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ORIGINAL ARTICLE NON-SURGICAL AESTHETIC

Randomized Double-Blind Controlled Study on the Safety and Efficacy of a Novel Injectable Cross-linked Hyaluronic Gel for the Correction of Moderate-to-Severe Nasolabial Wrinkles

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Abstract

Introduction The current study compares two hyaluronic acid fillers, Ial System Duo and Belotero Basic/Balance, for the treatment of wrinkles.

Materials and Methods This is a single-center, double-blind randomized controlled study. Inclusion criteria consisted of subjects with bilateral nasolabial wrinkles. Each subject was treated with both products: One was applied on the right side and the other on the left side of the face. The quantity of product injected and any problems or local reactions (erythema, edema, pain or itching) were recorded and reassessed at 3 and 6 months and then monthly until complete absorption of the product. The Wrinkle Severity Rating Scale (WSRS) and the Global Aesthetic Improvement Scale (GAIS) were used for the assessment, as well as an ultrasound measurement of the skin thickness.

Results Complete data were available for 59 subjects. At 3 and 6 months, both products showed improvement in the WSRS and GAIS score in the areas treated compared to pre-treatment assessments, although no significant differences were observed between them. No resulting significant differences were observed on skin thickness among the two products, which were completely reabsorbed in 285 ± 34 days (Ial System Duo) and 277 ± 34 days (Belotero Basic/Balance; Student's t test: $p = 0.2181$). No significant differences were observed with regard to the subject's satisfaction and adverse events.

Conclusions The Ial System Duo achieves long-term permanence (more than 9 months confirmed by ultrasound) in correction of moderate and severe wrinkles, similar to Belotero Basic/Balance. Both products showed a high safety profile and a high degree of subject and physician satisfaction.

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Keywords Skin wrinkles · Fillers · Esthetic surgery

Introduction

The current treatment of wrinkles for facial rejuvenation involves predominantly the use of soft tissue fillers and botulinum toxin A. The fillers provide structural support in the treatment of static lines, while botulinum toxin A is used for the attenuation of dynamic wrinkles. The choice of the treatment is based on more specific indications according to the physiologic and chronological age, ethnically associated facial morphotypes [1], and esthetic ideals based on sex and culture [2]. Many filling products exist that are biocompatible with good duration and variable mechanical properties [3]; however, hyaluronic acid (HA) is the most popular agent for intradermal injections to

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improve wrinkles and other cosmetic defects. HA is a glycosaminoglycan, a molecule in which a simple disaccharide is repeated multiple times creating a large hydrophilic molecule that confers hydration, turgor and flexibility to the skin [4]. It is degraded by a family of enzymes called hyaluronidases; various cross-linking techniques have been developed to prevent the rapid degradation and provide long-term treatment effects [5, 6]. The cross-linking technology, the uniformity and size of the particles, and the HA concentration of the filler determine its viscoelastic properties and therefore its clinical effect [7, 8].

Hyaluronic acid soft tissue fillers include a wide range of products with unique characteristics [9]. Recently, a new HA filler (Ial System Duo; Fidia Farmaceutici S.p.A., Abano Terme, Italy) has been introduced in clinical practice. This product derives from two components, HA auto-cross-linked and hyaluronic acid cross-linking through butanediol diglycidyl ether. The main difference with previous HA fillers derives from particular cross-linkages that confer the shape of a highly viscous biocompatible and absorbable gel, which exhibits improved viscoelastic properties and prolonged in vivo residence time compared to the native polymer in order to ensure a longer-lasting volumizing effect [10]. Such a product has been assessed in an initial longitudinal study on 20 females where it improved wrinkles and facial volumes in most subjects up to 9 months of follow-up [11]. A larger longitudinal study conducted on 60 females further confirmed such findings, replicating the results of the improvement for wrinkles and finding an amelioration in the Global Aesthetic Improvement Scale (GAIS) [12].

