibility of underlying musculature

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Appendix 2

Summary of the Validation of the Photometric Mid-Face Volume Deficit Scale

Summary of the Validation of the Photometric Mid-Face Volume Deficit Scale

JUVÉDERM VOLUMA™ XC

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1. HISTORY OF THE MFVDS

A shared understanding and vocabulary to describe grades of deficit and improvement are imperative to evaluating the effectiveness of volume restoration. As such, several standardized scales applicable to a region of interest have been developed to evaluate the effectiveness of facial treatments in a reliable and reproducible way. In order to measure treatment of facial lipoatrophy, defined as a "loss of facial fat due to aging, trauma, or diseases, manifested by flattening or indentation of normally convex contours," a 6-point classification system was developed and validated based on 3 criteria: contour, bony prominence, and the visibility of musculature.[1]

Using this classification system as a framework, Allergan developed the 6-point photometric Mid-Face Volume Deficit Scale (MFVDS) to grade mid-face volume deficit, shown in Figure 1 and Table 1. The range of grades (from Grade 0 "None" to Grade 5 "Severe") was intended to represent the full spectrum of mid-face volume deficit. A board-certified dermatologist, experienced in mid-face volumizing with dermal fillers, selected prototypical photographic images and contributed brief verbal descriptions of volume deficit characteristics that correlated with each of the 6 grades on the scale. Two subject images, with frontal and oblique views of each, were chosen to exemplify each grade.

On May 19, 2008, Allergan held a meeting of 9 aesthetic physicians to determine the level of inter- and intra-rater agreement with use of the MFVDS, and thereby, validate the scale for use by a similar population of raters. Using the MFVDS, Validating Investigators independently rated 20 digital 3D images and 18 live subjects in two rating sessions held 2 hours apart. The 3D images and live volunteers that were rated during the validation study were selected by the same board-certified dermatologist who assisted in scale development. The images and individuals were selected to cover the full range of possible volume deficit.

Results of this initial validation study were positive, and confirmed that the MFVDS scale could be used in a reliable and repeatable fashion. Inter- and intra-rater agreement was found to substantial for both rounds of evaluation. For the 3D images, inter-rater agreement was substantial (Round 1, Intra-Class Correlation (ICC) =0.771; Round 2, ICC = 0.804) and intra-rater agreement (mean-weighted kappa) was more than substantial (0.867). For the live subjects, inter-rater agreement was substantial for Round 1 (ICC = 0.630) but decreased to moderate for Round 2 (ICC = 0.499). Note that prior to Round 2, two Investigators left the meeting, which may have reduced the inter-rater agreement. Intra-rater agreement among the

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[1] Ascher B, Coleman S, Alster T, Bauer U, Burgess C et al. Full Scope of Effect of Facial Lipoatrophy: A Framework of Disease Understanding. *Dermatol Surg* 2006; 32:1058-69.

7 remaining Investigators who participated in both rating rounds remained substantial (mean weighted kappa = 0.744).

Figure 1. Original Mid-Face Volume Deficit Scale (MFVDS)

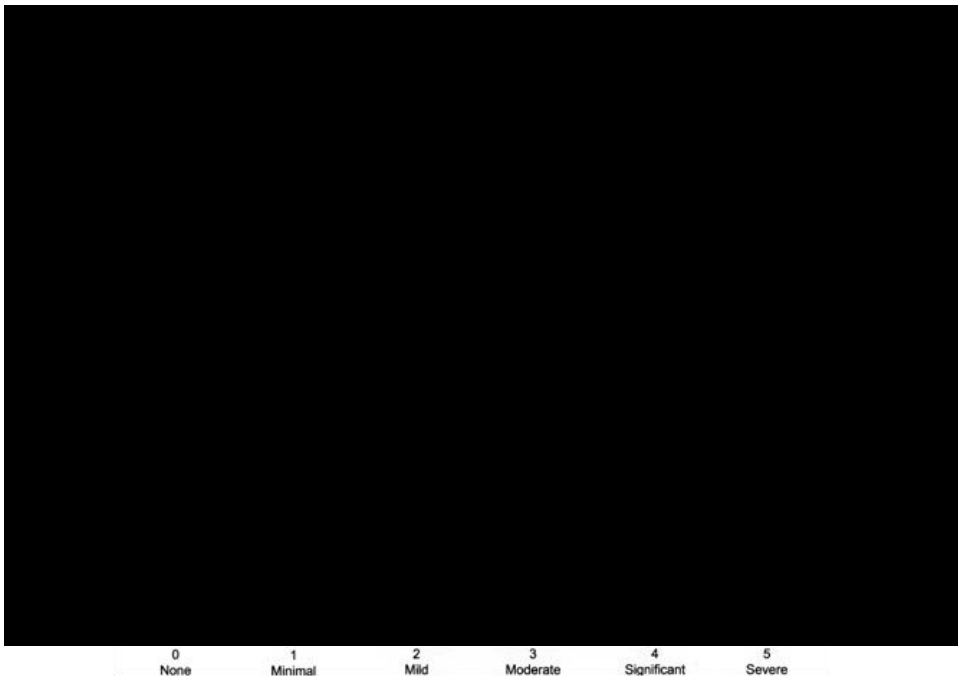


Table 1. Original Mid-Face Volume Deficit Scale (MFVDS)

SCORE	GRADE	DESCRIPTION
0	None	• Moon face • Fullness (convexity) of temporal, periorbital, cheek, pre-auricular, and/or perioral areas
1	Minimal	• Flattening of temporal, periorbital, cheek, pre-auricular, and/or perioral areas
2	Mild	• Mild concavity of temporal, periorbital, cheek, pre-auricular, and/or perioral areas • Mild tear troughs and/or nasolabial folds
3	Moderate	• Moderate concavity of temporal, periorbital, cheek, pre-auricular, and/or perioral areas • Moderate tear troughs and/or nasolabial folds • Mild prominence of bony landmarks • Mild visibility of musculature • Mild nasojugal folds and/or prejowl sulcus
4	Significant	• Significant concavity of temporal, periorbital, nasojugal, cheek, pre-auricular, and/or perioral areas • Significant tear troughs and/or nasolabial folds • Moderate prominence of bony landmarks • Moderate visibility of musculature • Moderate nasojugal folds and/or prejowl sulcus
5	Severe	• Severe (concavity) of temporal, periorbital, cheek, pre-auricular, and/or perioral areas • Severe tear troughs and/or nasolabial folds • Significant prominence of bony landmarks • Significant visibility of underlying musculature • Significant nasojugal folds and/or prejowl sulcus

