SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Injectable Dermal Filler

Device Trade Name: JUVÉDERM™

Applicant's Name and Address: Inamed Corporation
5540 Ekwill Street
Santa Barbara, California 93111

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P050047

Date of Notice of Approval to Applicant: June 2, 2006

II. INDICATIONS FOR USE

JUVÉDERM 30, JUVÉDERM 24HV and JUVÉDERM 30HV are injectable gels indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

III. CONTRAINDICATIONS

JUVÉDERM is contraindicated for patients with severe allergies manifested by a history of anaphylaxis or history or presence of multiple severe allergies.

JUVÉDERM contains trace amounts of gram positive bacterial proteins and is contraindicated for patients with a history of allergies to such material.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the JUVÉDERM labeling.

V. DEVICE DESCRIPTION

JUVÉDERM injectable gel is a sterile, biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant. JUVÉDERM consists of crosslinked hyaluronic acid (HA) formulated to a concentration of 22-26 mg/mL, suspended in a physiological buffer. HA is a naturally occurring polysaccharide of the extracellular matrix in human tissues, including skin. The HA in JUVÉDERM is produced by *Streptococcus equi* bacteria.

The HA used in JUVÉDERM has a molecular weight of approximately 2.5 million Daltons and is crosslinked by adding a minimum amount of BDDE (1,4-butanediol

diglycidyl ether) to form a 3-dimensional HA gel. The chemical stabilizing (crosslinking) process does not change the polyanionic character of the polysaccharide chain.

JUVÉDERM is available in three formulations (30, 24HV and 30HV) and is supplied in pre-filled disposable syringes. Juvederm 30 HV is a more highly crosslinked robust formulation, injected using a 27G needle for volumizing and correction of deeper folds and wrinkles. Juvederm 24HV is a highly crosslinked formulation that can be injected using a 30 G needle for more versatility in contouring and volumizing of facial wrinkles and folds. Juvederm 30 is a highly crosslinked formulation, injected using a 27G needle, for subtle correction of facial wrinkles and folds. Each syringe contains 0.8 mL of JUVÉDERM gel implant. The syringe is equipped with a Luer lock adaptor, a plunger rod with a latex free stopper, a tip cap and a backstop. Each syringe bears a label with the name of the product, lot number, expiration date, volume, and sterility information. Each Juvéderm filled syringe is packaged in a protective pouch and then placed into a cardboard labeled box along with sterile disposable standard 27G and/or 30G sterile needles, Directions for Use, and product labels.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Treatment of photo-damaged skin, with its associated wrinkling and changes in texture and pigmentation, is often accomplished by use of topical creams (e.g. retinoids), chemical peeling procedures or laser resurfacing. Deeper wrinkles, folds, scars, and other depressed lesions are often treated with surgery (e.g. rhytidectomy), Botox® Cosmetic injections, or by implantation of dermal filler substances (e.g. injection of collagen, other hyaluronic acid gels, or autologous fat). In these cases, correction of the depression is the goal of therapy.

VII. MARKETING HISTORY

Upon CE marking in 2000, Corneal first introduced a family of non-animal hyaluronate gel implants in Europe under the trade names of JUVÉDERM ® and Hydrafill®. The JUVÉDERM family of products was later introduced in Canada in 2002.

In 2004, Corneal and Inamed formed a partnership for the clinical development and commercial distribution of JUVÉDERM hyaluronate gel implants in Canada, Australia and the United States and in Europe under the trade name Hydrafill.

The device has not been withdrawn from marketing in any country for any reason related to the safety or effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

In a U.S. Investigational Device Exemptions (IDE) study 439 subjects at 11 centers were randomized to one of three cohorts (JUVÉDERM 30, JUVÉDERM 24HV or JUVÉDERM 30HV) and received JUVÉDERM injections in one side of the face (nasolabial fold [NLF]) and injections of an injectable bovine collagen (Control) in the

other side of the face. Subjects recorded their observations of treatment responses for each side of the face in pre-printed diaries during the first 14 days following each treatment. The diaries included check boxes for commonly expected treatment responses, e.g. redness, swelling, pain, bruising, and itching, at the injection/application sites. A diary was completed for each initial and subsequent "touch up" treatment. It should be noted that the study subjects were required to record the presence and level of severity for each observed treatment response as "Mild," "Moderate," "Severe," or "None." A summary of the maximum severity and duration of the subject observations is presented in Tables 1 through 6 on the following pages.