So far, there has been no comparative study among the Ial System Duo filler with a different filler to investigate results in the long term. The current study has been set up to compare the Ial System Duo versus Belotero Basic/Balance, a different HA filler that presents a cohesive polydensified matrix with sustainable long-term esthetic effects [13] indicated for the correction of moderate lines (e.g., moderate nasolabial wrinkles, glabellar lines) which is also suitable for lip enhancement and correction of facial atrophic scars. Belotero Basic/Balance was chosen as comparator because it has some similarity to Ial System Duo. Both fillers have similar indications, are both cross-linked through butanediol diglycidyl ether and are submitted to a second, but different, cross-linking process. The fillers chosen for this study also have a similar duration in tissues [14].

Materials and Methods

The study is a monocentric, double-blind, randomized controlled study of Ial System Duo (Fidia Farmaceutici S.p.A., Abano Terme, Italy) versus Belotero Basic/Balance (Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany). Belotero Basic has recently been renamed Belotero Balance, with no change in the product; in the current study, it is referred to as Belotero Basic/Balance. The study began after approval by the Ethics Committee of the Azienda Policlinico Umberto I in Rome (Protocol number: CE Pot. 776/12) and was conducted in accordance with the principles contained in the "Guidelines on clinical investigation: a guide for manufacturers and notified bodies—guidelines on medical devices" of the European Commission [15]. Written informed consent was obtained from each subject before participation in the study. The study was conducted between February 2013 and June 2014.

Inclusion criteria consisted of subjects of both sexes between 18 and 75 years old. Subjects had bilateral nasolabial wrinkles fully visible and approximately symmetrical with a score of 3 or 4 in the Wrinkle Severity Rating Scale (WSRS: 1 = absent, 2 = minor, 3 = moderate, 4 = severe, 5 = extreme) [16, 17]; agreed to return for the scheduled periodic checks; and had not planned the use of other beauty treatments (e.g., biomaterials implant, facelift, Botox injection, laser, chemical peel). Excluded from the study were subjects who underwent skin treatments for cosmetic correction (biomaterials implant, facelift, botulinum toxin injections, laser, chemical peel) during the 12 months preceding the survey; had a score less than 2 or greater than 4 in the WSRS; were previously treated with permanent fillers; had the tendency to develop hypertrophic, atrophic or dystrophic scars; had face-localized skin diseases (infections, dermatitis, dermatosis, psoriasis, eczema, acne, rosacea, herpes, etc.); were being treated with anticoagulants at the time of the study; had facial volume deficiency due to trauma or genetic defects; had known or presumed hypersensitivity to hyaluronic acid or its derivatives; had autoimmune diseases (systemic lupus erythematosus, scleroderma, etc.); possessed a history of severe allergies or severe shock or streptococcal diseases; ongoing neoplasm; suffered from serious clinical pathologies such as cardiovascular, neurological, renal, hepatic, pulmonary diseases or other conditions that, according to the investigator, precluded involvement in the study; were under therapy with immunosuppressant drugs; or were breastfeeding or had a known pregnancy, were suspected to be pregnant or planning a pregnancy.

Experimental Protocol

All subjects were assessed for eligibility in the study and asked to sign the informed consent form. The protocol included an initial visit with complete medical history, physical examination, assessment of the skin type according to the Fitzpatrick scale (from 1, very clear to 6, very dark), disclosure of treatments in progress, evaluation of the wrinkles according to the WSRS and ultrasound thickness of tissues.

The subjects, randomized in two groups, were treated with both products, one on each side of the face. The randomization list was generated to guarantee the balance of the two groups and to ensure an equitable distribution of the subjects based on the inoculated product first and on the side of the face affected by the single product (half of the subjects of both groups were treated with Ial System Duo on right side of the face and Belotero Basic/Balance on the left).

The technique used, the quantity of product injected and any problems or local reactions (erythema, edema, pain or itching) were recorded at each visit included the initial treatment until the time of their resolution. One assessor, unaware of the product used, scored the esthetic results. Therefore, only the clinician administering the treatment was aware of the product used; neither the subjects nor the assessor had knowledge of which product was administered.