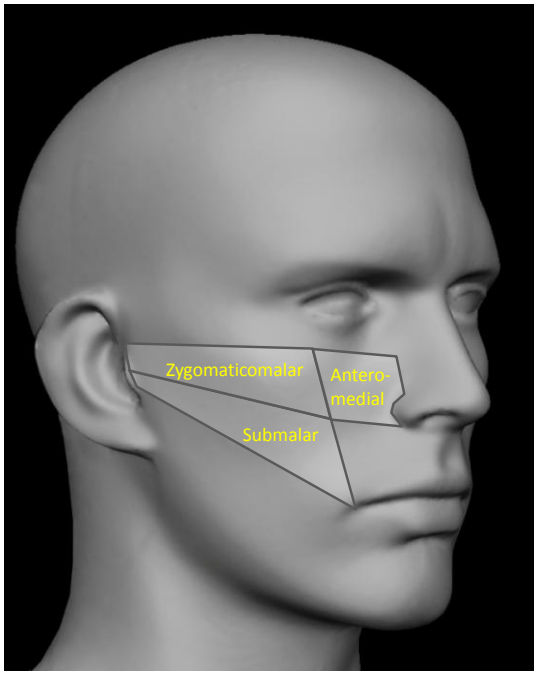
Following review of the MFVDS scale and the results of the scale validation, FDA suggested repeating the scale validation to make the findings more robust. The Agency suggested that the 2-hour time interval between reviews was too short to determine the degree of intra-rater consistency needed in an actual clinical trial, and that it was possible that scoring during Round 2 might have been based on the Investigator's recollection of the prior session. Thus, FDA recommended that the scale validation be repeated with a 2-week interval between assessments. They also recommended establishing the minimum difference in grades that corresponds to a clinically significant difference in mid-face volume. Finally, they recommended dividing the mid-face into specific treatment areas based on differing anatomical aspects and treatment algorithms, and validating the use of the MFVDS in these sub-regions.

As a result, the MFVDS was revised. Unique from the original MFVDS, the revised MFVDS identifies discrete mid-facial subunits that are volumizing treatment areas and describes each grade of volume deficit in detail. This summary describes re-validation of the MFVDS for use in the VOLUMA-002 clinical trial to measure mid-face volume deficit.

2. **MFVDS**

In consultation with aesthetic physicians, the mid-face was divided into 3 regions which can exhibit age-related volume loss: the zygomaticulomalar region, the submalar region, and the anteromedial region (Figure 2). The zygomaticulomalar complex, in particular, been described as the "hallmark of youth."[2] The area is characterized by a smooth S-shape when viewed from an oblique angle due to an anterior convexity from the lower eyelid onto the cheeks formed by mid-facial striated muscles combined with the skin and subdermal fat.

Figure 2. Mid-Face Regions



The 6-point MFVDS was expanded to allow to be used to evaluate deficit in each of the 3 regions, as well as overall mid-face volume deficit . The descriptions for each grade are now characterized by a level of concavity in each of the 3 mid-face regions as well as the presence and prominence of specific folds and areas of volume deficit. The scale itself is comprised of the revised MFVDS table and the same photographic guide including an additional view to exemplify each grade (Figure 3, Table2).

[2] Niamtu, J., Facial aging and regional enhancement in injectable fillers. *Cosmetic Dermatology* 2007; 20(5): 14-20

