SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: RHA® 2
RHA® 3
RHA® 4

Device Procode: LMH (Implant, Dermal, For Aesthetic Use)

Applicant's Name and Address: TEOXANE SA
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Rue de Lyon, 105
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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P170002

Date of FDA Notice of Approval: October 19, 2017

II. INDICATIONS FOR USE

RHA® 2 is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

RHA® 3 is indicated for injection into the mid-to-deep dermis for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

RHA® 4 is indicated for injection into the deep dermis to superficial subcutaneous tissue for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF), in adults aged 22 years or older.

III. CONTRAINDICATIONS

- RHA® 2, RHA® 3 and RHA® 4 are contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

- RHA® 2, RHA® 3 and RHA® 4 contain trace amounts of gram positive bacterial proteins, and are contraindicated for patients with a history of allergies to such material.
- RHA® 2, RHA® 3 and RHA® 4 should not be used in patients with previous hypersensitivity to local anesthetics of the amide type, such as lidocaine.
- RHA® 2, RHA® 3 and RHA® 4 should not be used in patients with bleeding disorders.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the RHA® 2, RHA® 3, and RHA® 4 labeling.

V. DEVICE DESCRIPTION

RHA® 2, RHA® 3, and RHA® 4 are viscoelastic, sterile, non-pyrogenic, clear, colorless, and biodegradable gel devices. They are produced with sodium Hyaluronic Acid (NaHA) with a concentration of 23 mg/g obtained from bacterial fermentation using a *Streptococcus equi* bacterial strain, crosslinked with 1,4-butanediol diglycidyl ether (BDDE) and reconstituted in a physiological buffer (pH 7.3). They contain 0.3% lidocaine hydrochloride to reduce pain on injection.
The devices exist in three formulations, from the least to the most cross-linked:

- RHA® 2 (least cross-linked)
- RHA® 3
- RHA® 4 (most cross-linked)

The product is supplied in a 1 ml syringe. RHA® 2 is supplied with two 30G ½ inch hypodermic needles and RHA® 3 and RHA® 4 are supplied with two 27G ½ inch hypodermic needles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF). Alternatives in the treatment of wrinkles, depressed lesions, and scars include invasive surgery (face-lift, rhytidectomy, etc.).

Less invasive alternatives include injection of other dermal fillers (collagen, calcium hydroxylapatite, microparticles of poly-L-lactic acid or other hyaluronic acid gels) or autologous fat transfer.

Treatment of very superficial and fine wrinkles and superficial texture of photo-damaged skin may also be accomplished using other technologies such as laser resurfacing, chemical peeling procedures or use of topical creams containing active ingredients such as retinoids or glycolic acid.

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Following CE marking on September 5, 2004, TEOXANE first introduced a family of non-animal cross-linked NaHA dermal fillers in Europe under the trade names of TEOSYAL®. On June 1, 2011, TEOXANE obtained the CE marking for the addition of 0.3% of lidocaine hydrochloride in their products, introducing a new family of NaHA dermal fillers under the trade names of TEOSYAL® PureSense. The TEOSYAL® and TEOSYAL® PureSense products have since been approved in several countries worldwide.

TEOXANE modified the current products to achieve specific viscoelastic properties well adapted to the treatment of dynamic wrinkles of the face. This led to the TEOSYAL® RHA® product line.

RHA® 2, RHA® 3, and RHA® 4 are marketed in Europe and other parts of the world as, respectively, TEOSYAL® RHA® 2, TEOSYAL® RHA® 3 and TEOSYAL® RHA® 4, and received CE marking clearance on October 2, 2014, as a variation to the TEOSYAL® PureSense range.

Currently, TEOXANE dermal fillers are available in the EU, and in more than 80 countries, including Argentina, Australia, Brazil, Canada, Korea, Mexico, Russia, Singapore, Switzerland, and Turkey.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Common treatment responses which can occur with the use of RHA® 2, RHA® 3, RHA® 4, and other dermal fillers, include bruising, discoloration, firmness (induration), itching, lumps/bumps (injection site mass), pain, redness, swelling and tenderness. All these common treatment responses were seen in the clinical studies.

In addition to the common treatment responses noted above, the following adverse events were reported from use in the nasolabial folds and other locations of the face, as part of the post-marketing surveillance on the use of RHA® 2, RHA® 3 and RHA® 4 outside the United States. These adverse events are listed in order of prevalence: inflammatory reaction, edema, unsatisfactory results, vascular skin disorder, implant migration, acne, anaphylactic reaction, blister, ecchymosis, granuloma, scar, papule, and skin necrosis following accidental injection of product into blood vessel.

Additionally, the following rare but serious adverse events that are associated with intravascular injection of other soft tissue filler material in the face have been reported in the literature: vision impairment (acute or permanent), blindness, cerebral ischemia or cerebral hemorrhage leading to stroke, skin necrosis, and damage to underlying facial structures.

The following adverse events were reported as part of post-marketing surveillance on the use of RHA® 2, RHA® 3 and RHA® 4 outside the United States when used in NLFs and other indications and were not reported as part of the clinical study. These adverse events are listed in order of decreasing order of frequency: inflammatory reaction, vascular complication, implant migration, overcorrection, unsatisfactory results, anaphylactic reaction, necrosis, abscess, acne, blister, granuloma, herpes breakout, hypersensitivity, injection, papule, scarring.

In some cases the symptoms resolved without any treatment. Reported treatments included the use of: hyaluronidase, antibiotics, anti-inflammatories (NSAID, steroids), antihistamines, anti-viral, analgesics, vasodilators, aloe vera, drainage, massage, and monitoring at the hospital. Outcomes for these reported events ranged from resolved to ongoing at the time of last contact.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

RHA® 2, RHA® 3, and RHA® 4 were extensively tested and characterized through physical and chemical testing (Table 1), and biocompatibility studies (Table 2). Preclinical testing results were adequate to support initiation of human clinical studies as dermal fillers.

Table 1: Physical and Chemical Testing – Requirements for RHA®

Test	Purpose	Results
NaHA content	To confirm the NaHA concentration meets specifications	Passed
Sterility	To ensure the product is sterile	Passed
Bacterial Endotoxins	To confirm the endotoxins count in the device meets specifications	Passed
pH	To confirm the pH of the gel meets specifications	Passed
Residual crosslinker content	To confirm the residual crosslinker content of the gel meets specifications	Passed
Lidocaine content	To confirm the lidocaine concentration of the gel meets specifications	Passed
Impurities deriving from Lidocaine Hydrochloride	To confirm impurities in the gel meet specifications	Passed
Extrusion force	To confirm the extrusion force meets specifications	Passed
Rheology: mechanical properties of the gel	To confirm phase angle δ of the gel meets specifications	Passed
Appearance of the device	To control visually the absence of irregularities and defects in the device	Passed

B. Biocompatibility Studies

Table 2: Summary of biocompatibility studies for RHA®

Test	Method	ISO Standard	Results
Cytotoxicity	In vitro mammalian cell culture test	ISO 10993-5	Same cytotoxic potential as control*.
Sensitization	Guinea pig maximization study	ISO 10993-10	No delayed sensitization.
Intracutaneous reactivity	Intradermal injection in rabbits.	ISO 10993-10	Similar level of reactivity as control*. Irritant at 3 days. RHA® 2 was non-irritant at Day 22; RHA® 3 was non-irritant at Day 25; and RHA® 4 was non-irritant at Day 26.
Pyrogenicity	Rabbit		Non-pyrogenic.
Genotoxicity	Ames test (bacterial reverse mutation study)	ISO 10993-3	Non-mutagenic
Genotoxicity	Mouse lymphoma assay	ISO 10993-3	Non- mutagenic.
Genotoxicity	Mouse peripheral blood micronucleus test	ISO 10993-3	Non-genotoxic.
Acute systemic toxicity	Mice intraperitoneal study	ISO 10993-11	No evidence of acute systemic toxicity.
Sub-acute and subchronic systemic toxicity	Intradermal injection in Sprague-Dawley	ISO 10993-11	There was no evidence of systemic toxicity after 4 weeks and 13 weeks of implantation.
Intradermal implantation	Intradermal implantation in rats	ISO 10993-6	The test articles were classified as non-irritant. After 52 weeks, degradation had started.

(*) Note: The control device was an FDA approved Hyaluronic Acid soft tissue filler, with similar characteristics to either RHA® 2 and RHA® 3 or RHA® 4, respectively. The control product is legally marketed with similar indications for use.

Stability data have been collected through 17 months at 25°C ± 2°C and 60% ± 5% relative humidity. At each time point, product was characterized via microbiological, physical, chemical, lidocaine hydrochloride content, and lidocaine-related degradant parameters. Conformance of real-time aged product with all specifications was confirmed.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed two clinical studies to establish a reasonable assurance of safety and effectiveness of injection into the mid to deep dermis with RHA® 2 and RHA® 3 or deep dermis to superficial subcutaneous tissue with RHA® 4 for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF) in adults aged 22 years or over in the US under IDE # G140028 and G140106. Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

A. Study Design

Subjects were treated between June 26, 2014, and October 6, 2014 for the RHA® 2 and RHA® 3 study (G140028). The database for this PMA reflected data collected through March 7, 2016, and included 147 treated subjects and 26 untreated controls. There were 5 US investigational sites.