Subjects presented for a first check 14 days after the initial treatment. The application was repeated (i.e., an additional treatment was administered) at the one-month follow-up if the initial correction was judged suboptimal on one or on each side. The subject was then reassessed at 3 and again at 6 months. From the 6-month follow-up to the end of the trial, follow-up visits were performed monthly until complete absorption of the product confirmed by ultrasound.

The ultrasound examination of treated areas (nasolabial folds) was performed by a blinded investigator using a Merlin 1101 ultrasound scanner (BKi Medical Corporation, Tokyo, Japan), with a high-resolution probe for small parts and the interposition of an ultrasound gel (Aquasonic gel 100, Parker Laboratory, Fairfield, NJ, USA). Before the first filler treatment and at each follow-up visit, the probe was directed bilaterally to a fixed facial examination point, 1 cm lateral from the alar base and 1 cm below on a sagittal line, along each nasolabial fold, to measure the upper, mid- and deep dermal thickness. The increase in thickness of the skin measurement after the filler infiltration, corresponding to wrinkle flattening, was evaluated during the examination. All scan images were acquired and saved. Using the sonoCT software program, it was possible to take measurements of the filler and soft tissues.

Outcomes

The main outcome was to evaluate the performance of Ial System Duo in terms of esthetic results. This evaluation has been made by the use of objective (WSRS—to assess the degree of filling of nasolabial folds) and subjective methods (Global Aesthetic Improvement Scale—GAIS), as well as standardized photographs of the subjects at different follow-ups. The WSRS variations between baseline and follow-ups for each treatment and the side of the face with the WSRS best performance for each subject at different times (the product that presented the best WSRS performance for single subject between Ial System Duo and Belotero Basic/Balance) were both analyzed. The GAIS consisted of a subjective score from 1 to 5: 1 = worsened, 2 = no variation, 3 = improved, 4 = much improved, 5 = very much improved [16, 18, 19].

Secondary objectives were to evaluate the persistence of the effects of Ial System Duo, the degree of satisfaction of the subjects and physicians and the safety of product. The persistence of the effects of Ial System Duo in the dermis was determined by conducting ultrasound measurements of dermal thickness at predetermined points. The permanence was estimated by ultrasound comparing dermal thickness at different time points with the original baseline thickness in the treated areas and determining the closest date in which the dermis thickness was similar to the baseline (the time point where no difference between baseline thickness and the following ultrasound thickness could be estimated). At follow up visits, the investigators and the subjects were blinded and unaware of which product was used on either side of the face. Subjects and assessing physicians were asked to assign a degree of satisfaction to the results of the treatments on each side of the face by the means of a scale from 0 (lowest satisfaction) to 10 (highest satisfaction).

The safety of the product was evaluated as any allergies or reactions manifested in the treatment period, and any unexpected adverse events were recorded at each visit. For the subjects treated at baseline and after 1 month, the presence and severity of local events were recorded (erythema, edema, redness, pain and itching). For these variables, a score was used as 0 = absent, 1 = mild, 2 = moderate, 3 = severe.

Sample Size Estimation

The calculation of the sample size was performed using an online calculator [20] and was based on the mean scores of the WSRS based on the following assumptions: alpha error = 0.025; power = 80%; non-inferiority margin for the difference of averages of = 0.25; estimated standard deviation = 0.5 [21]. Under these assumptions, at least 64 evaluable tests for each group were necessary. In our study,

this translates into 128 tests on both sides of the face for the 64 subjects involved.

Statistical Analysis

Data were entered in a suitable database, and the double data entry method was used. The calculations were performed using the SAS® statistical package, version 9.2 (100 SAS Campus Drive, Building T, Cary, NC 27513-2414, USA). Descriptive statistics for quantitative variables were the mean and standard deviation (mean ± SD) for parametric variables or median and range (minimum and maximum) for nonparametric variables. Descriptive statistics for qualitative variables were evaluated with occurrences and described with relative frequencies.

