SUMMARY REVIEW MEMO TEMPLATE

DATE: JANUARY 6, 2010

FROM: (b)(6)

SUBJECT: P050047/S005
JUVEDERM ULTRA XC AND JUVEDERM ULTRA PLUS XC

CONTACT: (b)(6) PHD

TO: THE RECORD

BACKGROUND/ REASON FOR SUPPLEMENT

P050047/S005 is a 180 Day Supplement for two wrinkle filler devices with lidocaine, Juvederm Ultra XC and Juvederm Ultra Plus XC. The 2 devices were studied in a clinical trial under G070227. The devices are identical to the approved Juvederm Ultra and Juvederm Ultra Plus (P050047) except for the addition of lidocaine. The purpose of adding lidocaine to the wrinkle fillers is to reduce pain upon injection.

REVIEW TEAM

Table 1 below lists the participants in this review team and the section of the PMA that was reviewed:

Reviewer	Role
(b)(6) CDRH/ODE/DGRND/PRSB	Lead Reviewer
(b)(6) MD, MPH CDRH/ODE/DGRND/PRSB	Clinical Reviewer
(b)(6) PhD CDRH/OSB/DBS	Statistics Reviewer
(b)(6) PEBA	BIMO Reviewer
(b)(6) EA/GSD	GMP Reviewer
(b)(6) CDRH/OCER/DUPSA/OPPB	Patient Labeling Reviewer
(b)(6) PhD CDER/OPS/ONDQA/DPA I	Lidocaine/Stability Study Reviewer

Table 1: Review team for P050047/S005

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INDICATIONS FOR USE

Juvederm Ultra XC and Juvederm Ultra Plus XC are indicated for injection into the mid to deep dermis for correction of moderate to severe facial wrinkles and folds (such as nasolabial folds).

DEVICE DESCRIPTION

Juvederm Ultra XC and Juvederm Ultra Plus XC are biodegradable, non-pyrogenic, viscoelastic, clear, colorless, homogenized gel implant. They consist of stabilized, hyaluronic acid (HA) produced by *Streptococcus equi* bacteria, formulated to a concentration of 24 mg/ml in a physiological buffer, along with 0.3% lidocaine.

PRECLINICAL/BENCH

Biocompatibility

Both Juvederm Ultra XC and Juvederm Ultra Plus XC, are considered implantable materials, in contact with tissue and bone for greater than 30 days based on ISO 10993-1. As such biocompatibility testing was performed on both formulations in conformance to Good Laboratory Practices (GLPs) and ISO 10993-1. The final product concentrations were tested for: cytotoxicity, dermal sensitization, intradermal/intracutaneous reactivity, acute systemic toxicity, pyrogenicity, subchronic toxicity (12 week), genotoxicity (bacterial reverse mutation, chromosomal aberration, and micronucleus study), muscle implantation (4 week & 12 week), inflammatory response and bacterial endotoxin. Based on the results of the biocompatibility testing, the products were found to be biocompatible.

Stability Data

Six month stability studies were conducted with each product being stored under long-term and intermediate conditions. The lidocaine reveiewer stated that based on the data, which show no trend in lidocaine-related degradants, a shelf life of 12 months is recommended for each product stored at USP controlled room temperature (25˚C with excursions permitted to 15˚C – 30˚C).

CLINICAL DATA

The study was a multicenter, double blinded, randomized, within-subject controlled study of the safety and effectiveness of JUVEDERM™ Injectable Gel with Lidocaine compared with JUVEDERM Injectable Gel without Lidocaine in Subjects desiring correction of their nasolabial folds (NLFs). There were 2 cohorts to this study: (1) Juvederm Ultra vs. Juvederm Ultra XC and (2) Juvederm Ultra Plus vs. Juvederm Ultra Plus XC. The purpose of the study was to examine the effectiveness of the addition of lidocaine in reducing procedural pain (pain during treatment). The duration of the study was 2 weeks. Subjects received a single treatment of Juvederm Ultra or Ultra Plus in one NLF and Juvederm Ultra Plus XC or Ultra Plus XC in the other NLF. Within 30 minutes

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after both NLFs were treated, the subjects rated procedural pain on an 11-point scale and a 5-point comparative scale. Both the Investigators and subjects rated NLF severity at baseline and 2 weeks after treatment using the 5-point NLF severity scale from the pivotal study. Subjects utilized an interactive voice response system diary to record common treatment site reactions for 14 days.