Figure 3. Revised Mid-Face Volume Deficit Scale

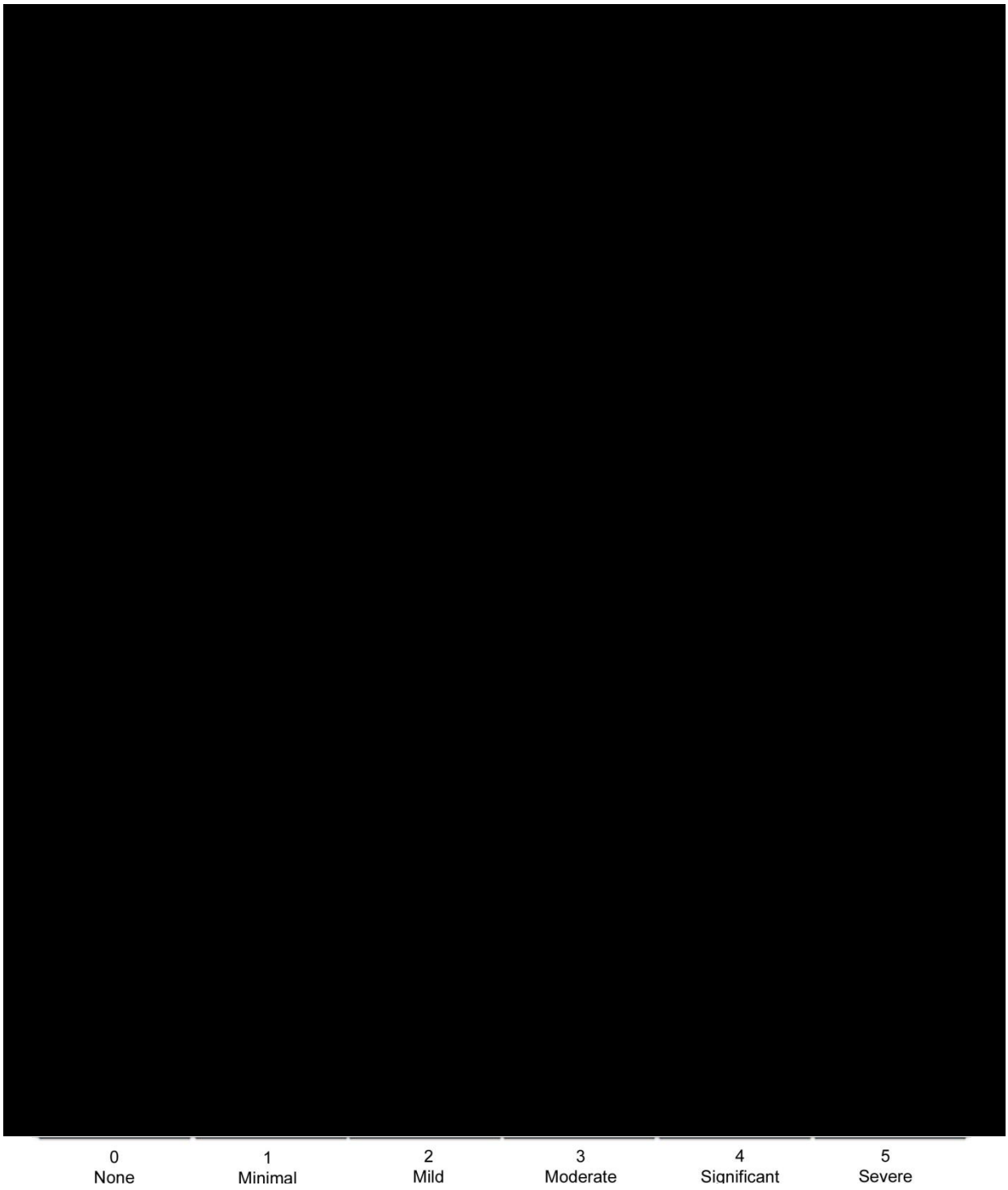


Table 2. Revised Mid-Face Volume Deficit Scale (MFVDS)

SCORE	GRADE	DESCRIPTION
0	None	• Moon face • Fullness (convexity) in the zygomaticomalar region, anteromedial cheek, and/or submalar region
1	Minimal	• Flattening in the zygomaticomalar region, anteromedial cheek, and/or submalar region
2	Mild	• Mild concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Mild tear troughs and/or nasolabial folds
3	Moderate	• Moderate concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Moderate tear troughs and/or nasolabial folds • Mild nasojugal folds and/or prejowl sulcus • Mild prominence of bony landmarks • Mild visibility of musculature
4	Significant	• Significant concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Significant tear troughs and/or nasolabial folds • Moderate nasojugal folds and/or prejowl sulcus • Moderate prominence of bony landmarks • Moderate visibility of musculature
5	Severe	• Wasting • Severe concavity in the zygomaticomalar region, anteromedial cheek, and/or submalar region • Severe tear troughs and/or nasolabial folds • Significant nasojugal folds and/or prejowl sulcus • Significant prominence of bony landmarks • Significant visibility of underlying musculature

3. SCALE VALIDATION METHODS

The goals of MFVDS re-validation were to: a) establish the scale can be used consistently by different raters and at different time-points and b) establish the point difference on the MFVDS that corresponds to a clinically significant difference in the mid-face volume deficit. Of note, the 3D images used in the validation included images taken from untreated volunteers as well as images taken from non-U.S. patients before and after mid-face volumizing treatment. All subjects provided written consent for the use of their images.

3.1 SCALE TRAINING

Each rater participating in the scale validation attended one of a series of web-based training teleconferences, each of which included multiple aesthetic physicians as well as Allergan and Canfield Scientific proctors. During the training session, raters learned about the development of the original MFVDS (and the results of its validation study), the mid-facial sub-units, and the objectives of the MFVDS re-validation project. They were also trained in the use of the revised MFVDS to evaluate overall mid-face volume deficit and mid-face volume deficit in each of the 3 mid-facial subunits. In order to familiarize the raters with the re-validation study procedure, during Phase 1 of the training, 3D digital images were presented as 10 pairs (frontal and bilateral oblique views of each subject). Raters then assessed whether each pair represented a clinically significant difference in overall mid-face volume deficit, and in deficit within each of the 3 mid-facial subunits. During Phase 2, the same 20 subjects' images were presented to raters again but un-paired and in a randomized order, and the raters used the MFVDS to rate both overall mid-face volume deficit as well as deficit in each of the 3 mid-facial subunits. During each phase, Allergan and Canfield proctors facilitated discussion of how the trainees were determining clinical difference, and assigning MFVDS ratings.

3.2 SCALE VALIDATION

Validation of the revised MFVDS scale began in February 2009. A total of 61 raters participated in the validation. To re-validate the MFVDS, each rater participated in 2 independent online test sessions separated by at least 14 days. Note that one rater completed only the first rating session.

During the first independent online test session (round 1) , raters viewed 22 pairs of subject images(44 images) and assessed whether each pair of images was clinically different (Yes/No). Later in the first session, each rater used the MFVDS to rate the overall, and sub-region volume deficit, for each 76 individual subjects' 3D images. These 76 images included

the 44 images used for assessing clinical difference, presented un-paired, along with 32 additional images, ordered in a random fashion.

During the second independent online test session (round 2), raters rated the same series of 76 subjects' 3D images using the MFVDS. The 3D images used in the validation study were taken from several sources, including images from the original MFVDS validation, but none of the images viewed during the training session were used during the test sessions.