To evaluate the statistical significance of differences in frequency distribution, a Chi-squared test was used, as well as a Fisher's exact test in case of 2 by 2 tables. To evaluate the statistical significance of differences in basal modifications of the WSRS scale obtained with the two products over time, the Wilcoxon test was applied at each check. All results were considered significant if less than 0.05 ($p < 0.05$).

Results

Sixty-five subjects were recruited; most subjects were women (Table 1). Twenty-five subjects (38.5%) had at least a concomitant pathology (Table 2). The WSRS severity index evaluation at baseline indicates that the nasolabial folds on the right and the left side of each subject's face were similar in severity (Table 3).

All 65 subjects received treatment by the same physician employing identical techniques; none of the subjects received local anesthesia and all subjects received the injection of both products with a linear insertion at the deep dermis level. After 30 days, it was considered appropriate to make an additional treatment (touch-up) in 13 subjects (20.3%): 8 bilaterally and 5 unilaterally. Altogether, 11 areas were touched up with Belotero Basic/Balance and 10 with Ial System Duo. The techniques and methods used for the additional treatments were identical to those used in the first treatment. A significantly larger amount of Belotero Basic/Balance was injected at the first treatment than the Ial System Duo; no significant differences were observed between the products during the additional treatments or the total product injected (Table 4).

Table 1 Clinical characteristics of subjects recruited

Subjects	65
Males	3 (4.6%)
Females	62 (95.4%)
Age (years): mean (± SD)	50.4 (± 8.3)
Skin type	
European light	1 (1.5%)
European light-medium-dark skin	55 (84.6%)
Medium-dark olive skin	7 (10.8%)
Dark or brown	2 (3.1%)

Aesthetic Results

The final follow-up visit was in July 2014, when the investigator declared complete reabsorption of both products based on ultrasound evaluation for each subject. Six subjects were lost to follow-up at 3 and 6 months, and therefore, complete data were available for 59 subjects. After 3 months, both products showed improvement in the WSRS in the areas treated (Wilcoxon test: $p < 0.0001$; Table 5). Comparing performances between the products showed that 33.3% of areas treated with Ial System Duo and 20.6% of those treated with Belotero Basic/Balance had an improvement of two WSRS points compared to baseline values (Fisher's test: $p = 0.1595$).

The approach to consider the "preference" of the blinded clinician to the performance achieved on both sides of the face for any treated subject, instead of using one product per patient and analyzing a larger population, allows for a more direct comparison of the effects of the product, eliminating the inter-subject variability of the response to the treatment. At 3 months, the Ial System Duo had better WSRS scores compared to Belotero Basic/Balance (Wilcoxon test, $p = 0.0039$); in 14.3%, the WSRS score achieved with the Ial System Duo was greater by at least one point compared to the Belotero Basic/Balance. These findings were confirmed at 6 months when again Ial System Duo had better scores compared to Belotero Basic/Balance (Wilcoxon test, $p = 0.0034$; Table 6), and in 20.3% of subjects, the Ial System Duo WSRS score was greater by at least one point compared to Belotero Basic/Balance (Fig. 1).

With regard to the GAIS score, there is no statistically significant difference between the percentage of subjects that improved the score at any time for areas treated with Ial System Duo versus Belotero Basic/Balance (Fisher's test: p = n.s.; Table 7). After 3 and 6 months from the treatment, the blinded investigator evaluated on each subject the results obtained with the two different fillers by the means of the GAIS scale. At the 3-month follow-

Table 2 Associated pathologies

Pathologies	*N*	% Subjects (*N* = 65)
Endocrine disorders	9	13.8
Cardiovascular	8	12.3
Immune system diseases	5	6.7
Metabolism disorders	4	6.2
Gastrointestinal disorders	3	4.6
Psychiatric disorders	3	4.6
Nervous disorders	1	1.5
Respiratory disorders, thoracic and mediastinal disorders	1	1.5
Previous neoplasia	1	1.5
Eye disorders	1	1.5

Table 3 WSRS score at baseline and tissue thickness

WSRS baseline	Right side	Left side	*p*
3 = Moderate	30 (46.2)	31 (47.7)	1.000
4 = Severe	35 (53.8)	34 (52.3)	
Tissue thickness: (mean ± SD)	10.53 (± 1.21)	10.66 (± 1.12)	0.53

