

## **RADIESSE® INJECTABLE IMPLANT**

### **Addendum to Instructions for Use (IN00053)**

#### **Mixing RADIESSE Injectable Implant with 2% Lidocaine HCl for the Correction of Moderate to Severe Facial Wrinkles and Folds, Such as Nasolabial Folds**

In a prospective, randomized split-face single-blind clinical study, 50 patients were injected with syringes of 1.3cc of RADIESSE injectable implant mixed with 0.2cc of 2% lidocaine HCl (lidocaine) in one nasolabial fold (Treatment) and RADIESSE injectable implant without the 2% lidocaine (Control) in the contralateral nasolabial fold at two investigational sites in the United States. The purpose of this study was to assess the effectiveness of RADIESSE injectable implant mixed with 2% lidocaine for the reduction of pain during injection and the incidence of adverse events through the 1 month follow-up period.

**CAUTION:** The clinical study that evaluated the mixing of 2% lidocaine and RADIESSE injectable implant was conducted ONLY on nasolabial folds. The safety and effectiveness for the mixing of 2% lidocaine and RADIESSE injectable implant for restoration and/or correction of the signs of facial fat loss (lipoatrophy) in people with human immunodeficiency virus has not been studied.

#### **Study Endpoints**

The two primary effectiveness endpoints of the study were to evaluate if a statistically significant reduction in pain existed in the Treatment nasolabial fold when compared to the Control nasolabial fold immediately after treatment using a validated visual analog scale (VAS) and to assess whether the observed differences in pain in the Treatment nasolabial fold when compared to the Control nasolabial fold were clinically meaningful immediately after treatment.

The secondary effectiveness endpoints assessed pain in the Treatment nasolabial fold when compared to the Control nasolabial fold at various times out to 1 month post treatment, aesthetic effectiveness out to one month after treatment and subject preference by analyzing the percent of patients favoring one treatment over the other.

#### **Study Population**

The inclusion criteria for the clinical study were that the patient was at least 18 years of age, was a candidate for nasolabial fold treatment using RADIESSE injectable implant, understood and accepted the obligation not to receive any other facial procedures in the lower half of the face for 1 month, understood and accepted the obligation to present for all scheduled follow-up visits, was logistically able to meet all study requirements and had approximately symmetrical nasolabial folds.

The exclusion criteria for the clinical study were patients that had received any type of treatment or procedures including surgery in the nasolabial folds, had received neurotoxins in the lower half of the face in the past 6 months, had received hyaluronic acid, calcium hydroxylapatite (CaHA) or collagen injections in the lower half of the face within the past 1 ½ years, had received polylactic acid, PMMA, silicone or any other permanent filler injections in the lower half of the face, had nasolabial folds that were too severe to be corrected in one treatment session, had a history of chronic or recurrent infection or inflammation that would preclude participation in the study, had a known bleeding disorder or were receiving medication that would likely increase the risk of bleeding, was female and of child bearing potential and was pregnant or not using acceptable method of birth control, had any history of hypersensitivity to Lidocaine or anesthetics of the amide type, had a history of anaphylaxis or multiple severe allergies, or had received any investigational product within 30 days prior to study enrollment or is planning to participate in another investigation during the course of this study.

#### **Study Results**

The first primary effectiveness endpoint of the study was to assess pain using the Visual Analog Scale (VAS) in the Treatment fold compared to the Control fold. The mean VAS scores at time zero resulted in a statistically significant reduction in pain in the Treatment fold compared to the Control fold. The mean difference in VAS scores was -3.85 and a paired t-test resulted in a p-value of <0.0001 (see Table 15).