Injection site responses reported by greater than 1% but less than 5% of subjects and not noted in the following tables were skin peeling and wrinkling in the JUVÉDERM 30 cohort; skin peeling and dryness in the JUVÉDERM 24HV cohort; and skin peeling and tingling in the JUVÉDERM 30HV cohort.

Table 1 – JUVÉDERM 30 vs. Control
Injection Site Responses by Maximum Severity
Occurring in >5% of Treated Subjects
(Number / % of Subject NLFs)

Injection Site Responses	TOTALS		JUVÉDERM 30 (N*=149 NLFS)			Control** (N*=149 NLFs)		
	JUVÉDERM 30 n‡ %	Control** n‡ %	Mild n‡ %	Mod† n‡ %	Severe n‡ %	Mild n‡ %	Mod† n‡ %	Severe n‡ %
Firmness	136	132	62	66	8	60	63	9
	91%	89%	42%	44%	5%	40%	42%	6%
Redness	134	132	73	44	17	63	54	15
	90%	89%	49%	30%	11%	42%	36%	10%
Swelling	132	128	65	58	9	81	43	4
	89%	86%	44%	39%	6%	54%	29%	3%
Pain/Tenderness	129	128	74	45	10	91	33	4
	87%	86%	50%	30%	7%	61%	22%	3%
Lumps/Bumps	123	122	65	49	9	64	50	8
	83%	82%	44%	33%	6%	43%	34%	5%
Bruising	91	79	49	27	15	51	25	3
	61%	53%	33%	18%	10%	34%	17%	2%
Discoloration	46	43	36	7	3	37	5	1
	31%	29%	24%	5%	2%	25%	3%	1%
Itching	42	52	31	10	1	38	11	3
	28%	35%	21%	7%	1%	26%	7%	2%

* Number of subject NLFs treated with the respective device
**A commercially available injectable bovine collagen
† Mod = Moderate
‡Number of subject NLFs with each specific injection site response

Table 2 – JUVÉDERM 24HV vs. Control
Injection Site Responses by Maximum Severity
Occurring in >5% of Treated Subjects
(Number / % of Subject NLFs)

Injection Site Responses	TOTALS		JUVÉDERM 24HV (N*=146 NLFS)			Control** (N*=146 NLFs)		
	JUVÉDERM 24HV n‡ %	Control** n‡ %	Mild n‡ %	Mod† n‡ %	Severe n‡ %	Mild n‡ %	Mod† n‡ %	Severe n‡ %
Redness	136 93%	130 89%	72 49%	48 33%	16 11%	69 47%	45 31%	16 11%
Pain/Tenderness	131 90%	128 88%	74 51%	45 31%	12 8%	87 60%	34 23%	7 5%
Firmness	129 88%	127 87%	66 45%	53 36%	10 7%	60 41%	56 38%	11 8%
Swelling	125 86%	122 84%	60 41%	54 37%	11 8%	77 53%	37 25%	8 5%
Lumps/Bumps	115 79%	122 84%	61 42%	45 31%	9 6%	66 45%	42 29%	14 10%
Bruising	86 59%	80 55%	43 29%	29 20%	14 10%	47 32%	27 18%	6 4%
Itching	52 36%	53 36%	42 29%	5 3%	5 3%	43 29%	7 5%	3 2%
Discoloration	48 33%	49 34%	31 21%	11 8%	6 4%	31 21%	15 10%	3 2%

* Number of subject NLFs treated with the respective device
**A commercially available injectable bovine collagen
† Mod = Moderate
‡Number of subject NLFs with each specific injection site response

Table 3 – JUVÉDERM 30HV vs. Control
Injection Site Responses by Maximum Severity
Occurring in >5% of Treated Subjects
(Number / % of Subject NLFs)