4. MFVDS VALIDATION RESULTS

4.1 MFVDS VALIDATION

To summarize the reliability and reproducibility of the MFVDS scale, 2 statistical measures were calculated. Inter-rater agreement, which reflects the degree to which all raters gave the same rating to a given subject, was measured by Shrout-Fleiss intra-class correlation ICC (2,1) (SF random). The random coefficient was chosen so that the results could be generalized to the use of the scale by potential future raters. Intra-rater agreement, which reflects each raters' ability to give consistent ratings to the same subject across the 2 rating sessions, was measured by weighted kappa coefficients using Fleiss-Cohen weights. Intra-rater agreement was calculated for each rater and then the agreement score (weighted kappa) was summarized. To establish the reliability of the scale, Allergan set the minimum acceptable level of inter-rater agreement and mean intra-rater agreement for its scale revalidation at "substantial," i.e., 0.60 or greater.[3,4] As shown in Tables 3 and 4, inter- and intra-rater agreement both for the overall mid-face as well as across the 3 sub-regions was substantial (≥ 0.60).

Table 3: Inter-rater (ICC) Agreement at Rounds 1 and 2

Mid-Facial Region	Round 1 (n = 61)	Round 2 (n = 60)
Overall Mid-face	0.73	0.73
Anteromedial Cheek	0.67	0.67
Submalar	0.67	0.65
Zygomaticomalar	0.64	0.65

Table 4: Intra-rater Agreement (mean weighted kappa) at Rounds 1 and 2

Mid-Facial Region (n = 60)	mean weighted kappa (SD)	95% CI for mean weighted kappa
Overall Mid-face	0.83 (0.070)	(0.807, 0.843)
Anteromedial Cheek	0.80 (0.073)	(0.779, 0.817)
Submalar	0.79 (0.087)	(0.770, 0.815)
Zygomaticomalar	0.78 (0.091)	(0.752, 0.798)

[3] Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. *Educational and Psychological Measurement* 1973; 33:613-9.
[4] Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977; 33:159-74.

4.2 CLINICAL SIGNIFICANCE

To establish the minimum difference in grades that corresponds to a clinically significant difference in mid-face volume, the difference in MFVDS ratings between paired images was summarized for all pairs judged as representing a clinically significant difference, and for all pairs judged as not clinically different. Descriptive statistics were calculated for each subset of image pairs. As described in Section 3, during Round 1, 61 physicians compared pairs of 3D images for a clinically significant difference between images and then subsequently rated each individual image using the MFVDS. The mean difference in MFVDS rating for overall mid-face assessments was 1.02 for image pairs judged as "clinically different" compared to 0.64 for image pairs identified as "not clinically different" (Table 5Table 6). Similarly, across the 3 mid-facial regions, the mean MFVDS rating for subjects paired as "clinically different" ranged from 1.09 to 1.15, and 0.75 to 0.80 for subjects paired as "not clinically different." Based on these results, a 1-point difference on MFVDS was established as representing a "clinically significantly difference".

Table 5: Difference in MFVDS Scores for Subject Pairs Deemed Clinically Different

Mid-Facial Region	n[a]	Mean	SD	Range (Min, Max)	95% CI for Mean
Overall Mid-face	972	1.02	0.85	0,5	(0.97, 1.07)
Anteromedial Cheek	855	1.09	0.90	0,5	(1.03, 1.15)
Submalar	814	1.15	0.94	0,5	(1.09, 1.22)
Zygomaticomalar	770	1.09	0.93	0,5	(1.02, 1.16)

[a] N = 1342 = 22 pairs x 61 raters; n = # of clinically different pairs

Table 6: Difference in MFVDS Scores for Subject Pairs Deemed Not Clinically Different

Mid-Facial Region	n[a]	Mean	SD	Range (Min, Max)	95% CI for Mean
Overall Mid-face	370	0.64	0.70	0,3	(0.56, 0.71)
Anteromedial Cheek	487	0.75	0.80	0,5	(0.68, 0.82)
Submalar	528	0.79	0.73	0,4	(0.73, 0.85)
Zygomaticomalar	572	0.80	0.75	0,3	(0.74, 0.87)

[a] N = 1342 = 22 pairs x 61 raters; n = # of not clinically different pairs

5. **CONCLUSION**

The results of the MFVDS re-validation confirmed those obtained during the original scale validation: the scale was validated to be reliable and reproducible for ratings of mid-face volume deficit in the overall mid-face. Additionally, the scale could be used to measure volume deficit in 3 distinct sub-regions of the mid-face. All measures of agreement were at the level of "substantial" or higher. Inter-rater agreement was greater than 0.64 and intra-rater agreement was greater than 0.78.

The MFVDS validation also demonstrated that clinically significantly differences in mid-face volume deficit (both overall as well as by region) could be observed and distinguished. For image pairs deemed clinically significantly different, the mean difference in MFVDS score was 1.02 compared to 0.64 for pairs that were not clinically different. This helped to establish that a 1-point difference on MFVDS corresponds to a clinically significant difference in the mid-face volume deficit.

Thus, the results of the MFVDS validation demonstrate that the MFVDS is a photometric tool that can be reliably used to measure mid-face volume deficit and identify clinically significant differences between deficits by different raters and across different timepoints.

Appendix 3

Literature Review

Juvéderm® VOLUMA XC
Modular PMA # M100003

A Literature Review of Hyaluronic Acid Fillers Used to Treat Mid-Face Volume Loss

July 26, 2011

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1.0 Introduction

Juvéderm® dermal fillers (Juvéderm® Ultra, Juvéderm® Ultra Plus, Juvéderm® Ultra XC and Juvéderm® Ultra Plus XC) are currently approved in the United States (US) for correction of facial wrinkles, folds, and lines, but are not yet approved for replenishing malar/buccal volume lost as the result of disease or aging. In support of US approval for Juvéderm® VOLUMA XC, a new dermal filler formulation that is intended to perform as a facial volumizer, a review of the published literature has been performed.