Subjects were initially treated between September 22, 2014, and December 19, 2014 for the RHA® 4 study (G140106). The database for this PMA reflected data collected through May 12, 2016, and included 118 treated subjects and 20 untreated controls. There were 5 US investigational sites.

The two clinical studies were essentially identical, with very minor differences for depth of injection and statistical consideration to take into account the number of products in each study.

Both studies were controlled, randomized, double-blinded, within subject (split-face), multicenter, prospective clinical studies. The design included a non-treatment group of subjects who were followed until the primary end-point, at which time, they exited the study. Both study durations were 15 months and included repeat treatment.

For each study the control group was an FDA approved Hyaluronic Acid soft tissue filler, with similar characteristics to either RHA® 2 and RHA® 3 or RHA® 4, respectively. Both control products are legally marketed alternatives with similar indications for use.

Safety Objective:
To evaluate the safety of three RHA® implant formulations versus their respective control. Safety was determined by the rates of Adverse Events (AEs) associated with the use of each study device. Safety was evaluated throughout the study, with subjects followed for up to 68 weeks following the original treatment (initial treatment or touch-up treatment) with the study devices. Safety was also specifically evaluated following early repeat treatment which could occur at 24, 36, or 52 weeks after baseline, as well as at 64 weeks.

Effectiveness Objective:

To demonstrate the non-inferiority of three RHA® implant formulations versus their respective control at 24 weeks for the correction of moderate to severe NLFs. Assessment of non-inferiority was based on a proprietary and validated 5-grade scale for scoring the severity of nasolabial folds, NLF-SRS (which for the purposes of this document will be referred to as WSRS), as rated by a Blinded Live Evaluator (BLE) at each investigational site.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in both pivotal studies was limited to subjects who met the following inclusion criteria

   - Outpatient, male or female of any race, 22 years of age or older. Female patients of childbearing potential must have a negative urine pregnancy test (UPT) at Visit 1 and practice a reliable method of contraception throughout the study.
   - Moderate to severe bilateral aging defects in the nasolabial area, with wrinkles classified as WSRS grade 3 or 4 (BLE and Treating Investigator must independently agree that the criterion is met; however, concordance of severity not required);
   - NLFs of the same WSRS grade on the left and right sides of the face (i.e., approximate bilateral symmetry);
   - Willing to abstain from facial aesthetic procedures/therapies that could interfere with the study evaluations (e.g., other soft tissue fillers, botulinum toxin injections (frontalis and glabella complex allowed), laser or chemical resurfacing, etc.) for the duration of the study.

   Patients were not permitted to enroll in either study if they met any of the following exclusion criteria:

   - Known hypersensitivity or previous allergic reaction to any component of the study devices (e.g., gram positive bacterial proteins, hyaluronic acid, lidocaine, etc.);
   - Known sensitivity to local anesthetics of the amide type, history of multiple severe allergies, history of anaphylactic shock;
   - Known susceptibility to keloid formation, hypertrophic scarring or skin pigmentation disorders;
   - Clinically significant (Investigator discretion) active skin disease within 6 months prior to study entry;
   - History of active chronic debilitating systemic disease, including insulin or non-insulin dependent diabetes;
   - History of connective tissue disease (rheumatoid arthritis, scleroderma, systemic lupus erythematosus);
   - History of malignancy, excluding non-melanoma skin cancer, within the past 5 years;
   - History of bleeding disorders;

- Need for continuous medical treatment within 2 weeks prior to Visit 1;
- Received/used a prohibited treatment/procedure within certain time periods;
- Exhibit a physical attribute(s) that may prevent assessment or treatment of NLFs such as excessive facial hair, traumatic or surgical facial scars, and/or excessive hyperpigmentation in the treatment areas;
- A condition or be in a situation that may put the subject at significant risk, may confound the study results, or may significantly interfere with the subject's participation in the study.

2. Follow-up Schedule

At Visit 1, subjects received injections of a RHA® implant formulation (i.e., RHA® 2, RHA® 3, or RHA® 4) into the left or right NLF, and injections of the associated control device into the contralateral NLF, to achieve optimal correction. The Treating Investigator (TI) determined the injection technique and depth of injection; for a given subject, the RHA® and control devices were to be injected at the same depth, and with the same technique. The maximum volume per administration of a study device into a single NLF was 3.0 mL per injection session, irrespective of the device.

After 14 days, additional NLF correction with the study devices was provided, if deemed necessary by the TI. Only the NLF requiring touch-up was treated using the same device as originally injected.

Following any injection (initial, touch up, retreatment), subjects were given a 14 day diary to daily record common treatment responses (CTR) and any other adverse observations. They were instructed to record the severity of each CTR as none, mild, moderate, or severe.

All subjects were scheduled to return for follow-up examinations at 2, 4, 12, 24, 36, 52, and 64 weeks after treatment.

The protocols for both studies had their primary efficacy endpoint (WSRS) evaluated at 24 weeks. Subjects were followed until 64 weeks to evaluate long term safety, safety of retreatment and other secondary endpoints. Subjects were offered retreatment at Week 24 or Week 36 (optional retreatment in case of facial asymmetry or if at least one NLF had returned to pre-treatment levels), and/or at Week 52 if they met specific criteria. Furthermore, retreatment was offered to all subjects attending the study visit at Week 64. Any retreatment was performed with the RHA® implant formulation used at the initial treatment, irrespective of the side of face treated (i.e., control devices were not used for retreatment).

The design included a no-treatment group of subjects who were followed until the primary endpoint (24 weeks), at which time they exited the study. The enrollment of untreated subjects was designed to minimize the risk of BLE bias of WSRS assessments at the primary endpoint. The untreated and treated subjects had the

same visit schedule for the BLE evaluation of their WSRS up to the primary endpoint.

The key timepoints are shown below in Table 3.

Table 3: Follow-up Schedule

	Initial Tx	**Touch-Up if necessary**			**Early retreatment if necessary**		**Repeat Treatment**		Safety after any retreatment or repeat treatment
	Baseline if no Touch-Up	Baseline if Touch-Up			Primary Endpoint				
	D-14 or D0	**D0 or W2**	**W4**	**W12**	**W24**	**W36**	**W52**	**W64**	**+4W**
Informed consent	X[a]								
Inclusion/exclusion criteria	X[a]								
UPT (if applicable)	X[a]	X[b]			X[b]	X[b]	X[b]	X[b]	
Demographics	X[a]								
Medical and surgical history	X[a]								
Randomization	X								
Injection	X	X[b]			X[b]	X[b]	X[b]	X[b]	
Photography	Pre[a]/Post	Pre/Post[b]	X	X	Pre/Post[b]	Pre/Post[b]	Pre/Post[b]	Pre/Post[b]	X
WSRS: BLE*	Pre[a]				X[c]	X[c]	X[c]	X[c]	
GAI: BLE					X[c]	X[c]	X[c]	X[c]	
WSRS: Tx Inv	Pre[a]/Post	Pre/Post[b]	X	X	X	X	X	X[c]	X
GAI (by subject)	Post	X[b]	X	X	X[c]	X[c]	X[c]	X[c]	X
FACE-Q (PROM)	Pre[a]/Post	Pre/Post[b]	X	X	X[c]	X[c]	X[c]	X[c]	X
Patient satisfaction	Post	Pre/Post[b]	X	X	X[c]	X[c]	X[c]	X[c]	X
14-day patient CTR diary	X	X[b]			X[b]	X[b]	X[b]	X[b]	
Adverse events	X	X	X	X	X	X	X	X	X
Concomitant medication	X[a]	X	X	X	X	X	X	X	X
Non treated subjects	X				X				

D: Day
W: Week
BLE = Blinded Live Evaluator (live evaluation)
Tx Inv = Treating Investigator
BL = Baseline
Tx = Treatment
re-Tx = Retreatment
GAI = Global Aesthetic Improvement
WSRS = Wrinkle Severity Rating Scale
Pre = Pre-treatment
Post = Post-treatment
**** =** BLE assessments precede Tx Inv assessments. BLE assessments always pre-treatment (if applicable). WSRS assessments precede GAI assessments.*
[a] *Limited assessments conducted on untreated control subjects*
[b] *If Treatment administered*
[c] *Assessment conducted prior to treatment (if applicable)*
Optional Re-Tx or Re-Tx (Conditional) available if significant loss of correction

If Optional Re-Tx provided at W24/W36, subject has a phone follow-up at 3D and 1-month post re-Tx. The subject completes a 14-day patient CTR diary after Optional Re-Tx. The following will be conducted at 1-month post re-Tx visit: WSRS, concomitant medications, photography, and AE assessment. Subjects receiving Optional Re-Tx at W24/W36 will be eligible to receive Re-Tx (Conditional) at W52 to attain optimal correction. Subjects receiving re-Tx at W52 exit the study 1 month after re-Tx. Subjects who have not received re-Tx at W52 will be followed up until 64 weeks (W64), and will be offered re-Tx at that time, and exit the study 1 month after re-Tx.