Chi-squared test and Student's *t* test were used for *p* calculation

Table 4 Quantity of products injected

Baseline treatment mean ml (± SD)	Belotero Basic/Balance	0.79 (± 0.14)	$p = 0.04$
	Ial System Duo	0.74 (± 0.14)	
Additional treatment mean ml (± SD)	Belotero Basic/Balance	0.65 (± 0.19)	$p = 0.67$
	Ial System Duo	0.61 (± 0.18)	
Total product injected mean ml (± SD)	Belotero Basic/Balance	0.89 (± 0.3)	$p = 0.33$
	Ial System Duo	0.84 (± 0.3)	

Student's *t* test was used for *p* calculation

Table 5 WSRS score at different moments of observation

	WSRS baseline				WSRS 1 month				WSRS 3 months				WSRS 6 months			
	Belotero Basic/Balance		Ial System Duo		Belotero Basic/Balance		Ial System Duo		Belotero Basic/Balance		Ial System Duo		Belotero Basic/Balance		Ial System Duo	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
1 = Absent	–	–	–	–	8	12.5	10	15.6	8	12.7	13	20.6	5	8.5	8	13.3
2 = Medium	–	–	–	–	25	39.1	26	40.6	27	42.9	25	39.7	23	39.0	22	36.7
3 = Moderate	31	47.7	30	46.2	30	46.9	28	43.8	27	42.9	25	39.7	23	39.0	28	46.7
4 = Severe	34	52.3	35	53.8	1	1.6	–	–	1	1.6	–	–	8	13.6	2	3.3
Total	65	100.0	65	100.0	64	100.0	64	100.0	63	100.0	63	100.0	59	100.0	60	100.0
p	0.86				0.73				0.50				0.19			

Chi-squared test was used for *p* calculation. *p* values refer to the comparison of the two products at each time point

up, in 4 subjects (6.3%) the treatment with Ial System Duo obtained a better score (Wilcoxon Test $p = 0.12$) than Belotero Basic/balance, and after 6 months, the number of subjects increased to 7 (11.9%) (Wilcoxon test $p = 0.016$; Table 8).

Persistence of the Product in the Dermis

With regard to the tissue thickness, no statistically significant differences were observed with the ultrasound measurements of the dermis between subjects at baseline

Table 6 Side scoring the best WSRS rating

	WSRS baseline		WSRS 3 months		WSRS 6 months	
	N	%	*N*	%	*N*	%
Best score for Belotero Basic/Balance side	1	1.5	–	–	1	1.7
Equal score for both sides	64	98.5	54	85.7	46	78.0
Best score for Ial System Duo side	–	–	9	14.3	12	20.3
Total	65	100.0	63	100.0	59	100.0
p	1.000		0.004		0.003	

Wilcoxon test was used for *p* calculation. *p* values refer to the comparison of the two products at each time point