Juvéderm® VOLUMA XC is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized sub-dermal filler formulated with lidocaine. Juvéderm® VOLUMA XC is approved in Canada, and the formulation without lidocaine is currently available in Europe but is still investigational in the United States. It consists of crosslinked hyaluronic acid (HA) produced by *Streptococcus equi* bacteria and formulated to a concentration of 20 mg/mL. VOLUMA contains a mix of low (90%) and high (10%) molecular weight HA. Higher molecular weight products have more repeating units in the polymer chain compared with low molecular weight products. The HA is crosslinked by adding a minimum amount of 1,4 butanediol diglycidyl ether to form a three-dimensional (3D) HA gel and is then mixed with phosphate buffer and 0.3% lidocaine. VOLUMA can be administered via a needle or cannula. Volumes typically range from 1 to 3cc on each side of the face.[1]

2.0 Abbreviations

3D	Three-dimensional
AEs	Adverse events
FLA	Facial lipoatrophy
GAIS	Global Aesthetic Improvement Scale
HA	Hyaluronic acid
HIV	Human immunodeficiency virus
HAART	Highly active antiretroviral therapy
NLF	Nasolabial fold
US	United States

3.0 Literature Search Methods

A broad-scoped literature search was conducted for articles with the terms ‘Voluma,’ ‘facial volume’ and ‘filler,’ or ‘facial lipoatrophy.’ Databases searched were Medline, PubMed, and Scopus. The search was limited to years 2000 to present (inclusive through

January 2011) to obtain the most current assessments of this topic, and only articles in the English language were included. This resulted in 351 references. The titles were manually reviewed for pertinence. Rejected articles included abstracts, animal studies, and studies focused solely on Botox® (although articles with both dermal fillers and Botox® were included). During review of the retrieved articles, 14 additional articles were identified and obtained, for a final total of 83 articles.

4.0 Facial Volume Loss Overview

Intrinsic and extrinsic aging (chronoaging and predominantly photoaging, respectively) manifests itself in the formation of wrinkles, folds, and lines, with the overall contour of the face dramatically changing.[2] Soft tissue volume lost through time reveals the bony structural elements of the face. Shrinking fat pads leave behind cheek depressions (sunken cheeks), and the deepening of folds, such as nasolabial folds (NLFs), becomes pronounced. The lips lose their voluptuousness and shape, becoming narrow. The aging face deflates more than it descends.[3] Yet because the root cause of aging is decreased cellular metabolism, the body becomes unable to replenish this lost volume.

As skin communicates not only age but also the ability to remain an active member of society, the pressure on individuals to conceal the signs of aging are tremendous.[4] Though an individual may feel healthy and active, the loss of facial volume and consequent alterations in facial appearance can suggest the opposite. Well-being should be a priority in any field of medicine and is increasingly becoming an important factor in health management. Correcting folds, wrinkles, thinning lips and asymmetry by restoring the natural contour of the face through replacement of lost volume can improve the psychological well-being of the individual.[5] As an individual ages, cellular senescence, bone resorption, atrophy of facial fat, the breakdown of collagen and elastic fibers coupled with the tolls of gravity and muscle pull over time, lead to loss of volume and pronounced folds in the skin.[6] The process is exacerbated by external factors introduced to the body such as smog, smoking and sun exposure.[7] Human Immunodeficiency Virus (HIV)-positive individuals experience a similar change in facial morphology: Facial lipoatrophy (FLA) is a severe yet common side effect of controlling infection through highly active antiretroviral therapy (HAART).[8]

4.1 Aging

Gravity is not the primary culprit responsible for sagging facial skin. Loss of facial volume is a significant offender.[3;9;10] Facial aging is different from one individual to another and isn't homogenous even in a single individual, varying widely across anatomical zones. Three zones of facial aging are usually described: The upper third of the face is essentially marked by expression lines, the middle third suffers mainly from skeletal and tissue involution processes, and the lower third is particularly subject to ptosis.[11,12] Similarly, underlying bony changes may occur differently. The skeleton of the midface below the inferior orbital rim undergoes significant changes while the anterior projection of the inferior orbital rim remains relatively fixed at its midpoint.[6;12] The

aging face becomes framed by bony contours wrapped with thin skin, appearing deflated and aged.[13]

Intrinsic aging (chronoaging) is essentially uncontrollable, and appears to evolve with periods of acceleration and deceleration at different times in a person's life. Extrinsic aging (predominantly photoaging) is dictated by a person's exposure to the elements and lifestyle habits, making its degree of influence more controllable (i.e., ultraviolet exposure, smoking, sleep, diet, muscle activity/facial expression and exercise). Temperature extremes, wind, and ultraviolet radiation are harsh on facial skin. Skin thickness reaches a maximum at age 35 in women and at age 45 in men, with a gradual decline thereafter. Facial fat exists as multiple well-delineated, independent compartments that have specific anatomic relationships to one another,[14] and there is good clinical evidence that individual fat compartments age independently.[15] Redistribution and loss of subcutaneous fat contributes to flat or hollow contours. Bony absorption of the maxilla and mandible begin in the 50s. In the nose, connections between the upper and lower lateral cartilages and support mechanisms of the tip and interdomal ligaments slowly weaken, so that the nose actually becomes longer.[16,17] The lower periorbital/cheek area is most significantly influenced by volume-related changes. The heart-shaped youthful face gives way to a more rectangular face with aging. Volume loss allows the appearance of shadows, as tissues fall and become tethered by the various retaining ligaments. Double contours arise in the lower eyelid and cheek, with exposed orbital fat creating a bulge above the exposed bony orbital rim which creates a hollow, and a second malar mound bulges below these with a corresponding malar septum hollow below that.[18,15] Loss of volume in one area may lead to the development of folds in a neighboring area. Muscle contractions may result in changes in underlying fat distribution, though still a preliminary concept. Bony remodeling causes a decrease in the space available for the soft tissue in the midface, although the degree to which bone loss effects the formation of NLFs is not yet fully elucidated.[19]

Two studies examined the degree of age-related volume loss. Forty-two mother-daughter pairs (15-91 years; no previous rejuvenation treatments) underwent 3D photographic imaging. The changes in facial structure secondary to aging were measured using volumetric comparisons of periorbital tissues between each daughter and her mother. A consistent pattern of volume difference and regression of soft tissues associated with the medial canthus nasojugal groove was demonstrated in the aged individual; volume difference in the tear trough ranged from 0.02cc to 1.27cc.[20] In another study, 60 females and 60 males underwent 3D scanning to obtain facial measurements. The orbital aperture width, area, and size increased significantly with age for both sexes. The glabellar and maxillary angles, and mandibular length and height decreased significantly with age for both sexes. The mandibular angle significantly increased with age for both sexes.[21]