3. Clinical Endpoints

With regards to safety, in both studies safety was evaluated through a 14-day patient Common Treatment Response (CTR) diary (after each injection), measures of injection site pain, and AE assessments at each visit.

Subjects recorded the presence, duration, and severity of CTRs that may occur following the injection of a dermal filler, for the first 14 days after each treatment (initial, touch-up, and retreatment(s)) in a patient diary: redness, pain, tenderness, firmness, swelling, lumps/bumps, bruising, itching, discoloration, and other.

CTRs were not considered AEs unless the duration and/or severity were in excess of that typically observed following injection of a dermal filler, and were clinically significant as determined by the TI. Additionally, CTRs that were present on the last day of diary entry, regardless of severity, were automatically recorded as AEs.

The TI assessed all AEs and recorded details of seriousness, severity, duration, and action taken with study device, as well as relationship to the study device. For statistical analysis, the maximal severity reported for the AE was used, even if the AE presented as being less severe at some point during the event.

Pain at the injection site(s) was self-assessed by the subject on each side of the face independently using a 100 mm Visual Analog Scale (VAS), with the left end representing “no pain” and the right end representing “worst pain”.

With regards to effectiveness, in both studies effectiveness was measured by assessing aesthetic improvement based on the WSRS (

Table 4) from pre-injection of the NLF treated with the RHA® implant formulation compared to the improvement from pre-injection of the NLF treated with the control device, as assessed by the BLE at 24 weeks after baseline.

Table 4: NLF-SRS (proprietary WSRS)

Grade	Name	Description
1	Absent	No nasolabial fold, continuous skin line
2	Mild	Shallow but visible fold, slight indentation
3	Moderate	Moderately deep nasolabial fold, clear facial feature visible
4	Severe	Very deep nasolabial fold, prominent 3 dimensional feature
5	Extreme	Extremely deep and long nasolabial fold, skin redundancy

The primary efficacy endpoint was the non-inferiority of the RHA® implant formulation versus the control at 24 weeks.

Secondary effectiveness endpoints included evaluation and comparison of NLF severity for each RHA® implant formulation versus control, using the validated 5-grade WSRS as rated by the BLE at other study visits and by the TI through the course of the study; proportions of responders based on the intra-individual change of at least one grade in the WSRS compared to pre-injection; Global Aesthetic Improvement (GAI) as assessed by the subject and the BLE; impact and effectiveness of study treatment from the subjects' perspective, as assessed by the nasolabial fold domain of the validated FACE-Q© patient-reported outcome measurement; and subject satisfaction.

With regard to success/failure criteria, a WSRS change of ≥ 1-grade was considered clinically significant and a pre-injection and post-injection difference of ≤ 0.5 grade between treatment groups was used as non-inferiority margin.

B. Accountability of PMA Cohort

For the study G140028, a total of 174 subjects were randomized to RHA® 2 / control device (n=74; Intent-to-Treat (ITT) population), RHA® 3 / control device (n=74; ITT population), or untreated controls (n=26). One subject was excluded from the ITT population of the RHA® 2 arm after withdrawing consent prior to injection, and another subject who was randomized to the RHA® 2 group was injected with RHA® 3, and therefore excluded from the RHA® 2 safety (SAFT) population and moved to the SAFT population of RHA® 3. No subject discontinued due to an adverse event.

For the study G140106, a total of 140 subjects were randomized with 120 subject allocated to RHA® 4 / control device and 20 subjects allocated to untreated control. Two subjects were excluded from the ITT population of the RHA® 4 arm after withdrawing consent prior to injection, and two subjects randomized to untreated control inadvertently received injections with RHA® 4 / control device and therefore were placed in the SAFT population for safety evaluations (SAFT population n=120), but not included in the ITT population for efficacy analyses (n=118; ITT population).

Table 5: Subject Accountability

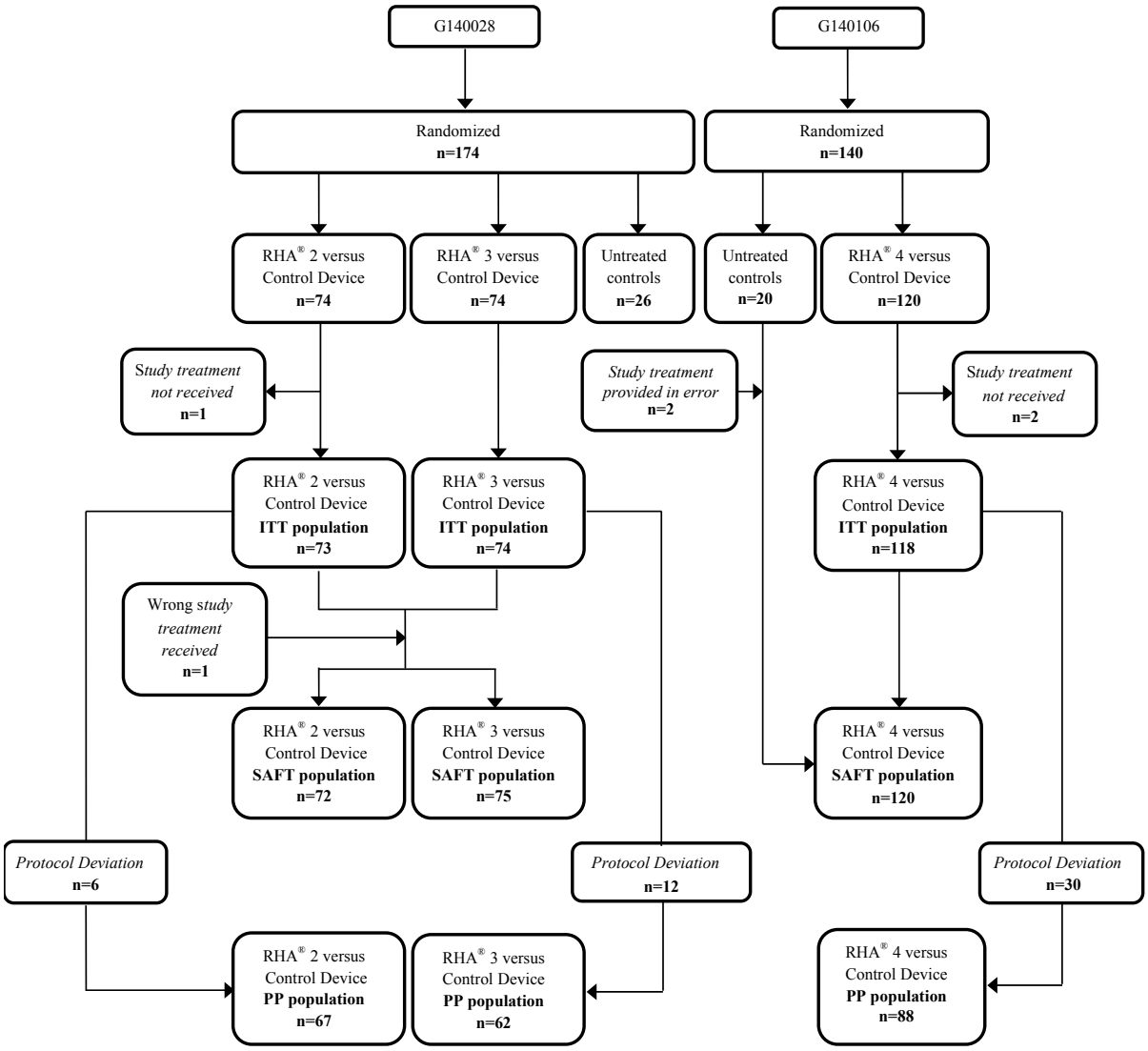
	RHA® 2 versus control device $n^a=74$			**RHA® 3 versus** control device $n^a=74$			**RHA® 4 versus** control device $n^a=120$		
	ITT $n^b=73$	**PP** $n^b=67$	**SAFT** $n^b=72$	**ITT** $n^b=74$	**PP** $n^b=62$	**SAFT** $n^b=75$	**ITT** $n^b=118$	**PP** $n^b=88$	**SAFT** $n^b=120$
Subject disposition per Visit									
24 weeks	72 98.6%	67 100.%	71 98.6%	72 97.3%	62 100.%	73 97.3%	107 90.7%	88 100.%	109 90.8%
52 weeks	68 93.2%	62 92.5%	67 93.1%	66 89.2%	56 90.3%	67 89.3%	107 90.7%	77 87.5%	108 90.0%
64 weeks[c]	52 71.2%	47 70.1%	51 70.8%	54 73.0%	47 75.8%	55 73.3%	90 76.3%	65 73.9%	90 75.0%

[a] *Number of subjects enrolled in each treatment group*

[b] *Number of subjects in each population at randomization (ITT), at first injection (SAFT), or at the primary endpoint (PP).*

[c] *Studies were extended from 52 to 64 weeks after studies had already been initiated. Subjects who did not consent to the extension, as well as subjects who were eligible for retreatment at 52 weeks, exited the study before 64 weeks.*

Figure 1: Disposition of Subjects



C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a pivotal study performed in the United States.