Table 15. VISUAL ANALOG SCALE (VAS) SCORE AT TIME ZERO

	Treatment	Control
Mean	2.8	6.6
Median	2.5	7.0
St. Deviation	1.9	2.2
Minimum	0.0	2.0
Maximum	8.5	10.0
Mean Difference	3.85	
p-value	<0.0001	

The second primary effectiveness endpoint of the study was to assess percentage of patients in which there was a clinically meaningful reduction in pain in the Treatment fold. Forty-five (45) of the 50 patients (90%) recorded VAS scores of at least 2.0cm lower for the Treatment fold compared to the Control fold, demonstrating a clinically meaningful reduction in pain (see Table 16).

Table 16. VAS SCORE ≥ 2.0cm LOWER IN TREATMENT VS. CONTROL (N=50)

N	%
45	90.0% C.I. 78.2%-96.7%
p <0.0001	

A secondary effectiveness endpoint of the study was to assess pain in the Treatment fold compared to the Control fold at various times out to 1 month. The Treatment fold showed a statistically significant reduction in pain at four time points within the first hour (p < 0.0001) when compared to the Control fold. At 2 weeks and 1 month, there was no difference between the Treatment and Control folds as all pain ratings for both groups were 0 (no pain) (see Table 17).

Table 17. VAS SCORE AFTER TIME ZERO (N=50)

	15 min		30 min		45 min		60 min		2 Week		1 Month	
	Tx	Control	Tx	Control	Tx	Control	Tx	Control	Tx	Control	Tx	Control
Mean	0.9	3.4	0.7	2.5	0.5	1.8	0.3	1.3	0.0	0.0	0.0	0.0
Median	0.5	3.0	0.5	2.3	0.0	1.0	0.0	0.5	0.0	0.0	0.0	0.0
SD	1.0	2.2	1.0	2.1	0.8	1.8	0.7	1.6	0.0	0.0	0.0	0.0
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	4.0	8.0	5.0	7.5	3.5	6.5	3.0	6.0	0.0	0.0	0.0	0.0
p-value	< 0.0001		< 0.0001		< 0.0001		< 0.0001		N/A		N/A	

Another effectiveness endpoint assessed aesthetic improvement on the Global Aesthetic Improvement Scale (GAIS) at 2 weeks and 1 month post treatment. All patients in both groups were at least "Improved" (see Table 18).

Table 18. GAIS DISTRIBUTION (N/%)

Rating	2 Weeks		1 Month	
	Treatment	Control	Treatment	Control
Very Much Improved	29 (58.0)	26 (52.0)	31 (62.0)	28 (56.0)
Much Improved	16 (32.0)	18 (36.0)	12 (24.0)	20 (40.0)
Improved	5 (10.0)	6 (12.0)	7 (14.0)	2 (4.0)
No Change	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worse	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
TOTAL IMPROVED	50 (100.0)	50 (100.0)	50 (100.0)	50 (100.0)
p-value	1.0000		1.0000	

The adverse events reported during this study were generally expected, mild in nature and short in duration and are detailed in the tables below. Adverse events were reported through patient diaries and by the principal investigators, with the majority of adverse events reported through the patient diaries. Adverse events are presented by time point and in total for the Treatment and Control groups. The majority of adverse events were reported in the  $\leq 14$  day time period. There was no statistical difference with respect to occurrence of patient diary reported adverse events between the 2 groups (see Table 19). There were 2 adverse events reported by the investigators (depression for one patient and redness for one patient in the Control nasolabial fold).

Table 19. ADVERSE EVENTS REPORTED IN PATIENT DIARIES  
N = 50

Adverse Event	Number of Adverse Events Reported						
	$\leq 14$ Days		$> 14$ Days		Total		p-value
	Treatment	Control	Treatment	Control	Treatment	Control	
Bruising	26	25	0	0	26	25	1.0000
Itching	11	12	2	4	13	16	0.1573
Pain	22	25	0	0	22	25	0.5271
Redness	29	32	0	0	29	32	0.4795
Swelling	47	44	0	0	47	44	0.4795
Other	5	4	1	2	6	6	N/A

\* "Other" adverse events for both Treatment and Control groups include bleeding, small bump, numbness, needle marks, nostril sensitivity and skin tightness.