4.2 HIV-Related Facial Lipoatrophy

HAART has improved the clinical prognosis of patients with HIV but has undesirable side effects such as lipodystrophy syndrome.[22;23] Key aspects of lipodystrophy are central lipohypertrophy (fat accumulation in abdomen, breast, or dorsocervial spine

"buffalo hump") and peripheral lipostrophy (fat loss in limbs, buttocks, and face). The incidence of lipodystrophy syndrome has been reported to be as high as 83% in patients receiving HAART. Volume depletion due to aging is typically mild to moderate whereas when due to HIV it is moderate to severe, and facial volume loss has become a characteristic marker of HIV. Some patients with FLA fail to adhere to therapy or discontinue HAART due to low self-esteem and self-image.[24]

FLA is most visible as a reduction in the buccal fat pads, such that the cheeks appear to sink into the face. More pronounced NLFs and malar, preauricular, periocular, and temple concavities are also linked with this degenerative change.[25] FLA severity (mild, moderate, or severe) is often based on the size of the area affected, muscle or bone prominence, and shadowing.[24] Ascher et al (2006), representing the Facial Lipoatrophy Panel, developed a concise definition of FLA: "Loss of facial fat due to aging, trauma or disease, manifested by flattening or indentation of normally convex contours."[26] In 2002, James et al performed an extensive search of the literature concerning FLA and developed a 4-point severity scale, since no scale had been published to date.[27] Based on that 4-point scale, the Facial Lipoatrophy Panel developed a 6-point photographic grading scale (Grades 0-5, where 0 is no FLA and 5 is severe FLA) with the intention of the scale being used across physician specialties to diagnose a lipoatrophic patient.[26]

Low self-esteem, depression, feelings of loss of control, relationship problems, fear of stigmatization, decreased sexual activity, and social isolation are consequences of worsening FLA.[26,27] Gender differences do occur; facial fat loss does not seem to be as prevalent in women as it is in men, and women are more likely to experience neck lipohypertrophy whereas men are found to have more lipoatrophy.[28]

5.0 Treatment for Facial Volume Loss

Goals for restoring natural contours to the depleted face can be thought of as a 2-step approach: 1) to diminish the depth of various grooves and creases throughout the face (i.e., the NLF, glabellar crease, and nasojugal groove), and 2) to provide volume augmentation to atrophied tissues (i.e., malar and submalar regions and lips).[29] Consensus recommendations for the midface are to restore the malar contour first, followed by the orbital-malar groove and the nasojugal groove, which is the most complicated. When malar contour is restored, it results in a lift of the face and diminution of the NLFs, affecting how the folds are to be treated and sometimes negating the need for treatment.[12] Current treatments available for treating HIV-facial lipoatrophy are medical therapy, surgical treatment, and/or permanent or temporary dermal and subdermal fillers.[30]

Facelift surgery is often utilized,[31] but facelift surgery is not flexible. As Lambros (2008) states "A young face is not an old face with tight cheek skin."[32] Lifting the soft tissue envelope may help to reduce wrinkles and sag, but loss of volume, particularly around the eyes and cheek, cannot be completely corrected by traditional surgical procedures.[6,13,33] Malar implants are another surgical option. However, in addition to being an invasive

procedure,[34] as the FLA progresses, the implants alone become insufficient to fill in the hollows that develop.[28] Implants may even accentuate the gaunt appearance associated with HIV-FLA since FLA is a dynamic process.[24,13] This concern also pertains to permanent fillers, which in addition to being inflexible in a dynamic process are extremely difficult to remove if unacceptable cosmetic results or adverse events (AEs) should occur.[23]

Various dermal fillers have been utilized successfully for volume restoration.[35,36;37] Liquid silicone, although used extensively over the years, had side effects such as chronic cellulitis, nodules, foreign body reactions and migration. This resulted in many physicians seeking other filler options.[25;38] Fat transfer is a popular option since there are no foreign body reaction risks. The best results of autologous fat transplantation occur in sites with minimal motion when compared with mobile or dynamic areas (such as lips or marionette lines).[29] The process of injecting fat is not new, andt although the techniques for harvesting fat have improved, the process is not without problems.[39] One of the main obstacles in using fat as a filling agent is volume loss due to reabsorption and loss of viability,[40] possibly as high as 50% loss with long-term follow-up. Rare complications of fat grafting include hypertrophy and fat emboli.[39] When used in large volumes, oil cysts and calcifications are also reported.[41] Fat transfer is less effective at finer contouring, and duration is unpredictable.[13,18,29,42] There is also the potential for additional injury incurred at the fat donation site,[25] and prolonged edema and ecchymosis limit the therapy to those who can afford an extended recovery time.[43] Over-correction is often required as the degree of fat loss is frequently unpredictable,[44] and more than one fat grafting session may be required for some facial augmentation locations.[3] Patients with HIV-lipodystrophy may also not have sufficient fat stores for harvesting.[27,30] One author has observed that fat grafting has greater success in younger patients (<40 years of age) than in older patients (>60),[29] which is troublesome considering older patients are usually the target population for facial restoration.