Injection Site Responses	TOTALS		JUVÉDERM 30HV (N*=144 NLFS)			Control** (N*=144 NLFs)		
	JUVÉDERM 30HV n‡ %	Control** n‡ %	Mild n‡ %	Mod† n‡ %	Severe n‡ %	Mild n‡ %	Mod† n‡ %	Severe n‡ %
Redness	129 90%	128 89%	61 42%	61 42%	7 5%	71 49%	42 29%	15 10%
Pain/Tenderness	129 90%	123 85%	68 47%	46 32%	15 10%	86 60%	32 22%	5 3%
Firmness	127 88%	122 85%	59 41%	53 37%	15 10%	62 43%	51 35%	9 6%
Swelling	124 86%	121 84%	61 42%	50 35%	13 9%	71 49%	41 28%	9 6%
Lumps/Bumps	120 83%	113 78%	57 40%	53 37%	10 7%	66 46%	40 28%	7 5%
Bruising	87 60%	69 48%	47 33%	33 23%	7 5%	38 26%	25 17%	6 4%
Itching	49 34%	51 35%	38 26%	9 6%	2 1%	39 27%	9 6%	3 2%
Discoloration	49 34%	43 30%	29 20%	15 10%	5 3%	31 22%	9 6%	3 2%

* Number of subject NLFs treated with the respective device
**A commercially available injectable bovine collagen
† Mod = Moderate
‡Number of subject NLFs with each specific injection site response

Table 4 - JUVÉDERM 30 vs. Control
Duration of Injection Site Responses
Occurring in > 5% of Treated Subjects
(Number / % of Subject NLFs)

Injection Site Response	JUVÉDERM 30 (N*=149 NLFs) n† %				Control** (N*=149 NLFs) n† %			
Duration‡	≤3 Days	4-7 Days	8-14 Days	>14 Days	≤3 Days	4-7 Days	8-14 Days	>14 Days
Firmness	40 27%	26 17%	21 14%	49 33%	34 23%	28 19%	14 9%	56 38%
Redness	68 46%	40 27%	14 9%	12 8%	51 34%	37 25%	14 9%	30 20%
Swelling	48 32%	44 30%	28 19%	12 8%	63 42%	43 29%	14 9%	8 5%
Pain/Tenderness	73 49%	36 24%	15 10%	5 3%	60 40%	39 26%	21 14%	8 5%
Lumps/Bumps	38 26%	27 18%	21 14%	37 25%	16 11%	21 14%	21 14%	64 43%
Bruising	30 20%	34 23%	24 16%	3 2%	41 28%	30 20%	7 5%	1 1%
Discoloration	31 21%	8 5%	4 3%	3 2%	26 17%	11 7%	3 2%	3 2%
Itching	23 15%	14 9%	3 2%	2 1%	24 16%	12 8%	9 6%	7 5%

*Number of subject NLFs treated with the respective device
**A commercially available injectable bovine collagen
†Number of subject NLFs with each specific injection site response by maximum duration
‡Duration refers to number of days from symptom onset until resolution, irrespective of date of implantation.

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Table 5 - JUVÉDERM 24HV vs. Control
Duration of Injection Site Responses
Occurring in > 5% of Treated Subjects
(Number / % of Subject NLFs)

Injection Site Response	**JUVÉDERM 24HV (N*=146 NLFs) n† %**				**Control** (N*=146 NLFs) n† %**			
Duration‡	≤3 Days	4-7 Days	8-14 Days	>14 Days	≤3 Days	4-7 Days	8-14 Days	>14 Days
Redness	60 41%	50 34%	8 5%	18 12%	46 32%	46 32%	10 7%	28 19%
Pain/Tenderness	61 42%	46 32%	18 12%	6 4%	49 34%	53 36%	14 10%	12 8%
Firmness	29 20%	34 23%	20 14%	46 32%	25 17%	28 19%	20 14%	54 37%
Swelling	38 26%	48 33%	22 15%	17 12%	54 37%	38 26%	20 14%	10 7%
Lumps/Bumps	26 18%	32 22%	18 12%	39 27%	16 11%	18 12%	19 13%	69 47%
Bruising	29 20%	28 19%	24 16%	5 3%	35 24%	27 18%	10 7%	8 5%
Itching	25 17%	15 10%	7 5%	5 3%	21 14%	17 12%	4 3%	11 8%
Discoloration	22 15%	12 8%	4 3%	10 7%	26 18%	9 6%	3 2%	11 8%

*Number of subject NLFs treated with the respective device

**A commercially available injectable bovine collagen

†Number of subject NLFs with each specific injection site response by maximum duration

‡Duration refers to number of days from symptom onset until resolution, irrespective of date of implantation.