Subjects desiring correction of their NLFs with an injectable dermal filler were recruited for these two studies. The inclusion and exclusion criteria of both studies were identical. The study population included female and male subjects who were ≥ 22 years old. Both studies ensured that subjects meeting the inclusion criteria were representative of gender and ethnicity of the U.S. population who may use a RHA® implant formulation. Specifically, in both studies, there were at least 25% of subjects with Fitzpatrick skin type IV to VI and at least 8% of subjects were male.

Table 6: Demographic Characteristics at Baseline

	RHA® 2 versus control device *n=73*	**RHA® 3 versus** control device *n=74*	**RHA® 4 versus** control device *n=118*
Age (years)			
Mean ± SD	55.5 ± 10.9	55.7 ± 9.4	57.4 ± 10.0
Min, Max	34, 79	26, 77	27, 86
Gender			
Male	11 (15.1%)	6 (8.1%)	12 (10.2%)
Female	62 (84.9%)	68 (91.9%)	106 (89.8%)
Race			
Caucasian	59 (80.8%)	62 (83.8%)	97 (82.2%)
Black	9 (12.3%)	7 (9.5%)	19 (16.1%)
Am.Indian/N. Alask.	0 (0.0%)	0 (0.0%)	1 (0.8%)
N. Hawaiian/P. Isl.	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	2 (2.7%)	0 (0.0%)	1 (0.8%)
Other	3 (4.1%)	5 (6.8%)	0 (0.0%)
Ethnicity			
Hispanic/Latino	21 (28.8%)	21 (28.4%)	30 (25.4%)
Not Hispanic/Latino	52 (71.2%)	53 (71.6%)	88 (74.6%)
Fitzpatrick Skin Type			
I	1 (1.4%)	4 (5.4%)	4 (3.4%)
II	24 (32.9%)	21 (28.4%)	21 (17.8%)
III	20 (27.4%)	19 (25.7%)	40 (33.9%)
IV	17 (23.3%)	20 (27.0%)	31 (26.3%)
V	7 (9.6%)	7 (9.5%)	14 (11.9%)
VI	4 (5.5%)	3 (4.1%)	8 (6.8%)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 147 (RHA® 2 and RHA® 3 study) and 120 (RHA® 4 sudy) subjects available for up to 64 week evaluation. The common treatment responses for this study are presented below in Table 7 to Table 12. Adverse effects are reported in Table 13 to Table 15.

Safety of the RHA® implant formulations was evaluated through a 14-day patient Common Treatment Response (CTR) diary which was completed after each injection, AE asessments at each visit, and measurement of injection site pain.

Common Treatment Responses after Initial Treatment

CTR data for initial treatment are presented in Table 7 to Table 12 below. CTRs for touch-up and repeat treatment were of the same proportions.

The maximal severity for 90.7% of CTRs experienced with RHA® in both studies (all cohorts) was "mild" or "moderate", with minimal differences between RHA® implant formulations and control treatments. Of all the CTRs recorded on the last day of the diaries, only two subjects noted "severe" CTRs. None of the CTRs reported as "severe" by the subject were considered to be severe when evaluated by the TI.

In NLFs treated with RHA® 3, higher proportions of CTRs were noted for lumps/bumps than for NLFs treated with the control (Table 8). In NLFs treated with the control device, higher proportions of "severe" CTRs were noted for firmness, lumps/bumps, pain, redness, swelling, and tenderness, than for NLFs treated with RHA® 4 (Table 9).

Table 7: CTRs by Maximum Severity after initial treatment with RHA® 2 and the control device

	Totals *n[a]=72*		**RHA® 2** *n[a]=72*			**Control device** *n[a]=72*		
	RHA® 2 n[b] %	**Control** n[b] %	**Mild** n[b] %	**Mod.** n[b] %	**Sev.** n[b] %	**Mild** n[b] %	**Mod.** n[b] %	**Sev.** n[b] %
Common Treatment Response								
Bruising	36 50.0%	41 56.9%	15 20.8%	16 22.2%	5 6.9%	23 31.9%	9 12.5%	9 12.5%
Discoloration	24 33.3%	27 37.5%	12 16.7%	7 9.7%	5 6.9%	14 19.4%	8 11.1%	5 6.9%
Firmness	46 63.9%	48 66.7%	23 31.9%	20 27.8%	3 4.2%	27 37.5%	20 27.8%	1 1.4%
Itching	12 16.7%	15 20.8%	9 12.5%	3 4.2%	0 0.0%	10 13.9%	4 5.6%	1 1.4%
Lump/Bumps	38 52.8%	37 51.4%	21 29.2%	14 19.4%	3 4.2%	22 30.6%	13 18.1%	2 2.8%
Pain	19 26.4%	16 22.2%	13 18.1%	6 8.3%	0 0.0%	11 15.3%	5 6.9%	0 0.0%
Redness	45 62.5%	49 68.1%	31 43.1%	13 18.1%	1 1.4%	36 50.0%	11 15.3%	2 2.8%
Swelling	42 58.3%	45 62.5%	27 37.5%	13 18.1%	2 2.8%	31 43.1%	13 18.1%	1 1.4%
Tenderness	44 61.1%	40 55.6%	34 47.2%	10 13.9%	0 0.0%	31 43.1%	9 12.5%	0 0.0%

[a] *Number of subjects present in the SAFT population*
[b] *Number of subjects' NLF with any specific Common Treatment Response*
Note: Mod. = Moderate, Sev. = Severe

Table 8: CTRs by Maximum Severity after initial treatment with RHA® 3 and the control device

	Totals *n[a]=75*		**RHA® 3** *n[a]=75*			**Control device** *n[a]=75*		
	RHA® 3 n[b] %	**Control** n[b] %	**Mild** n[b] %	**Mod.** n[b] %	**Sev.** n[b] %	**Mild** n[b] %	**Mod.** n[b] %	**Sev.** n[b] %
Common Treatment Response								
Bruising	42 56.0%	38 50.7%	20 26.7%	15 20.0%	7 9.3%	12 16.0%	20 26.7%	6 8.0%
Discoloration	22 29.3%	22 29.3%	7 9.3%	11 14.7%	4 5.3%	10 13.3%	8 10.7%	4 5.3%
Firmness	48 64.0%	45 60.0%	21 28.0%	21 28.0%	6 8.0%	22 29.3%	21 28.0%	2 2.7%
Itching	13 17.3%	11 14.7%	7 9.3%	4 5.3%	2 2.7%	5 6.7%	4 5.3%	2 2.7%
Lump/Bumps	49 65.3%	40 53.3%	21 28.0%	21 28.0%	7 9.3%	22 29.3%	14 18.7%	4 5.3%
Pain	30 40.0%	23 30.7%	21 28.0%	6 8.0%	3 4.0%	18 24.0%	4 5.3%	1 1.3%
Redness	43 57.3%	42 56.0%	26 34.7%	14 18.7%	3 4.0%	26 34.7%	15 20.0%	1 1.3%
Swelling	41 54.7%	38 50.7%	22 29.3%	15 20.0%	4 5.3%	22 29.3%	15 20.0%	1 1.3%
Tenderness	44 58.7%	37 49.3%	29 38.7%	12 16.0%	3 4.0%	26 34.7%	10 13.3%	1 1.3%

[a] *Number of subjects present in the SAFT population*

[b] *Number of subjects' NLF with any specific Common Treatment Response*

Note: Mod. = Moderate, Sev. = Severe

Table 9: CTRs by Maximum Severity after initial treatment with RHA® 4 and the control device

	Totals *n[a]=120*		**RHA® 4** *n[a]=120*			**Control device** *n[a]=120*		
	RHA® 4 n[b] %	**Control** n[b] %	**Mild** n[b] %	**Mod.** n[b] %	**Sev.** n[b] %	**Mild** n[b] %	**Mod.** n[b] %	**Sev.** n[b] %
Common Treatment Response								
Bruising	70 58.3	72 60.0	35 29.2	26 21.7	9 7.5	37 30.8	25 20.8	10 8.3
Discoloration	50 41.7	56 46.7	30 25.0	16 13.3	4 3.3	30 25.0	20 16.7	6 5.0
Firmness	91 75.8	93 77.5	36 30.0	46 38.3	9 7.5	13 10.8	50 41.7	30 25.0
Itching	30 25.0	44 36.7	25 20.8	5 4.2	0 0.0	28 23.3	14 11.7	2 1.7
Lump/Bumps	81 67.5	90 75.0	36 30.0	33 27.5	12 10.0	28 23.3	37 30.8	25 20.8
Pain	66 55.0	87 72.5	42 35.0	19 15.8	5 4.2	30 25.0	40 33.3	17 14.2
Redness	84 70.0	91 75.8	42 35.0	38 31.7	4 3.3	32 26.7	42 35.0	17 14.2
Swelling	97 80.8	104 86.7	41 34.2	44 36.7	12 10.0	21 17.5	38 31.7	45 37.5
Tenderness	90 75.0	95 79.2	53 44.2	30 25.0	7 5.8	23 19.2	45 37.5	27 22.5

[a] *Number of subjects present in the SAFT population*
[b] *Number of subjects' NLF with any specific Common Treatment Response*
Note: Mod. = Moderate, Sev. = Severe

By Day 7, 68.7% of CTRs experienced with RHA® in both studies (all cohorts) had resolved. By Day 14, 82.8% of CTRs experienced with RHA® were resolved. Differences were noted between treatment groups with regard to the duration of some CTRs.