Biodegradable fillers are preferable when there is a potential for recovery of the underlying conditions, as is the case for mild HIV-associated FLA.[45] Biodegradable products offer a good safety profile, but maintenance of aesthetic benefits necessitates reinjection over time and can require a great deal of product for moderate to severe FLA.[45,46] Two synthetic dermal fillers have been approved by the FDA for HIV-associated FLA. Poly-L-lactic acid (Sculptra) was approved in 2004 for HIV-associated FLA. Drawbacks of Sculptra are that the results are not immediate and may require multiple treatments,[47] and, more seriously, skin nodules and granulomatous reactions have been reported.[25,42,48,49,50] Radiesse, a calcium hydroxylapatite filler, was approved in 2006 but is associated with AEs including textural changes, nodules, and granulomas.[48] If placement of the product is not optimal or AEs occur, the filler is not reversible and removal is difficult.[49] BioAlcamid (polyalkylamide gel), which is not currently FDA approved, can result in infection, asymmetry, or gel migration.[40,49] One author indicated that although early results with BioAlcamid were favorable, extended follow-up results have revealed significant long-term problems that should result in restricted or discontinued use.[51]

Because of their longevity, effectiveness, safety, and reversibility, HA products have become a popular option for facial volume restoration.[13,16,37;52;53,54,52] HA is a major component of the extracellular matrix, and due to its polyanionic and hydrogen-bonding nature, it is capable of binding large amounts of water. Because of the properties of HA, different formulations varying in HA concentration and degree of crosslinking can be manufactured to specifically target the individual needs of the patient. AEs are usually transient and or minor in severity, consisting primarily of procedure-related edema, pain or tenderness, erythema, pruritis, ecchymosis, and injection site bleeding.[45]

As a filler, HA is capable of providing volume to the targeted area, reducing the appearance of folds and restoring the natural 3D contour of the region to which it is applied.[55,56] Crosslinked HA-based dermal fillers have been used successfully to improve fine lines[57] and moderate to severe folds such as nasolabial folds[58,59] and for the reconstruction of scars and soft-tissue deficits.[60,61,62,63] HA is used for patients who do not have a severe degree of aging, or for those who do have a greater degree of aging but wish to avoid the expense and recovery period associated with more invasive procedures.[18] One small study demonstrated that HA injections resulted in a perceived reduction in apparent age of approximately 6 to 7 years after 2 to 4 weeks.[64]

As effective as dermal fillers are at correcting lines and wrinkles, current FDA-approved temporary fillers may not adequately meet the need for durable, global facial rejuvenation and volume replacement.[58] In addition, to achieve adequate volumization, larger quantities of product would be required.[65]

In response to the lack of an ideal filling agent for volume augmentation,[66] Restylane SubQ and Juvéderm® VOLUMA were developed. Both products are available in Europe but are investigational in the United States. Literature pertaining to Restylane SubQ is included in this review since the product has a similar indication in Europe as Juvéderm® VOLUMA. Although Juvéderm® VOLUMA is currently being evaluated for healthy subjects under an Investigation Device Exemption, studies pertaining to HIV-FLA are also provided below to provide background on the clinical effectiveness and safety of dermal fillers for mid-face facial rejuvenation.

5.1 Restylane SubQ

Restylane SubQ is indicated for facial contouring and chin/cheek augmentation and consists of 20 mg/mL HA. SubQ has the largest particle size in the Restylane facial filler range, with 1000 particles/mL,[67] and it is considered to be an effective alternative to fat transfer for mid-facial augmentation and contouring,[68] although caution is advised when using it in patients with poor soft-tissue coverage to avoid product palpability and mobility.[69] Several clinical studies have been conducted on SubQ in HIV-positive patients,[70,71] as well as for cheek or chin augmentation.[44, 66,72,73,74] SubQ was deemed effective at improving appearances with AEs typical of other HA dermal fillers (swelling, tenderness, redness, bruising, pain). Overall conclusions were that this large-particle HA filler provided relatively long-lasting esthetic correction and was well-tolerated.

Recently, 4 cases of delayed hypersensitivity to SubQ were reported; all 4 cases were successfully treated with hyaluronidase.[75]

5.2 Juvéderm® VOLUMA

Juvéderm® VOLUMA has greater viscosity and elasticity than approved products Juvéderm® Ultra and Ultra Plus.[76] Its action is derived from a thick HA reserved for deep planes, and results are excellent for 6 to 18 months with few AEs.[77, 78,79] VOLUMA has a unique combination of high cohesivity (the tendency of the gel to stick together and hold its form) and high viscosity, which gives it a greater lift capacity (the ability to oppose deformation and flattening) than most other HA fillers.[52] The addition of low molecular weight HA improves the cross-linking efficiency and produces this high cohesivity and viscosity, which also reduces migration potential.[49,78] The soft nature of VOLUMA allows it to be readily molded and manipulated while its cohesiveness allows it to maintain its shape.[80] One author prefers VOLUMA for eyebrow correction because it is the easier to incorporate over that body surface compared to SubQ beads, and also uses VOLUMA in the temples and cheeks to correct hollowing as well as for chin enhancement.[81] For clinical investigations in the US, VOLUMA formulated with 0.3% lidocaine is being utilized. The addition of lidocaine to HA dermal fillers provides greater patient comfort during the injection process and does not affect the rheological properties of the dermal filler itself.[82;83]

Table 1 provides the details of the clinical studies conducted on VOLUMA outside the US thus far. In general, patients and Investigators were highly satisfied with the results of the treatment, and no serious AEs occurred.

Bechara et al (2008) treated 21 males with HIV-FLA with Juvéderm® VOLUMA in a prospective, open-label, single center study. The aesthetic outcome was assessed using the Global Aesthetic Improvement Scale (GAIS) every 3 months until 12 months after implantation, patient satisfaction was collected, and changes in quality of life were recorded using the Dermatology Life Quality Index. All 21 patients showed improved or better scores on the GAIS through 9 months, and all but one were still improved or better at 12 months. Quality of life was significantly improved, the vast majority (90.5%) would recommend VOLUMA, and all but one (95%) thought the treatment was beneficial. Side effects were as expected (mild erythema, swelling, and discrete bruising).[22]