There were 72 subjects enrolled and randomized in the study, including 36 subjects enrolled in the Juvederm Ultra cohort and 36 subjects enrolled in the Juvederm Ultra Plus cohort. Most of the subjects were women (96%) of Caucasian descent (78%) with Fitzpatrick Skin Types II or III (68%). Fitzpatrick Skin Types IV, V, or VI comprised 28% of treated subjects. The median age at study entry was 53 years. The demographics are summarized in table 2 below:

			Product	
Characteristic		% (n/N)	Juvéderm Ultra (N = 36 Subjects) % (n/N)	Juvéderm Ultra Plus (N = 36 Subjects) % (n/N)
Gender	Female	96% (69/72)	94% (34/36)	97% (35/36)
	Male	4% (3/72)	6% (2/36)	3% (1/36)
Age (yrs)	N	72	36	36
	Mean	53.8	51.9	55.6
	Standard Deviation	8.55	9.03	7.75
	Median	53	52	55.5
	Range (Min, Max)	(32, 80)	(32, 73)	(43, 80)
Ethnicity	Caucasian	78% (56/72)	75% (27/36)	81% (29/36)
	African American	17% (12/72)	19% (7/36)	14% (5/36)
	Hispanic	1% (1/72)	0% (0/36)	3% (1/36)
	Asian	1% (1/72)	3% (1/36)	0% (0/36)
	Other	3% (2/72)	3% (1/36)	3% (1/36)
Fitzpatrick Skin Type	I	4% (3/72)	6% (2/36)	3% (1/36)
	II	43% (31/72)	44% (16/36)	42% (15/36)
	III	25% (18/72)	14% (5/36)	36% (13/36)
	IV	13% (9/72)	19% (7/36)	6% (2/36)
	V	7% (5/72)	8% (3/36)	6% (2/36)
	VI	8% (6/72)	8% (3/36)	8% (3/36)

Table 2: Demographics of subjects in study

The comparative procedure pain score results show that 64% of subjects reported Juvederm with lidocaine (referred to as JULIDO) as less painful and 29% of subjects reported Juvederm with lidocaine as slightly less painful than Juvederm (referred to as JUVDRM). The results are summarized in table 3 below:

		Product	
	% (n/N)	Ultra (N = 36 Subjects) % (n/N)	Ultra Plus (N = 36 Subjects) % (n/N)
JULIDO is Less Painful than JUVDRM	64% (46/72)	64% (23/36)	64% (23/36)
JULIDO is Slightly Less Painful than JUVDRM	29% (21/72)	31% (11/36)	28% (10/36)
No Difference Between JULIDO and JUVDRM	0% (0/72)	0% (0/36)	0% (0/36)
JULIDO is Slightly More Painful than JUVDRM	4% (3/72)	6% (2/36)	3% (1/36)
JULIDO is More Painful than JUVDRM	3% (2/72)	0% (0/36)	6% (2/36)

Table 3: Subject comparison of comparative procedural pain score

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NLF severity scores for all formulations of Juvederm improved more than 1 point after treatment. The results are summarized in table 4 below:

		JULIDO		JUVDRM	
		Ultra (N=36 NLFs)	Ultra Plus (N=36 NLFs)	Ultra (N=36 NLFs)	Ultra Plus (N=36 NLFs)
Investigator	Mean Baseline	2.3	2.8	2.3	2.8
	Mean Final Visit	0.7	1.0	0.7	1.0
	Mean Improvement*	1.6	1.8	1.6	1.8
Subject	Mean Baseline	2.7	2.9	2.7	2.9
	Mean Final Visit	0.7	1.0	0.6	1.0
	Mean Improvement*	2.0	1.9	2.1	1.9

Table 4: Assessment of NLF Severity

Both Juvederm with lidocaine and Juvederm had similar safety profiles. Tables 5-7 summarize the adverse events by severity, duration and product, respectively.

		Severity*			
CTRs	**%(n/N)**	**Mild %(n/N)**	**Moderate %(n/N)**	**Severe %(n/N)**	**95% CI for Difference****
JULIDO (N=72 NLFs)	99% (71/72)	97% (70/72)	51% (37/72)	14% (10/72)	(-3.32%,6.09%)
Redness	78% (56/72)	57% (41/72)	19% (14/72)	1% (1/72)	(-9.43%,9.43%)
Pain	47% (34/72)	32% (23/72)	15% (11/72)	0% (0/72)	(-30.00%,-3.33%)
Tenderness	71% (51/72)	58% (42/72)	10% (7/72)	3% (2/72)	(-24.64%,-0.36%)
Firmness	88% (63/72)	60% (43/72)	21% (15/72)	7% (5/72)	(-13.15%,2.04%)
Swelling	82% (59/72)	58% (42/72)	22% (16/72)	1% (1/72)	(-10.41%,7.63%)
Lumps/Bumps	65% (47/72)	42% (30/72)	21% (15/72)	3% (2/72)	(-13.65%,8.09%)
Bruising	76% (55/72)	47% (34/72)	19% (14/72)	10% (7/72)	(-6.33%,14.67%)
Itching	29% (21/72)	29% (21/72)	0% (0/72)	0% (0/72)	(-12.61%,9.83%)
Discoloration	69% (50/72)	51% (37/72)	10% (7/72)	8% (6/72)	(-2.38%,19.05%)
JUVDRM (N=72 NLFs)	97% (70/72)	94% (68/72)	58% (42/72)	15% (11/72)	
Redness	78% (56/72)	54% (39/72)	24% (17/72)	0% (0/72)	
Pain	64% (46/72)	43% (31/72)	14% (10/72)	7% (5/72)	
Tenderness	83% (60/72)	60% (43/72)	18% (13/72)	6% (4/72)	
Firmness	93% (67/72)	63% (45/72)	26% (19/72)	4% (3/72)	
Swelling	83% (60/72)	53% (38/72)	29% (21/72)	1% (1/72)	
Lumps/Bumps	68% (49/72)	44% (32/72)	21% (15/72)	3% (2/72)	
Bruising	72% (52/72)	43% (31/72)	24% (17/72)	6% (4/72)	
Itching	31% (22/72)	29% (21/72)	1% (1/72)	0% (0/72)	
Discoloration	61% (44/72)	39% (28/72)	19% (14/72)	3% (2/72)	