Table 10: CTRs by duration after initial treatment with RHA® 2 and the control device

	RHA® 2 $n^a=72$				Control device $n^a=72$			
	≤3 days n[b] %	**4-≤7 days** n[b] %	**8- ≤14 days** n[b] %	**Last day[c,d]** n[b] %	**≤3 days** n[b] %	**4-≤7 days** n[b] %	**8-≤14 days** n[b] %	**Last day[c,d]** n[b] %
Common Treatment Response								
Bruising	7 9.7%	13 18.1%	16 22.2%	4 5.6%	10 13.9%	16 22.2%	15 20.8%	3 4.2%
Discoloration	11 15.3%	4 5.6%	9 12.5%	3 4.2%	8 11.1%	10 13.9%	9 12.5%	3 4.2%
Firmness	13 18.1%	11 15.3%	22 30.6%	14 19.4%	16 22.2%	13 18.1%	19 26.4%	12 16.7%
Itching	5 6.9%	4 5.6%	3 4.2%	3 4.2%	9 12.5%	2 2.8%	4 5.6%	3 4.2%
Lump/Bumps	11 15.3%	13 18.1%	14 19.4%	12 16.7%	14 19.4%	11 15.3%	12 16.7%	6 8.3%
Pain	11 15.3%	4 5.6%	4 5.6%	3 4.2%	7 9.7%	5 6.9%	4 5.6%	2 2.8%
Redness	28 38.9%	13 18.1%	4 5.6%	1 1.4%	29 40.3%	14 19.4%	6 8.3%	3 4.2%
Swelling	19 26.4%	11 15.3%	12 16.7%	5 6.9%	22 30.6%	15 20.8%	8 11.1%	3 4.2%
Tenderness	23 31.9%	9 12.5%	12 16.7%	5 6.9%	21 29.2%	10 13.9%	9 12.5%	1 1.4%

[a] *Number of subjects present in the SAFT population*
[d] *Number of subjects' NLF with each specific CTR by maximum duration*
[c] *Events ongoing on last day of diary ; these events are automatically elevated to AE*
[d] *Events in Last day column are included in 8-≤14 days column*

Table 11: CTRs by duration after initial treatment with RHA® 3 and the control device

	RHA® 3 $n^a=75$				Control device $n^a=75$			
	≤3 days n[b] %	**4-≤7 days** n[b] %	**8- ≤14 days** n[b] %	**Last day[c,d]** n[b] %	**≤3 days** n[b] %	**4-≤7 days** n[b] %	**8-≤14 days** n[b] %	**Last day[c,d]** n[b] %
Common Treatment Response								
Bruising	11 14.7%	19 25.3%	12 16.0%	4 5.3%	11 14.7%	16 21.3%	11 14.7%	1 1.3%
Discoloration	10 13.3%	6 8.0%	6 8.0%	4 5.3%	13 17.3%	5 6.7%	4 5.3%	3 4.0%
Firmness	18 24.0%	7 9.3%	23 30.7%	9 12.0%	16 21.3%	14 18.7%	15 20.0%	3 4.0%
Itching	9 12.0%	4 5.3%	0 0.0%	0 0.0%	8 10.7%	3 4.0%	0 0.0%	0 0.0%
Lump/Bumps	17 22.7%	11 14.7%	21 28.0%	12 16.0%	15 20.0%	13 17.3%	12 16.0%	6 8.0%
Pain	21 28.0%	7 9.3%	2 2.7%	0 0.0%	18 24.0%	3 4.0%	2 2.7%	1 1.3%
Redness	27 36.0%	9 12.0%	7 9.3%	2 2.7%	27 36.0%	10 13.3%	5 6.7%	2 2.7%
Swelling	18 24.0%	12 16.0%	11 14.7%	5 6.7%	19 25.3%	11 14.7%	8 10.7%	4 5.3%
Tenderness	17 22.7%	13 17.3%	14 18.7%	5 6.7%	17 22.7%	13 17.3%	7 9.3%	3 4.0%

[a] *Number of subjects present in the SAFT population*
[b] *Number of subjects' NLF with each specific CTR by maximum duration*
[c] *Events ongoing on last day of diary ; these events are automatically elevated to AE*
[d] *Events in Last day column are included in 8-≤14 days column*

Table 12: CTRs by duration after initial treatment with RHA® 4 and the control device

	RHA® 4 n^a=120				Control device n^a=120			
	≤3 days n^b %	4-≤7 days n^b %	8- ≤14 days n^b %	Last day[c,d] n^b %	≤3 days n^b %	4-≤7 days n^b %	8-≤14 days n^b %	Last day[c,d] n^b %
Common Treatment Response								
Bruising	22 18.3%	28 23.3%	20 16.7%	8 6.7%	37 30.8%	28 23.3%	7 5.8%	4 3.3%
Discoloration	28 23.3%	10 8.3%	12 10.0%	10 8.3%	34 28.3%	14 11.7%	8 6.7%	4 3.3%
Firmness	16 13.3%	20 16.7%	55 45.8%	35 29.2%	13 10.8%	26 21.7%	54 45.0%	26 21.7%
Itching	20 16.7%	8 6.7%	2 1.7%	2 1.7%	24 20.0%	14 11.7%	6 5.0%	3 2.5%
Lump/Bumps	19 15.8%	14 11.7%	48 40.0%	36 30.0%	25 20.8%	24 20.0%	41 34.2%	27 22.5%
Pain	48 40.0%	12 10.0%	6 5.0%	3 2.5%	54 45.0%	25 20.8%	8 6.7%	2 1.7%
Redness	42 35.0%	30 25.0%	12 10.0%	8 6.7%	42 35.0%	37 30.8%	12 10.0%	7 5.8%
Swelling	36 30.0%	29 24.2%	32 26.7%	16 13.3%	27 22.5%	50 41.7%	27 22.5%	11 9.2%
Tenderness	41 34.2%	22 18.3%	27 22.5%	14 11.7%	26 21.7%	39 32.5%	30 25.0%	8 6.7%

[a] *Number of subjects present in the SAFT population*
[b] *Number of subjects' NLF with each specific CTR by maximum duration*
[c] *Events ongoing on last day of diary ; these events are automatically elevated to AE*
[d] *Events in Last day column are included in 8-≤14 days column*

The TI reviewed all CTRs to ensure they were elevated as appropriate to the status of an AE. CTRs were not considered AEs unless the duration and/or severity were in excess of that typically observed following injection of a dermal filler, and were clinically significant as determined by the TI. However, CTRs that were noted on the last day of the CTR diary were recorded automatically as AEs regardless of their severity (14-day rule). Overall, in all 3 cohorts, for CTRs that were automatically elevated to the level of an AE after 14 days, the TI determined that none of the AEs were of "severe" intensity.

Treatment Related Adverse Events

All Treatment-Related Adverse Events were the types and frequency of events that are typically experienced following the injection of a dermal filler, 97.8% of those in the RHA® groups were based on CTR diary entries (present on the last diary day Table 16 to Table 18), the onset of all events was temporally associated with a recent injection of a study device, and all events were mild or moderate in intensity (no severe Treatment-Related Adverse Events were reported in any of the treatment groups). There were no late onset Treatment-Related Adverse Events, and no events were deemed to be a granuloma.

Adverse Events incidence rates were not negatively correlated with higher Fitzpatrick skin type; compared to subjects of skin types I-III, a smaller proportion of subjects of skin types IV-VI experienced Treatment-Related Adverse Events (Table 13 to Table 15).
Treatment-Related Adverse Event rates were similar in the RHA® groups compared to the control.