#### Technique for Mixing RADIESSE injectable implant and 2% Lidocaine HCl

**CAUTION:** Do not use the RADIESSE injectable implant and 2% lidocaine mixture later than 2 hours after mixing.

**CAUTION:** The assembled components are intended for one-time use only.

Within the clinical study, the following components were used:

- Sterile 27 gauge, 0.5" regular-wall needle with Luer lock connector (not supplied by BioForm Medical, Inc.).
- 3.0cc sterile polypropylene luer-lock syringe (BD 309585)
- 0.2cc of Hospira, Inc. (NDC 0409-4277-02) 2% lidocaine HCl for injection, USP solution (not supplied by BioForm Medical, Inc.)
- Sterile Female-to-female luer lock connector (Braun FDC1000 or Baxa 13901)
- 1.3cc syringe of RADIESSE injectable implant

The 3.0cc sterile polypropylene mixing syringe (BD 309585) and the female-to-female luer lock connector (Baxa 13901) are separately available in the BioForm Medical Accessory Kit. Neither the lidocaine nor the sterile 27 gauge, 0.5" needle are supplied by BioForm Medical, Inc.

#### Component Assembly and Mixing Instructions

1. Assemble the components and perform the mixing using sterile technique (see Figure 1).



Figure 1 :Left to right: Female-to-female luer lock connector, RADIESSE syringe, 3.0cc mixing syringe, sterile 27 gauge, 0.5" needle

2. Draw the lidocaine into a 3.0 cc sterile polypropylene mixing syringe fitted with a sterile 27 gauge, 0.5" needle.
3. Tap the mixing syringe, containing lidocaine and depress its push rod to remove all excess air.
4. Remove the sterile 27gauge, 0.5" needle.

- Firmly connect the mixing syringe to the RADIESSE syringe using the female-to-female luer lock connector (see Figures 2 and 3).



Figure 2

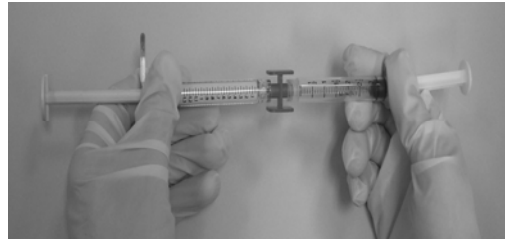


Figure 3

- Mix the lidocaine and RADIESSE injectable implant by alternately depressing the plungers, first on the mixing syringe and then on the RADIESSE syringe for ten mixing strokes (each mixing stroke is one complete compression of the mixing syringe plunger followed by one complete compression of the RADIESSE syringe plunger). Plungers are compressed firmly and quickly, at about two compressions per second.



Figure 4

- After mixing, remove the mixing syringe and the female-to-female luer lock connector and discard.
- Fit the syringe containing the lidocaine and RADIESSE mixture with an injection needle.
- Proceed with the injection of the RADIESSE injectable implant.

The clinical study was conducted by mixing 0.2cc of 2% lidocaine with 1.3cc of RADIESSE injectable implant in the 3.0cc BD syringe. The table below provides the ratio of 2% lidocaine to be mixed with the various syringe volumes of RADIESSE injectable implant. These ratios result in the same concentration of 2% lidocaine (w/v%) in RADIESSE injectable implant that was mixed in the clinical study after accounting for the dead space in the RADIESSE and 3.0cc BD mixing syringes (see Table 20).

Table 20. LIDOCAINE CONCENTRATION

RADIESSE (cc)	2% Lidocaine (cc)	Resulting Lidocaine Concentration (w/v%)
0.3	0.02	0.30% - 0.33%
0.8	0.11	0.31% - 0.32%
1.3	0.20	0.31% - 0.32%
1.5	0.26	0.31% - 0.32%

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