Table 5: Summary of AE by severity

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CTRs	%(n/N)	Duration* 1-3 Days %(n/N)	4-7 Days %(n/N)	8-14 Days %(n/N)	> 14 Days %(n/N)
JULIDO (N=72 NLFs)	99% (71/72)	94% (68/72)	61% (44/72)	36% (26/72)	28% (20/72)
Redness	78% (56/72)	54% (39/72)	13% (9/72)	6% (4/72)	6% (4/72)
Pain	47% (34/72)	43% (31/72)	1% (1/72)	1% (1/72)	1% (1/72)
Tenderness	71% (51/72)	44% (32/72)	15% (11/72)	8% (6/72)	3% (2/72)
Firmness	88% (63/72)	33% (24/72)	26% (19/72)	15% (11/72)	13% (9/72)
Swelling	82% (59/72)	50% (36/72)	19% (14/72)	8% (6/72)	4% (3/72)
Lumps/Bumps	65% (47/72)	28% (20/72)	17% (12/72)	6% (4/72)	15% (11/72)
Bruising	76% (55/72)	29% (21/72)	21% (15/72)	18% (13/72)	8% (6/72)
Itching	29% (21/72)	22% (16/72)	6% (4/72)	0% (0/72)	1% (1/72)
Discoloration	69% (50/72)	40% (29/72)	10% (7/72)	8% (6/72)	11% (8/72)
JUVDRM (N=72 NLFs)	97% (70/72)	90% (65/72)	64% (46/72)	33% (24/72)	25% (18/72)
Redness	78% (56/72)	54% (39/72)	13% (9/72)	6% (4/72)	6% (4/72)
Pain	64% (46/72)	58% (42/72)	4% (3/72)	0% (0/72)	1% (1/72)
Tenderness	83% (60/72)	58% (42/72)	18% (13/72)	4% (3/72)	3% (2/72)
Firmness	93% (67/72)	42% (30/72)	25% (18/72)	15% (11/72)	11% (8/72)
Swelling	83% (60/72)	53% (38/72)	19% (14/72)	6% (4/72)	6% (4/72)
Lumps/Bumps	68% (49/72)	32% (23/72)	15% (11/72)	6% (4/72)	15% (11/72)
Bruising	72% (52/72)	26% (19/72)	26% (19/72)	13% (9/72)	7% (5/72)
Itching	31% (22/72)	28% (20/72)	1% (1/72)	0% (0/72)	1% (1/72)
Discoloration	61% (44/72)	31% (22/72)	14% (10/72)	8% (6/72)	8% (6/72)

Table 6: Summary of AE by duration

System Organ Class/ Preferred Term	Ultra JULIDO (N=36 NLFs) % (n/N)	Ultra JUVDRM (N=36 NLFs) % (n/N)	Ultra Plus JULIDO (N=36 NLFs) % (n/N)	Ultra Plus JUVDRM (N=36 NLFs) % (n/N)
One or More Adverse Event	25% (9/36)	28% (10/36)	33% (12/36)	28% (10/36)
General disorders and administration site conditions	25% (9/36)	28% (10/36)	33% (12/36)	28% (10/36)
Application site bruising	8% (3/36)	8% (3/36)	8% (3/36)	6% (2/36)
Injection site discoloration	8% (3/36)	6% (2/36)	14% (5/36)	11% (4/36)
Injection site erythema	8% (3/36)	8% (3/36)	6% (2/36)	6% (2/36)
Injection site induration	19% (7/36)	17% (6/36)	11% (4/36)	14% (5/36)
Injection site nodule	11% (4/36)	11% (4/36)	19% (7/36)	22% (8/36)
Injection site edema	8% (3/36)	11% (4/36)	3% (1/36)	6% (2/36)
Injection site pain	8% (3/36)	3% (1/36)	0% (0/36)	3% (1/36)
Injection site pruritus	3% (1/36)	3% (1/36)	0% (0/36)	0% (0/36)

Table 7: Summary of AE by product

The clinician stated that overall, the safety profile of the Juvederm devices with lidocaine is reportedly very similar to the safety profile of the device without lidocaine. She noted that many adverse events occurred more often in the study device as compared to the control. She noted that although it is not a major issue, this information should be included in the labeling. The sponsor included tables for injection site responses by maximum severity and a table for duration of injection site responses in their labeling.

The statistician stated that there does not appear to be any significant site-by-treatment interaction, or significant differences between the proposed device and the control. He

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