Table 13: Adverse Events Overview – RHA® 2 versus the control device

		RHA® 2 *n[a]=72*	**Control device** *n[a]=72*	**All** *n[a]=72*
Subjects with any TRAE[b]	**Subjects**	**31 (43.1%)**	**23 (31.9%)**	**35 (48.6%)**
	Events	**79**	**59**	**138**
Fitzpatrick I-III – any TRAE[b]	Subjects	21 (46.7%)	14 (31.1%)	24 (53.3%)
	Events	54	42	96
Fitzpatrick IV-VI – any TRAE[b]	Subjects	10 (37.0%)	9 (33.3%)	11 (40.7%)
	Events	25	17	42
Subjects with SAE[c]	Subjects	2 (2.8%)	2 (2.8%)	2 (2.8%)
	Events	2	2	2
Subjects with any TRSAE[d]	Subjects	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Events	0	0	0
Subjects with UADE[e]	Subjects	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Events	0	0	0

[a] *Number of subjects present in the SAFT population*
[b] *TRAE= Treatment-Related AEs (events Investigator deems to be "possibly related", "probably related", or "definitely related")*
[c] *SAE= Serious AEs*
[d] *TRSAE= Treatment-Related Serious AEs*
[e] *UADE= Unexpected Adverse Device Effects*
NOTE: Number of Subjects/Events (% in parenthesis)

Table 14: Adverse Events Overview – RHA® 3 versus the control device

		RHA® 3 *n[a]=75*	**Control device** *n[a]=75*	**All** *n[a]=75*
Subjects with any TRAE[b]	**Subjects Events**	**27 (36.0%) 94**	**26 (34.7%) 61**	**31 (41.3%) 154**
Fitzpatrick I-III - any TRAE[b]	Subjects Events	21 (47.7%) 73	19 (43.2%) 42	23 (52.3%) 114
Fitzpatrick IV-VI - any TRAE[b]	Subjects Events	6 (19.4%) 21	7 (22.6%) 19	8 (25.8%) 40
Subjects with SAE[c]	Subjects Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Subjects with any TRSAE[d]	Subjects Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Subjects with UADE[e]	Subjects Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0

[a] *Number of subjects present in the SAFT population*
[b] *TRAE= Treatment-Related AEs (events Investigator deems to be "possibly related", "probably related", or "definitely related")*
[c] *SAE= Serious AEs*
[d] *TRSAE= Treatment-Related Serious AEs*
[e] *UADE= Unexpected Adverse Device Effects*
NOTE: Number of Subjects/Events (% in parenthesis)

Table 15: Adverse Events Overview – RHA® 4 versus the control device

		RHA® 4 *n[a]=120*	**Control device** *n[a]=120*	**All** *n[a]=120*
Subjects with any TRAE[b]	**Subjects Events**	**71 (59.2%) 212**	**62 (51.7%) 170**	**77 (64.2%) 364**
Fitzpatrick I-III - any TRAE[b]	Subjects Events	46 (68.7%) 140	37(55.2%) 106	48 (71.6%) 236
Fitzpatrick IV-VI - any TRAE[b]	Subjects Events	25 (47.2%) 72	25(47.2%) 64	29 (54.7%) 128
Subjects with SAE[c]	Subjects Events	3 (2.5%) 3	3 (2.5%) 3	3 (2.5%) 3
Subjects with any TRSAE[d]	Subjects Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0
Subjects with UADE[e]	Subjects Events	0 (0.0%) 0	0 (0.0%) 0	0 (0.0%) 0

[a] *Number of subjects present in the SAFT population*
[b] *TRAE= Treatment-Related AEs (events Investigator deems to be "possibly related", "probably related", or "definitely related")*
[c] *SAE= Serious AEs*
[d] *TRSAE= Treatment-Related Serious AEs*

[e] *UADE= Unexpected Adverse Device Effects*
NOTE: Number of Subjects/Events (% in parenthesis)

Table 16: Treatment Related Adverse Events - RHA® 2 versus the control device

	RHA® 2			Control device		
	Subjects *n[a]=72*	**Events** *n[b]=79*		**Subjects** *n[a]=72*	**Events** *n[b]=59*	
		Diary[c]	**TI[d]**		**Diary[c]**	**TI[d]**
Subjects reporting any TRAE	**31 (43.1%)**	**78**	**1**	**23 (31.9%)**	**59**	**--**
General disorders and administration site conditions	**31 (43.1%)**	**78**	**1**	**23 (31.9%)**	**59**	**--**
Injection Site Discoloration	3 (4.2%)	3	--	5 (6.9%)	5	--
Injection Site Erythema	2 (2.8%)	2	--	4 (5.6%)	4	--
Injection Site Hematoma	5 (6.9%)	5	1	4 (5.6%)	5	--
Injection Site Firmness	20 (27.8%)	25	--	17 (23.6%)	20	--
Injection Site Lumps/Bumps	15 (20.8%)	18	--	7 (9.7%)	9	--
Injection Site Pain	4 (5.6%)	4	--	4 (5.6%)	4	--
Injection Site Pruritus	4 (5.6%)	5	--	3 (4.2%)	4	--
Injection Site Scab	1 (1.4%)	1	--	1 (1.4%)	1	--
Injection Site Swelling	6 (8.3%)	7	--	3 (4.2%)	4	--
Tenderness	7 (9.7%)	8	--	3 (4.2%)	3	--

[a] *Number of subjects present in the SAFT population*
[b] *Total number of Treatment Related Adverse Events reported*
[c] *Number of Treatment Related Adverse Events from CTRs that were automatically elevated as required by the 14-day rule*
[d] *Number of Treatment Related Adverse Events identified by the Treating Investigators*

Table 17: Treatment Related Adverse Events - RHA® 3 versus the control device

	RHA® 3			Control device		
	Subjects *n[a]=75*	**Events** *n[b]=94*		**Subjects** *n[a]=75*	**Events** *n[b]=61*	
		Diary[c]	**TI[d]**		**Diary[c]**	**TI[d]**
Subjects reporting any TRAE	**27 (36.0%)**	**94**	**--**	**26 (34.7%)**	**61**	**--**
General disorders and administration site conditions	**25 (33.3%)**	**90**	**--**	**23 (30.7%)**	**57**	**--**
Injection Site Discoloration	4 (5.3%)	4	--	4 (5.3%)	4	--
Injection Site Erythema	5 (6.7%)	7	--	5 (6.7%)	7	--
Injection Site Hematoma	5 (6.7%)	6	--	5 (6.7%)	6	--
Injection Site Hemorrhage	1 (1.3%)	1	--	--	--	--
Injection Site Firmness	19 (25.3%)	25	--	8 (10.7%)	11	--
Injection Site Lumps/Bumps	17 (22.7%)	22	--	14 (18.7%)	16	--
Injection Site Pain	2 (2.7%)	2	--	2 (2.7%)	2	--
Injection Site Pruritus	1 (1.3%)	1	--	--	--	--
Injection Site Swelling	9 (12.0%)	11	--	5 (6.7%)	7	--
Tenderness	10 (13.3%)	11	--	4 (5.3%)	4	--
Skin and subcutaneous tissue disorders	**4 (5.33%)**	**4**	**--**	**4 (5.33%)**	**4**	**--**
Rash	1 (1.3%)	1	--	1 (1.3%)	1	--
Skin Burning Sensation	--	--	--	1 (1.3%)	1	--
Skin Swelling	1 (1.3%)	1	--	1 (1.3%)	1	--
Skin Tightness	1 (1.3%)	1	--	1 (1.3%)	1	--
Skin Wrinkling	1 (1.3%)	1	--	--	--	--

[a] *Number of subjects present in the SAFT population*
[b] *Total number of Treatment Related Adverse Events reported*
[c] *Number of Treatment Related Adverse Events from CTRs that were automatically elevated as required by the 14-day rule*
[d] *Number of Treatment Related Adverse Events identified by the Treating Investigators*

Table 18: Treatment Related Adverse Events - RHA® 4 versus the control device

	RHA® 4			Control device		
	Subjects n^a=120	Events n^b=212		Subjects n^a=120	Events n^b=170	
		Diary[c]	TI[d]		Diary[c]	TI[d]
Subjects reporting any TRAE	**71 (59.2%)**	**201**	**11**	**62 (51.7%)**	**158**	**12**
General disorders and administration site conditions	**70 (58.3%)**	**188**	**7**	**59 (49.2%)**	**141**	**7**
Device Dislocation	--	--	--	1 (0.8%)	1	--
Drooping Lip	1 (0.8%)	1	--	1 (0.8%)	1	--
Injection Site Discoloration	13 (10.8%)	12	1	5 (4.2%)	4	1
Injection Site Erythema	8 (6.7%)	8	--	8 (6.7%)	8	--
Injection Site Exfoliation	1 (0.8%)	1	--	1 (0.8%)	1	--
Injection Site Hematoma	8 (6.7%)	8	--	4 (3.3%)	5	--
Injection Site Firmness	45 (37.5%)	51	1	34 (28.3%)	38	1
Injection Lumps/Bumps	45 (37.5%)	51	--	33 (27.5%)	41	1
Injection Site Pain	6 (5.0%)	6	1	5 (4.2%)	4	1
Injection Site Paraesthesia	2 (1.7%)	2	--	3 (2.5%)	2	1
Injection Site Pruritus	2 (1.7%)	2	--	3 (2.5%)	3	--
Injection Site Swelling	23 (19.2%)	24	3	17 (14.2%)	19	1
Injection Site Warmth	--	--	--	1 (0.8%)	1	--
Tenderness	19 (15.8%)	21	1	12 (10.0%)	13	1
Xerosis	1 (0.8%)	1	--	--	--	--
Eye disorders	**2 (1.7%)**	**2**	**--**	**2 (1.7%)**	**3**	**--**
Eye Pain	1 (0.8%)	1	--	1 (0.8%)	1	--
Eye Swelling	1 (0.8%)	1	--	1 (0.8%)	1	--
Lacrimation Increased	--	--	--	1 (0.8%)	1	--
Gastrointestinal Disorders	**--**	**--**	**--**	**2 (1.7%)**	**2**	**--**
Lip Swelling	--	--	--	2 (1.7%)	2	--
Musculoskeletal and connective tissue disorders	**1 (0.8%)**	**1**	**--**	**2 (1.7%)**	**2**	**--**
Neck Pain	--	--	--	1 (0.8%)	1	--
Temporoman. Joint Syndrome	1 (0.8%)	1	--	1 (0.8%)	1	--
Nervous system disorders	**4 (3.3%)**	**5**	**1**	**4 (3.3%)**	**6**	**1**
Headache	4 (3.3%)	5	1	4 (3.3%)	6	1
Skin and subcutaneous tissue disorders	**7 (5.8%)**	**5**	**3**	**8 (6.7%)**	**4**	**4**
Acne	2 (1.7%)	1	1	2 (1.7%)	1	1
Dry Skin	--	--	--	1 (0.8%)	0	1
Needle Track Marks	1 (0.8%)	1	--	1 (0.8%)	1	--
Skin Wrinkling	--	--	--	1 (0.8%)	1	--
Telangiectasia	5 (4.2%)	3	2	3 (2.5%)	1	2