Table 6 - JUVÉDERM 30HV vs. Control
Duration of Injection Site Responses
Occurring in > 5% of Treated Subjects
(Number / % of Subject NLFs)

Injection Site Response	**JUVÉDERM 30HV (N*=144 NLFs) n† %**				**Control** (N*=144 NLFs) n† %**			
Duration‡	≤3 Days	4-7 Days	8-14 Days	>14 Days	≤3 Days	4-7 Days	8-14 Days	>14 Days
Redness	56 39%	43 30%	10 7%	20 14%	53 37%	37 26%	13 9%	25 17%
Pain/Tenderness	59 41%	37 26%	25 17%	8 6%	55 38%	44 31%	17 12%	7 5%
Firmness	24 17%	29 20%	18 13%	56 39%	28 19%	26 18%	16 11%	52 36%
Swelling	31 22%	49 34%	21 15%	23 16%	53 37%	47 33%	13 9%	8 6%
Lumps/Bumps	32 22%	24 17%	19 13%	45 31%	15 10%	26 18%	14 10%	58 40%
Bruising	25 17%	31 22%	22 15%	9 6%	26 18%	29 20%	11 8%	3 2%
Itching	32 22%	9 6%	6 4%	2 1%	24 17%	18 13%	6 4%	3 2%
Discoloration	22 15%	11 8%	4 3%	12 8%	27 19%	5 3%	5 3%	6 4%

*Number of subject NLFs treated with the respective device
**A commercially available injectable bovine collagen
†Number of subject NLFs with each specific injection site response by maximum duration
‡Duration refers to number of days from symptom onset until resolution, irrespective of date of implantation.

Surveillance Outside the United States

In postmarket surveillance for JUVÉDERM products in countries outside the United States, one anaphylaxis reaction has been reported. Reported treatment included administration of antihistamine medications with subsequent resolution. Additionally, injection site responses (e.g. swelling, redness, infection, tenderness, induration, itching at the injection site) have been reported after treatment with JUVÉDERM.

IX. SUMMARY OF PRECLINICAL STUDIES

Biocompatibility

The following biocompatibility testing has been conducted:

Test	Results
Cytotoxicity (Agar Overlay Microplate Assay)	Non cytotoxic
Pyrogenicity (Rabbits)	Non pyrogenic
Bacterial Endotoxin (Kinetic-Chromogenic Test)	<20EU/syringe
Acute Systemic Toxicity: Direct intraperitoneal administration in mice	Non toxic
Subchronic Toxicity (12 weeks): Direct intradermal administration in rats	Non toxic
Intradermal Reactivity: Direct intradermal administration in rabbits	Slight irritation
Genotoxicity • Bacterial Reverse Mutation (Ames Assay) • *In Vitro* Chromosomal Aberration Study • Mouse Bone Marrow Micronucleus Study	 • Non mutagenic • Non genotoxic • Non genotoxic
Skin Sensitization: Maximization assay in Guinea pigs	Non sensitizer
Intradermal Implantation (1, 3, 6, and 9 months): Direct intramuscular administration in rabbits	Well tolerated
Muscle Implantation (4 & 12 weeks): Direct intramuscular administration in rabbits	Well tolerated
Subcutaneous Implantation (3 and 13 days)	No chronic inflammation

JUVÉDERM passed all biocompatibility testing based on the International Organization for Standardization (ISO) 10993-1. The device was shown to be non-mutagenic by ISO genotoxicity requirements, i.e. bacterial reverse mutation (Ames assay), *in vitro* chromosomal aberration study, and mouse bone marrow micronucleus study.

Inamed assessed the potential cancer risk of residual BDDE from lifetime use of JUVÉDERM dermal fillers. BDDE, a material used in the manufacturing process of

JUVÉDERM, is a sensitizer and has also been found to be a mutagen in Drosophila.[1] An animal study was performed by an independent laboratory to study the carcinogenicity potential of BDDE.[2] Based on the results of this study, a cancer risk assessment of the use of BDDE as a crosslinking agent was performed.[3] Through applying both a linear extrapolation method and a dose-response model (bench mark dose (BMD)), it was concluded that the excess cancer risk was minimal. Estimated excess cancer risk ranged from 1×10^{-5} to 1×10^{-8} from lifetime exposure to residual BDDE.