Raspaldo (2008) conducted a retrospective analysis of 102 patients (93 females, 9 males) treated with VOLUMA. Follow-up occurred at 1 month and again at 6 to 18 months later, with assessments using GAIS, reduction in volume loss, and patient-assessed efficacy using a 5-point scale (1 = very good, 5 = very bad). GAIS results showed that nearly all of the patients (100 of 102) were rated as much or very much improved at 1 month, and 82 patients were still much or very much improved at the second follow-up visit (with an additional 18 patients rated as improved). At baseline, most patients (66) had stage II volume loss, defined as evidence of early soft tissue ptosis or atrophy slightly

visible); or stage III volume loss (34), defined as visible depression or descent. Two patients had stage IV volume loss (severe depression or atrophy). After the first treatment, 89 patients were assessed as stage I (normal) and 13 at stage II. No patients were stage III or IV. All patients considered VOLUMA to be either very good (71 patients) or good (29 patients). The vast majority of patients (98) would recommend the treatment to others and found the treatment to be beneficial (100). Reported adverse events were overcorrection (4), hematoma (3), swelling (1), and hypersensitivity (1). The hematomas were considered related to the injection process rather than to VOLUMA itself.[1]

Hoffman and the Juvéderm VOLUMA Study Investigators Group (2009) conducted a prospective, open-label, nonrandomized pan-European evaluation of 70 patients (91% female) under the care of 15 physicians (4 were dermatologists, 6 were plastic surgeons, and 5 were aesthetic practitioners). The study comprised 2 visits, the injection day and follow-up 14 days after treatment. Effectiveness was assessed by scores on the Facial Volume Loss Scale and GAIS. The mean volume loss scores improved from 3.7 to 2.1 ($P < .001$), indicating an improvement in esthetic outcome. All patients were rated as improved, much improved, or very much improved by the investigators, and 99% of patients rated themselves as improved, much improved, or very much improved on the GAIS. Adverse events were as expected, with 24 patients experiencing a reaction of bruising, pain, swelling, and 1 infection. Physicians would recommend VOLUMA to colleagues (98% of 67 treatment sessions), and patients would recommend the treatment to their friends (98%).[84]

Cattin (2010) described a single injection technique for Juvéderm® VOLUMA or ULTRA PLUS in midface rejuvenation. The author had used the technique in more than 60 patients over a period of approximately 18 months, with no significant adverse events and the only complications reported were a small needle mark at the entry point.[80]

Fischer (2010) presented the results of a post-marketing study in Europe involving 20 injectors (10 aesthetic practitioners, 5 plastic surgeons, 4 dermatologists, and 1 general surgeon) from 7 countries (Germany, Italy, Spain, United Kingdom, Sweden, Netherlands, and Belgium). A total of 84 patients (88% female) were recruited who had received Restylane SubQ less than 2 years previously and now required re-treatment. Most patients received treatment to the malar area and the chin. Injectors rated the overall cosmetic effect as improved in 98% of cases and rated VOLUMA as significantly better, much better, or very much better than their previous experience with Restylane in 69% of cases ($P < 0.001$). Injectors expressed a preference for VOLUMA versus SubQ in 71.4% of their patients ($P < 0.0001$), and all injectors said they would recommend VOLUMA to a patient who was seeking volumizing treatment. The majority of patients (98%) rated the overall cosmetic effect as improved, much improved, or very much improved, and nearly all patients (96.4%) said they would recommend VOLUMA to friends. Seven patients reported a transient AE (4 with bruising, 2 with swelling, and 1 with type not reported).[85]

Table 1. Clinical Studies Conducted with Juvéderm® VOLUMA

Author, Year	Patient Population	Timeframe	Effectiveness	Safety
Bechara, 2008[22]	21 HIV patients with FLA	9 months 12 months	• 100% much improved at 9 months; 76.2% much improved at 12 months • 12-mo QOL significantly improved • 90.5% would recommend VOLUMA, 95.2% felt treatment was beneficial	Mild erythema (38.1%), swelling (19%), bruising (19%)
Raspaldo, 2008[a,1]	102 patients	1 month 6-18 months	• 101 patients were rated as improved, much improved, or very much improved at 1 month • 100 of 101 patients were also rated as improved, much improved, or very much improved at 18 months • Investigator assessment of the overall volumizing effect was very good or good in 93 patients	Overcorrection (4), bruising (3), swelling (1), hypersensitivity (1)
Hoffmann, 2009[b,84]	70 patients	2 weeks	• Mean volume loss declined from 3.7 to 2.1 ($P < 0.001$) on 5-point scale. • 88% of physicians and 76% of patients rated very much or much improved. • 92% of patients were very likely or quite likely to return for treatment • 98% of patients would recommend this treatment to friends	Bruising (7), Pain and bruising (4), swelling (3), bruising and swelling (3), pain and swelling (2), pain (2), bruising and bleeding (1), infection and swelling (1), not specified (1)
Cattin, 2010 [c,80]	60 patients	18 months	Single injection technique at the subdermal level and above the muscle reduced bruising and swelling and increased patient comfort (observational)	Small needle mark at entry point
Fischer, 2010 [c,85]	84 patients treated with SubQ <2 years previously	Unspecified	• 75% of physicians found VOLUMA fairly or very easy to inject • 84.5% found VOLUMA easy to sculpt/massage. • 98% of patients and physicians rated effect as improved • 69.1% of physicians rated VOLUMA better than SubQ • 61% of patients expressed preference for VOLUMA	Bruising (4), swelling (2), AE not specified 91)

[a]Study sponsored by Allergan
[c] Allergan provided product for the study but no other financial assistance was provided
[c]Allergan provided manuscript editorial assistance

6.0 Conclusion

Whether due to disease or the inevitable effects of aging, facial volume restoration has become a much sought-after procedure for many people. While several different treatment options exist, there are drawbacks associated with each of them, including invasiveness (surgery), inconsistent results (fat transfer), and safety (Sculptra, Radiesse, and BioAlcamid). HA dermal fillers provide the best alternative, especially the newer, more viscous fillers such as Juvéderm® VOLUMA with Lidocaine. Specially formulated to provide volumization, VOLUMA has been shown in several clinical studies conducted in Europe to be effective, to yield high patient and physician satisfaction, and to have no serious safety issues.

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