[a] *Number of subjects present in the SAFT population*
[b] *Total number of Treatment Related Adverse Events reported*

[c] *Number of Treatment Related Adverse Events from CTRs that were automatically elevated as required by the the 14-day rule*
[d] *Number of Treatment Related Adverse Events identified by the Treating Investigators*

For both studies, NLFs treated with the RHA® device experienced higher rates of treatment-related lumps/bumps and firmness compared to NLFs treated with the control. These differences were not statistically significant.

Details for AEs as determined by the TI, which were not noted on the last day of the CTR diaries follow:

All treatment-related AEs with RHA® 2 were based on subjects' diary entries (CTRs) except one (injection site bruising; mild) which was reported by the Treating Investigator at time of initial injection and which resolved in 12 days.

All treatment-related AEs with RHA® 3 were based on subjects' diary entries.

There were 11 treatment-related AEs (all of mild severity) in 11 subjects reported by the Treating Investigator with RHA® 4 which consisted of acne, discoloration, firmness, headache, pain, swelling, telangiectasia, and tenderness.

All Treatment-Related AEs (experienced in either treatment cohort) that were temporally associated with initial and/or touch-up injections resolved prior to study exit. Treatment-Related AEs following retreatment were similar in type, frequency, duration, and severity to those observed from the initial or touch-up treatments. While the majority of Treatment-Related AEs that were associated with later "retreatment" injections had resolved by the time of study exit, a total of 18 events experienced by 4 subjects in the RHA® 2 group, 2 events experienced by 1 subject in the RHA® 3 group and 2 events experienced by 2 subjects in the RHA® 4 group remained, and were ongoing at study exit. Subjects were followed for 4 weeks following retreatment at Week 52 or 64 and investigators determined that those ongoing Treatment-Related AEs did not require additional visits.

There were no reports of Treatment-Related Serious Adverse Events or Unexpected Adverse Device Effects in either study, no deaths, and no subjects prematurely withdrew due to a Treatment-Related Adverse Event.

Pain at injection

For all three groups, the highest levels of pain were noted during study injections, and pain levels were similar between the RHA® devices and their respective control. Pain rapidly diminished after 5 minutes and had nearly disappeared by 30 minutes post injection. Similar pain response was noted following touch-up injection, with no significant differences noted between treatment groups for all three groups.

Extent of exposure

The number of treatment sessions needed to obtain optimal cosmetic results (OCR) was slightly higher for the control device than with the RHA® implant formulations as shown by Table 19 below).

Table 19: Number of treatment sessions

	RHA® 2 versus Control device		**RHA® 3 versus Control device**		**RHA® 4 versus Control device**	
	RHA® 2	control	RHA® 3	control	RHA® 4	control
Touch-up treatment at 2 weeks						
n[a]	*n=73*		*n=74*		*n=118*	
n[b]	47	49	50	53	32	47
%	64.4%	67.1%	67.6%	71.6%	27.1%	39.8%
Optional early retreatment at 24 weeks						
n[a]	*n=72*		*n=72*		*n=107*	
n[b]	1	1	0	0	7	7
%	1.4%	1.4%	0.0%	0.0%	6.5%	6.5%
Optional early retreatment at 36 weeks						
n[a]	*n=70*		*n=67*		*n=107*	
n[b]	4	4	5	5	3	6
%	5.7%	5.7%	7.5%	7.5%	2.8%	5.6%
Conditional repeat treatment at 52 weeks						
n[a]	*n=68*		*n=66*		*n=107*	
n[b]	9	11	11	11	13	15
%	13.2%	16.3%	16.7%	16.7%	12.1%	14.0%
Repeat treatment at 64 weeks						
n[a]	*n=52*		*n=54*		*n=90*	
n[b]	45	46	43	42	64	65
%	86.5%	88.5%	79.6%	77.8%	71.1%	72.2%

[a] *Number of subject present in the ITT populations at each follow-up visit*
[b] *Number of subjects who received treatment at the follow-up visit*

The same injection technique was used for both NLFs for each individual subject and for any given injection session.

For RHA® 2 / control device, the initial treatment was administered using linear threading in the majority of subjects (50.7%), while linear threading/fan-like injections were implemented in 39.7% of subjects. The multiple punctate pools technique was implemented in 5.5% of subjects.

For RHA® 3 / control device, the initial treatment was administered using linear threading in the majority of subjects (47.3%), while linear threading/fan-like injections were implemented in 44.6% of subjects. Techniques implementing

multiple punctate pools and linear threading/multiple punctate pools were each implemented in 8.1% of subjects.

For RHA® 4 / control device, initial treatment was administered using either linear threading or multiple punctate pools in the majority of subjects (35.6% and 30.5% of subjects, respectively).

Similar proportions were noted with touch-up injections.

2. Effectiveness Results

The analysis of effectiveness was based on the 147 evaluable subjects (RHA® 2 and RHA® 3 study) and the 118 evaluable subjects (RHA® 4 study) at the 24 week time point. Key effectiveness outcomes are presented in

Table 20 and Table 21.

The primary efficacy endpoint was the non-inferiority of the RHA® implant formulation versus the control at 24 weeks after baseline, based on the Blinded Live Evaluator assessment of the WSRS improvement from pre-treatment (the upper limit of the two-sided confidence interval for the mean difference for the change from pre-treatment, between RHA® and the control treatment must be ≤ 0.5). Results showed that all three formulations of RHA® were not inferior to their respective control, which were shown to be effective active control devices (see

Table 20). Analyses were also conducted using the ITT population and non-inferiority was confirmed for each formulation.
The average WSRS score of untreated subjects did not change from enrollment to primary endpoint at 24 weeks.

Following the primary endpoint at 24 weeks, non-inferiority was maintained at all subsequent study visits for RHA® 2 and RHA® 3.

At 24 weeks, the upper limit of the two-sided confidence interval for the mean difference for the change from pre-treatment, between RHA® 4 and the control treatment was < 0, as well as at all subsequent visits through 64 weeks, even if additional assessments to achieve superiority did not reach predetermined threshold. In addition, the rates of responders (proportion of NLFs with a ≥ 1-grade improvement between pre-injection enrollment visit and 24 weeks after baseline on the WSRS as assessed by the BLE) were 97.7% with RHA® 4 versus 89.6% with the control treatment.

Table 20: WSRS by Blinded Live Evaluator at 24 weeks after baseline (primary outcome)

	RHA® 2 versus Control device *n^a=67*		**RHA® 3 versus Control device** *n^a=62*		**RHA® 4 versus Control device** *n^a=88*	
	RHA® 2	control	RHA® 3	control	RHA® 4	control
WSRS improvement difference between groups[b]						
Mean	-0.03		-0.10		-0.18	
CI	[-0.17 , 0.11]		[-0.25 , 0.06]		[-0.29 , -0.07]	
WSRS Responders[c]						
n	56	55	57	55	86	79
%	83.6%	82.1%	91.9%	88.7%	97.7%	89.6%

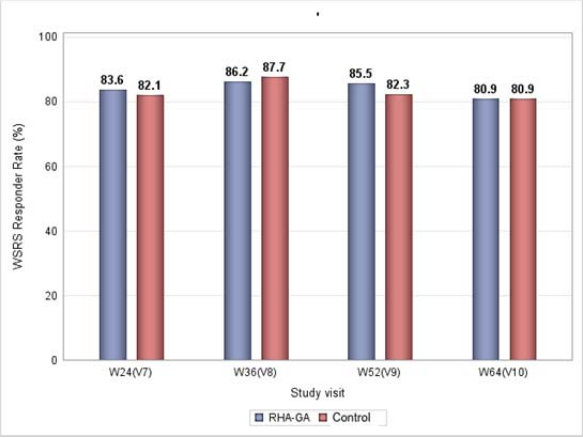
[a] *Number of subjects present in the PP populations at 24 weeks after baseline*
[b] *Lower values mean better improvement with RHA® than with the control devices*
[c] *At least 1-grade improvement from pre-treatment*

For both the investigational and control device, results showed a progressive increase in the WSRS score, consistent with the reduced effect of the dermal fillers over time.