Inamed's carcinogenicity risk assessment assumes a worst-case dose of 2 ppm of residual BDDE present in JUVÉDERM. Assuming the worst-case scenario where JUVÉDERM contains 2 ppm of residual BDDE, and the tumorigenic dose that was obtained from the CIBA-GEIGY study, the estimated excess cancer risk ranged from 2×10^{-5} to 5×10^{-9} from lifetime exposure to residual BDDE in the dermal filler. In conclusion, the calculated risk of cancer associated with the use of JUVÉDERM is minimal.

The preclinical testing and the BDDE cancer assessment indicated that JUVÉDERM was safe to be evaluated in clinical studies.

Chemical and Physical Characterization

All three formulations of JUVÉDERM (30, 24HV, and 30HV) hyaluronate gel implants have been extensively tested and characterized, through physical and chemical analyses. Oxygen derived free radical and enzymatic degradation assays were also performed on JUVÉDERM gel implants to ensure that they naturally degrade within the body during their clinical lifespan.

Based on all the chemical and physical testing of the raw material sodium hyaluronate and the finished JUVÉDERM products that have been performed, there was sufficient data to demonstrate that JUVÉDERM hyaluronate gel implants were appropriate for evaluation in clinical studies as dermal fillers.

X. SUMMARY OF CLINICAL STUDIES

Pivotal Study

The clinical basis for approval for this pre-marking application is the outcome of a

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[1] P. Foureman, J.M. Mason, R. Valencia, and S. Zimmering, *Chemical Mutagenesis Testing in Drosophila*, Environmental Molecular Mutagenesis 1994; 23:57-63.

[2] CIBA-GEIGY: *A Cutaneous Carcinogenicity Study with Mice on the Diglycidyl Ether of 1,4-Butane Diol* with Attachments and Cover Letter Dated 09/28/87; National Technical Information Service, NTIS/OTS0513957

[3] U.S. Food and Drug Administration (FDA) Cancer Risk Assessment, Advisory Panel Briefing Information, PMA P020023, (Restylane), 2003 Nov *{http://www.fda.gov/ohrms/dockets/ac/03/briefing/4004b1_02_Cancer%20Risk%20Assessment.htm}*

prospective, randomized Pivotal Clinical Study performed in the United States.

The JUVÉDERM clinical trial included a treatment phase with an initial treatment to the nasolabial folds and up to two touch–up treatments as appropriate at 2-week intervals. The safety and efficacy follow-up phase included assessment at 4-week intervals through 24-weeks after the last treatment.

Devices

The investigational devices used in the study were three formulations of JUVÉDERM injectable gel (JUVÉDERM 30, JUVÉDERM 24HV and JUVÉDERM 30HV). JUVÉDERM is a non-animal, hyaluronic acid-based, lightly crosslinked dermal filler. The JUVÉDERM products were delivered during the study via a 1.0cc syringe (0.8 mL fill volume) and a 30 gauge needle.

The control device was a commercially available collagen implant composed of purified bovine dermal collagen cross linked with glutaraldehyde, dispersed in phosphate buffered saline and 0.3% lidocaine. The collagen implant is a PMA-approved device indicated for the correction of contour deficiencies of soft tissue. The collagen implant was delivered during the study via 1.0cc syringe (1.0 mL fill volume) and a 30 gauge needle.

Primary Objectives

The primary objectives of this study were to evaluate the safety and effectiveness of JUVÉDERM injectable gel compared to a commercially available control device in subjects seeking augmentation correction of bilateral, moderate to severe nasolabial folds.

Effectiveness Objective: To evaluate three JUVÉDERM implant formulations (JUVÉDERM 30, JUVÉDERM 24HV and JUVÉDERM 30HV) versus control collagen implants, first in terms of non-inferiority and second in terms of superiority, in the correction of moderate to severe NLFs. Co-primary efficacy analyses compared NLF severity scores for each treatment group at Week 12 following the last device treatment. Independent Expert Reviewer NLF severity scores were based on live assessments using a validated 5-point photographic scale; subjects used a similar 5-point non-photographic NLF severity scale.