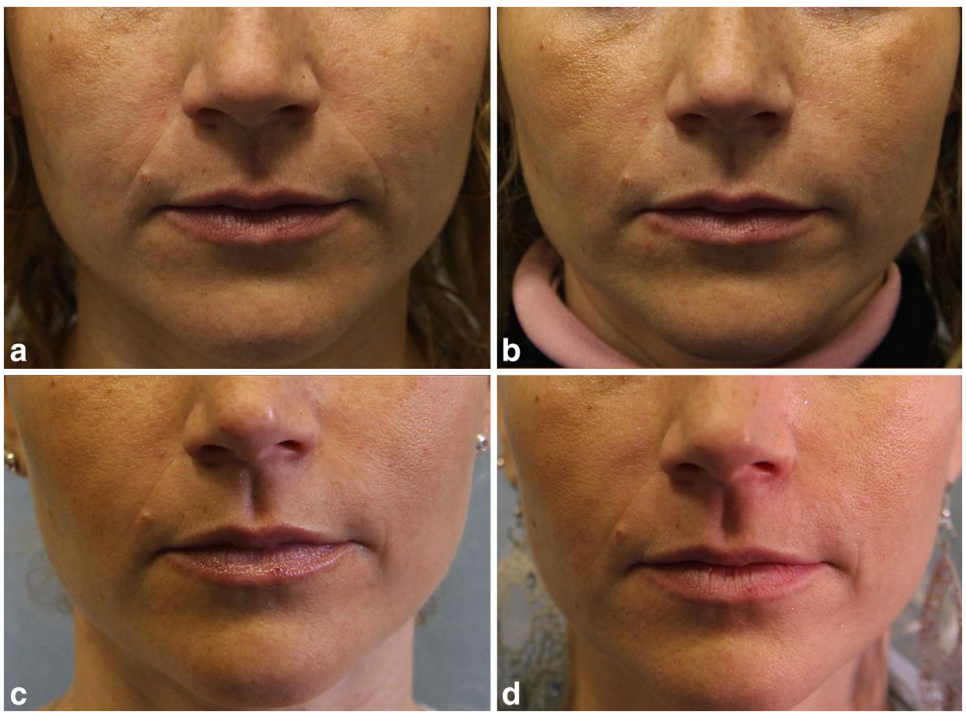

Fig. 1 Female subject aged 43, WSRS score 3. No touch-up procedures were performed on this subject. Baseline (**a**), 1 month after filler injection (**b**), 3 months after the procedure (**c**) and 6 months after the procedure (**d**)

Table 7 GAIS score at different moments of observation

	GAIS 1 month				GAIS 3 months				GAIS 6 months			
	Belotero Basic/Balance		Ial System Duo		Belotero Basic/Balance		Ial System Duo		Belotero Basic/Balance		Ial System Duo	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
1 = Clear improvement	28	43.8	31	48.4	25	39.7	29	46.0	17	28.8	20	33.3
2 = Good improvement	35	54.7	32	50.0	37	58.7	33	52.4	37	62.7	39	65.0
3 = Improvement	1	1.6	1	1.6	1	1.6	1	1.6	5	8.5	1	1.7
Total	64	100.0	64	100.0	63	100.0	63	100.0	59	100.0	60	100.0
p	0.87				0.77				0.23			

Chi-squared test was used for *p* calculation. *p* values refer to the comparison of the two products at each time point

(Belotero Basic/Balance side 10.6 ± 1.2 mm, Ial System Duo side 10.6 ± 1.1 mm; Student's *t* test $p = 0.9042$), at 3 months (Belotero Basic/Balance side 12.1 ± 1.0 mm, Ial System Duo side 12.2 ± 0.8 mm; Student's *t* test $p = 0.8832$), or 6 months (Belotero Basic/Balance side 11.6 ± 1.0 mm, Ial System Duo side 11.6 ± 1.0 mm;

Table 8 Side scoring the best GAIS rating

	GAIS 3 months		GAIS 6 months	
	N	%	*N*	%
Best score for Belotero Basic/Balance side	–	–	–	–
Equal score for both sides	59	93.7	52	88.1
Best score for Ial System Duo side	4	6.3	7	11.9
Total	63	100.0	59	100.0

Wilcoxon test was used for p calculation

Student's t test $p = 0.7684$; Fig. 2). The permanence of the products in the dermis was evaluated by ultrasound examination measuring the dermal thickness before treatment and considering the fillers reabsorbed when the dermal thickness was similar to baseline measurement. The complete reabsorption of Belotero Basic/Balance took place over a period of 277 ± 34 days, whereas for Ial System Duo the average time of permanence in situ was 285 ± 34 days (Student's t test: $p = 0.2181$).