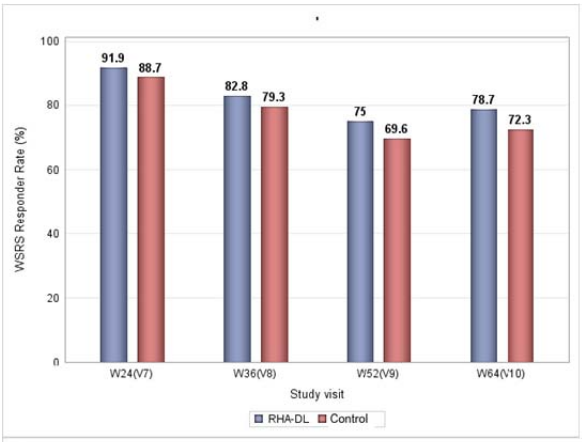
At most time points, the RHA® 2, RHA® 3, and RHA® 4 responder rates were either slightly higher or the same as the control side.

The responder rates, as assessed by the Treating Investigator, were generally higher than the BLE assessments (Figure 2). The responder rates, from both assessment by the BLE and the TI, decrease over time for all three formulations of RHA®, indicating an expected loss of treatment effect.

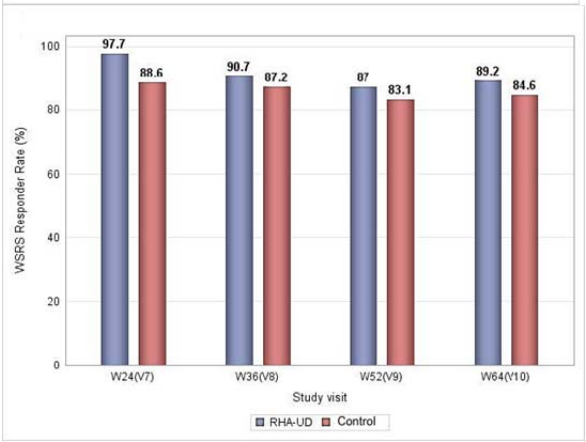
Figure 2: WSRS rate of responders, as assessed by the Blinded Live Evaluator, throughout the follow-up period



RHA® 2 versus the control device



RHA® 3 versus the control device



RHA® 4 versus the control device

PP populations at the respective follow-up visits
Rate of responders: ≥ 1 grade difference from pre-treatment on the WSRS

The subject-assessed GAI scores after RHA® treatment were reported as improved or much improved, by at least 88% of the subjects at 24 weeks after baseline and by at least 82% of the subjects at 64 weeks after baseline (Table 21). GAI as assessed by the BLE was similar between all treatment groups throughout the study and consistently indicated high levels of aesthetic improvement.

Table 21: GAI scores reported as improved and much improved by the subjects at 24 and 64 weeks after baseline

	RHA® 2 versus Control device *n^a=67*		**RHA® 3 versus Control device** *n^a=62*		**RHA® 4 versus Control device** *n^a=88*	
	RHA® 2	control	RHA® 3	control	RHA® 4	control
At 24 weeks (%)	88.1%	88.1%	88.7%	88.7%	93.2%	88.6%
At 64 weeks (%)	83.6%	83.6%	82.3%	75.8%	87.2%	79.6%

n^a : Per protocol population

Impact and effectiveness of study treatment procedures, from the subjects' perspective, was assessed at every in-clinic study visit (before and after treatment with a study device, if applicable), using the nasolabial fold domain of the validated FACE-Q© patient-reported outcome measurement questionnaire. At all time points, for all subjects, and all treatment formulations, scores were higher than pre-injection scores, indicating subject-perceived improvement in their NLFs (including when the face was relaxed or smiling). For RHA® 2, RHA® 3 and RHA® 4, mean score improved from 24 to more than 60, 23 to more than 63 and 24 to more than 70 respectively, throughout the follow-up period.

Subject satisfaction was similar between RHA® 2 and the control device, as well as between RHA® 3 and the control device, across all time points, and there was a significant difference between RHA® 4 and the control device at all time points from 12 weeks, indicating higher satisfaction with RHA® 4 versus control. For RHA® 2 and RHA® 3, more than 90% of the subjects reported to be satisfied or very satisfied 24 weeks after initial treatment and the rate of satisfaction remained at more than 86% for RHA® 2 and 82% for RHA® 3 at 64 weeks. For RHA® 4, more than 93% of the subjects reported to be satisfied or very satisfied from Week 24 to Week 64. All RHA® implant formulations and their respective control, across all time points, demonstrated a high degree of subject satisfaction with the treatment.

3. Subgroup Analyses

Treatment cohorts were stratified based on Fitzpatrick skin type. In both studies, and for all treatments, subjects with Fitzpatrick skin types I-III experienced a higher rate of Treatment-Related AEs than subjects with Fitzpatrick skin types IV-VI (see Table 13 to Table 15, above).

Comparative assessments between genders could not be adequately conducted due to the small number of male subjects enrolled into the studies.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study G140028 included 5 investigators and the pivotal clinical study G140106 also included 5 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c),

and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

None

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the General and Plastic Surgery Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Study results clearly demonstrate that RHA® 2, RHA® 3, and RHA® 4, are all non-inferior to their respective control at 24 weeks after treatment, for the correction of Nasolabial Folds when administered as an initial treatment followed by optimization of correction via an optional touch-up treatment in adults aged 22 years or older. Additionally, the proportion of responders at 24 weeks in the RHA® groups were well above the threshold required to confirm the presence of a clinically meaningful change (83.6% with RHA® 2, 91.9% with RHA® 3, and 97.7% with RHA® 4).
In all treatment groups, at 24 weeks, the average improvement in the WSRS from pre-injection was ≥ 1-grade. As such, it can be assumed with assurance that all RHA® formulations are effective.

As a secondary outcome measure, non-inferiority was maintained throughout the study for all RHA® implant formulations (at 36 weeks, 52 weeks, and 64 weeks after treatment).

Lastly, all study devices provided high levels of aesthetic improvement, responder rates were high, as assessed by the BLE and the TI, and showed a decrease over time, indicating an expected loss of treatment effect. Each treatment group presented very high subject satisfaction rates throughout the study (i.e., ≥ 87.2% of subjects satisfied or very satisfied with RHA® after Touch-Up visit).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical studies conducted to support PMA approval as described above.

Study treatment with three different RHA® formulations appeared to be safe and well tolerated. There were no reports of deaths, Treatment-Related Serious Adverse Events or Unexpected Adverse Device Effects in the study.

Treatment-Related Adverse Events rates were not negatively correlated with higher Fitzpatrick skin type.

All Treatment-Related Adverse Events were types of events that are typically experienced following the injection of a dermal filler, the onset of all events was temporally associated with a recent injection of a study device, and all events were mild or moderate in intensity (no severe Treatment-Related Adverse Events were reported in any of the treatment groups). There were no late onset Treatment-Related Adverse Events, and no events were deemed to be a granuloma.

Importantly, 97.8% of the Treatment-Related Adverse Events were based on the elevation of Common Treatment Responses that were present on the last diary day, and were typical and expected signs and symptoms observed following the injection of a dermal filler.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in clinical studies conducted to support PMA approval as described above.

The studies were randomized, double blinded, and prospective, utilizing a validated scale (WSRS) assessed by Blinded Live Evaluators to determine the primary efficacy endpoint. This is a strong study design for determining an aesthetic outcome. Non-inferiority was confirmed for all three formulations versus their respective control. Treatment Related Adverse Events were all typical and expected in association with injection of a dermal filler, and did not occur at rates different from those expected. Subjects reported high levels of satisfaction with their results, as assessed by multiple evaluation tools. Based on the safety and effectiveness conclusions drawn from the pivotal clinical studies, it is reasonable to conclude that the benefits of the use of RHA®2, RHA® 3, and RHA® 4, outweigh the risks when used in accordance with the Instructions For Use.

1. Patient perspectives considered during the review included:
    - Global Aesthetic Improvement (GAI) as assessed by the subject

- Impact and effectiveness of study treatment from the subjects' perspective as assessed by the nasolabial fold domain of the validated FACE-Q© patient-reported outcome measurement
- Subject satisfaction survey

In conclusion, given the available information above, the data support that for the correction of moderate to severe dynamic facial wrinkles and folds, such as nasolabial folds (NLF) in adults aged 22 years or over the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The benefits and risks of dermal fillers are sufficiently well understood for patients to make informed decisions about their use.

XIV. CDRH DECISION

CDRH issued an approval order on October 19, 2017.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.