Safety Objective: To evaluate treatment site responses and adverse events as recorded by study subjects and Investigators following treatment with JUVÉDERM implants vs. control collagen implants. Pre-printed diary forms were to be used by subjects to record specific signs and symptoms observed each day during the first 14 days after treatment. For each of the 14 days after initial and touch-up treatments subjects were instructed to rate each of a list of common treatment responses as "Mild," "Moderate," "Severe," or "None." It should be noted that subjects were encouraged to record all signs and symptoms in their diaries. The Investigator reviewed each subject's diary entries, treated the symptoms as appropriate, followed the subject, and captured the symptom as an adverse event (AE) with its probable cause, any action taken, and outcome on the

appropriate case report forms. Safety was determined by the rate of AEs associated with the use of each product.

Secondary Objectives

The secondary study objectives for this study were as follows:

- Evaluation of Independent Expert Reviewer NLF severity scores and subject NLF severity scores averaged over the 3 visits nearest Week 12.
- Evaluation of treatment effect longevity based on Independent Expert Reviewer NLF severity scores and subject NLF severity scores from Week 2 through Week 24 compared with pretreatment.
- Evaluation of Investigator live NLF severity scores made over the duration of the study.
- Evaluation of Independent Expert Reviewer live assessments of optimal (full) NLF correction at 2 weeks after each treatment and 4 weeks after the last treatment.
- Evaluation of subject observations of the effects of treatment during the first 14 days after each treatment.
- Evaluation of subject product preference assessments at the end of the study.

Study Design

The clinical study was a prospective, double-blind, randomized, three-armed, within-subject controlled, multi-center study conducted to evaluate the safety and efficacy of JUVÉDERM injectable gel implants when used as a dermal filler. The index treatment sites chosen for all subjects in this study were the nasolabial folds (NLFs). Eligible subjects signed an IRB-approved consent for treatment, underwent a physical examination, NLF severity assessment, and facial photography. In addition, women of childbearing potential underwent a urine pregnancy test. Blood samples were collected prior to treatment and at 4 and 24 weeks after the last treatment for routine hematology and chemistry; frozen serum samples were retained for antibody titer evaluation.

Subjects were randomized to one of three cohorts (JUVÉDERM 30, JUVÉDERM 24HV, or JUVÉDERM 30HV) and underwent treatment with JUVÉDERM on one side of the face and a commercially available collagen injectable implant on the opposite side to achieve optimal correction in both NLFs.

The Investigator administered up to three bilateral treatments (initial treatment and up to two touch-ups) approximately 2 weeks apart. The Independent Expert Reviewer (IER) and the subject remained masked to the treatment assignment.

Routine follow-up visits for safety and efficacy occurred at 3 and 7 days, 2 weeks after each treatment, and at 4, 8, 12, 16, 20 and 24 weeks after the last NLF treatment. Standardized facial photography was performed at each office visit. The Investigator, Independent Expert Reviewer and subject independently evaluated the NLF severity using a 5-point (range 0 to 4) scale. Subjects maintained a preprinted diary of their treatment responses and severity for 14 days after each treatment. Treatment site responses and other adverse events (AEs) were monitored throughout the study.

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Skin Type and Gender Bias

The majority of subjects enrolled in the clinical study were Caucasian (74.5%), who most commonly represent Fitzpatrick skin types I-III. Minority populations, who more commonly represent Fitzpatrick skin types IV-VI, comprised 25.5% of the study group. The 95% confidence intervals around the Independent Expert Reviewers' mean scores for severity of Caucasian and non-Caucasian subjects at 12 and 24 weeks overlapped, indicating that there is no bias upward or downward due to skin type.

Women made up a majority of the subjects in the U.S. trial (91.8%). Gender was represented as may be expected in the U.S. market.

Subject Enrollment

A total of 439 subjects were randomized and treated with JUVÉDERM 30, JUVÉDERM 24HV or JUVÉDERM 30HV; 423 (96.4%) completed the 24 week follow-up period.

Study Population Criteria

- Be men or women, greater than 30 years of age;
- Have 2 fully visible bilateral NLFs, which are approximately symmetrical and have reasonable expectation for correction by an intradermal injection procedure, as described in the protocol;
- Have severity scores of 2 or 3 on the 5-point photographic NLF severity scale (range 0 to 4) for both nasolabial folds, as judged by the Investigator;
- Agree to refrain from undergoing other anti-wrinkle treatments in the nasolabial fold areas and around the mouth during the study;
- If female of child-bearing potential (not sterile nor post menopausal for at least 1 year), have a negative urine pregnancy test and agree to use oral contraceptives or another medically acceptable form of birth control (2 forms of contraception, e.g., condoms and spermicide) for at least 1 month prior to treatment and for the duration of the study;
- Be able to understand and comply with the study requirements;
- Be willing to provide written Informed Consent prior to any study-related procedures being performed;
- Have no history of hypersensitivity reaction to or contraindication for treatment with bovine collagen;
- Have not had various aesthetic facial therapies within specified wash-out periods prior to study entry;
- Have no history of anaphylaxis, multiple severe allergies, atopy or allergy to meat, lidocaine or hyaluronic acid products or plans to undergo desensitization therapy;
- Have no active inflammation, infection, cancerous or pre-cancerous lesion or unhealed wound in the NLF area; and
- Have no history of connective tissue disease (e.g., rheumatoid arthritis, juvenile rheumatoid arthritis, scleroderma, systemic lupus erythematosus).

Effectiveness Assessments

Treatment effectiveness was assessed at each follow-up visit. The subject, Investigator and Independent Expert Reviewer independently assessed the severity of the subject's NLFs at each specified time point. The Independent Expert Reviewer and the subject remained masked to treatment randomization throughout the study.

The Independent Expert Reviewer made live assessments of the severity of the subject's NLFs using a validated 5-point photographic scale and comparing each NLF to the photographic scale and respective descriptions. The scale represents the spectrum of NLF severity from least to most severe (0-4). The subject performed self-assessments using a mirror and the numerical and narrative descriptions on the same 5-point NLF severity scale but without photographs. The Independent Reviewer and the subject rated the right and left NLFs individually and independently from each other and from their baseline scores.

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

Study Demographics

The majority of the subjects in each cohort were Caucasian and female with a median age between 48 and 50 years. Sufficient numbers of persons-of-color were enrolled without additional recruitment efforts. Table 7 presents subject demographics for the efficacy population in each cohort.

Table 7 – Demographics and Pretreatment Characteristics of the Effectiveness Populations

Demographic	JUVÉDERM 30 N=147†		JUVÉDERM 24HV N=146†		JUVÉDERM 30HV N=146†	
Gender [Number / %]						
Female	136	93 %	135	92%	132	90%
Male	11	7%	11	8%	14	10%
Age (years)						
Mean	49		50		48	
Median	49		50		48	
Range	30-70		31-75		26-74	
Ethnicity [Number / %]						
Caucasian	115	78%	105	72%	107	73%
African American	14	10%	18	12%	17	12%
Hispanic	16	11%	15	10%	20	14%
Asian	1	1%	7	5%	0	0%
Other	1	1%	1	1	2	1%
Fitzpatrick Skin Phototype [Number /%]						
I	6	4%	4	3%	8	5%
II	39	27%	34	23%	34	23%
III	48	33%	55	38%	51	35%
IV	34	23%	24	16%	31	21%
V	15	10%	24	16%	18	12%
VI	5	3%	5	3%	4	3%
Mean Baseline NLF Severity Score*						
JUVÉDERM NLF	2.5		2.6		2.6	
Control** NLF	2.6		2.6		2.6	

† Number of randomized subjects in the respective treatment group.

* NLF Severity was ranked on a 5-point scale from None (0) to Extreme (4)

** A commercially available injectable bovine collagen implant

Masking

Because the control collagen implant is off-white to creamy in color and JUVÉDERM is clear, it was not feasible to mask the treating Investigator. However, the Independent Expert Reviewer and the subject remained masked throughout the study and were not permitted to refer to their own previous assessments, each other's previous or current assessments or any of the Investigator's assessments. Subjects wore blindfolds during treatment. No one other than the Investigator, Study Coordinator and the subject were allowed in the examination room during the injection process. The Investigator and Study Coordinator were instructed to refrain from commenting on specific product assignments in the presence of the subject, Independent Expert Reviewer and other office personnel. The subject, Investigator and Independent Expert Reviewer independently assessed the severity of the subject's NLFs at each specified time point using the 5-point NLF severity scale.

Safety Conclusions

Subjects reported treatment site responses with similar frequency, severity, and duration for JUVÉDERM and Control. Most treatment site responses were mild or moderate and did not require intervention. The majority of events lasted 7 days or less, and treatment-emergent events not associated with a nasolabial fold were primarily reported as unrelated to the treatment. There were no serious adverse events related to JUVÉDERM treatment, although one clinically significant event (injection site abscess) was deemed to be related to Control treatment.

No trends were seen for changes in physical examinations, vital signs and hematology and chemistry determinations over the course of the study. For additional information regarding reported adverse events see Tables 1-6 above.

Effectiveness Conclusions

In order to establish effectiveness, JUVÉDERM was compared to Control in terms of non-inferiority and superiority. The primary effectiveness end point for the study was the Independent Expert Reviewer NLF severity scores over the post-treatment follow-up period. Effectiveness of device treatment was demonstrated by a lowering of the NLF severity score. Results based on the Independent Expert Reviewers' assessments of NLF severity are presented in Tables 8-10.

Table 8 – JUVÉDERM 30 vs. Control
Independent Expert Reviewer's
NLF Severity Scores

		Juvéderm 30 (N*=147 NLFs)		Control ** (N*=147 NLFs)	
	n§	NLF Severity†	Improvement since Baseline†	NLF Severity†	Improvement since Baseline†
Baseline	147	2.5	–	2.6	–
Week 2	146	0.6	1.9	0.7	1.8
Week 12	133	0.9	1.6	1.5	1.0
Week 24	143	1.4	1.2	2.1	0.5

* Number of subject NLFs treated with the respective device
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§ Number of subjects NLFs with data at baseline and the specified time point
† Mean score

Table 9 – JUVÉDERM 24HV vs. Control
Independent Expert Reviewer's
NLF Severity Scores

		JUVÉDERM 24HV (N*=146 NLFs)		Control** (N*=146 NLFs)	
	n§	NLF Severity†	Improvement since Baseline†	NLF Severity†	Improvement since Baseline†
Baseline	146	2.6	–	2.6	–
Week 2	142	0.6	2.0	0.7	1.9
Week 12	129	0.9	1.7	1.6	1.0
Week 24	138	1.3	1.3	2.3	0.3

*Number of subject NLFs treated with the respective device
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§ Number of subjects NLFs with data at baseline and the specified time point
†Mean score

Table 10 – JUVÉDERM 30HV vs. Control
Independent Expert Reviewer's
NLF Severity Scores

		JUVÉDERM 30HV (N*=146 NLFs)		Control** (N*=146 NLFs)	
	n§	NLF Severity†	Improvement since Baseline†	NLF Severity†	Improvement since Baseline†
Baseline	146	2.6	–	2.6	–
Week 2	143	0.5	2.1	0.7	1.9
Week 12	129	0.9	1.6	1.7	0.9
Week 24	139	1.2	1.4	2.2	0.4

*Number of subject NLFs treated with the respective device
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§ Number of subjects NLFs with data at baseline and the specified time point
†Mean score

All three Juvéderm formulations achieved non-inferiority to Control at week 12. JUVÉDERM 30 achieved non-inferiority to Control at Week 24 with mean NLF severity improvement of 1.2 versus 0.5. Clinical superiority was achieved at Week 24 by both JUVÉDERM 24HV and JUVÉDERM 30HV. For JUVÉDERM 24HV the mean NLF severity improvement was 1.3 compared to 0.3 for the Control (P<0.0001). At Week 24, JUVÉDERM 30HV NLFs had a mean severity improvement of 1.4 versus 0.4 for Control (P<0.0001). At their 24-Week follow up visits: 78% of patients preferred JUVÉDERM 30, 88% preferred JUVÉDERM 24HV, and 84% preferred JUVÉDERM 30HV.

XI. CONCLUSIONS DRAWN FROM THE STUDIES

Based on the Independent Expert Reviewers' assessments and study subjects' assessments, reasonable assurance of effectiveness has been shown for the JUVÉDERM injectable gel Implants. Reasonable assurance of safety has also been demonstrated by the lack of severe adverse events and by the short duration of the treatment responses observed.

Therefore it is reasonable to conclude that the benefits of the use of the device for the target population outweigh the risks of illness or injury when used as indicated in accordance with the directions for use.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) 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 Panel, an FDA advisory committee, for review and recommendation

because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

FDA issued an approval order on June 2, 2006.

The applicant's manufacturing facility, Corneal Industrie, located in Pringy, France was inspected on March 1, 2006 and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.