Subject and Physician Satisfaction

Scores expressing satisfaction with the results of the treatment of the subjects and the clinical evaluators unaware of the product's application side were ranked by means of a rating scale from 0 (lowest satisfaction) to 10 (highest satisfaction). In the analysis, no significant differences were observed between subject's satisfaction with Ial System Duo and Belotero Basic/Balance at the various time points of observation: 1 month (Belotero Basic/

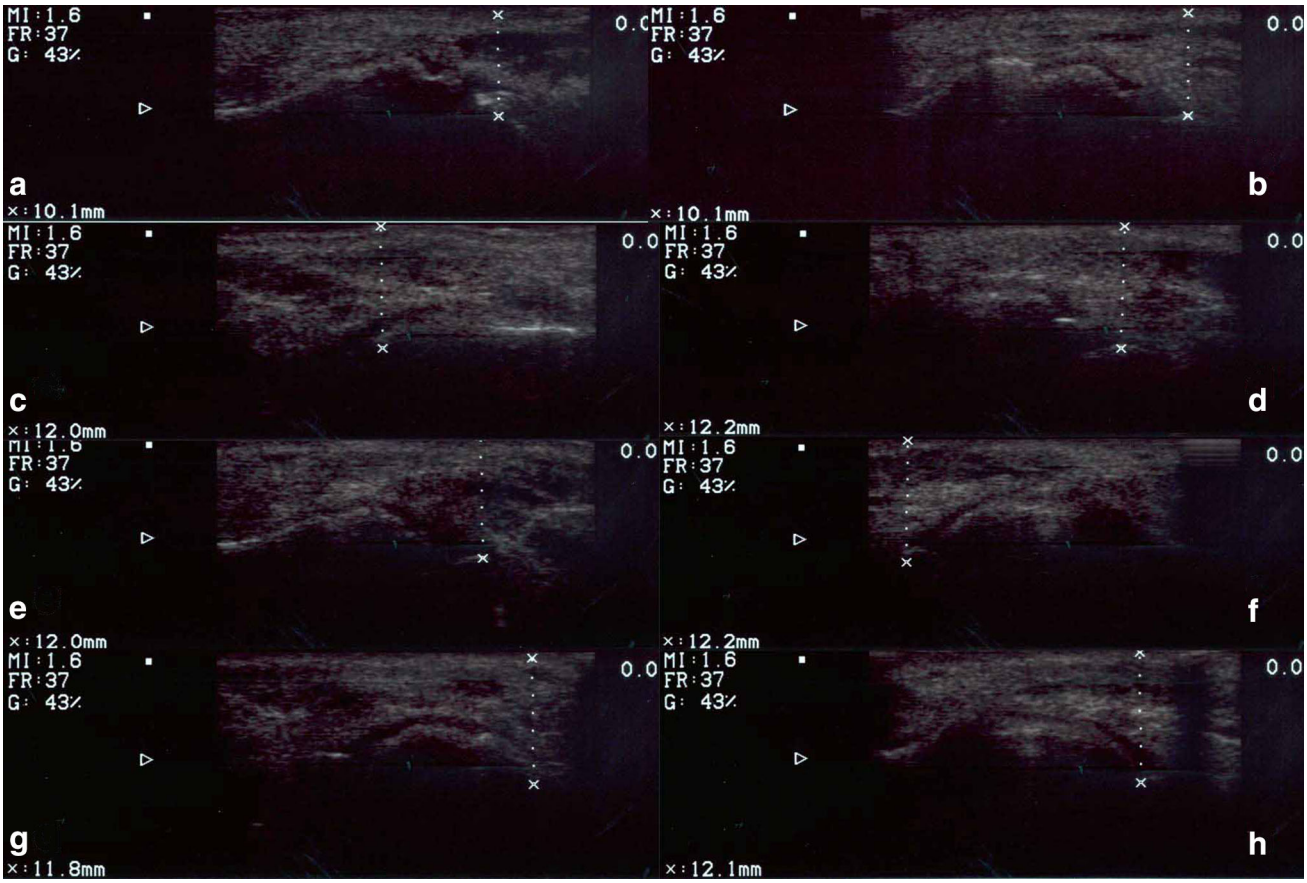

Fig. 2 Same patient, ultrasound measurements of skin thickness. Baseline: 10.1 mm at left side (**a**), 10.1 mm at right side (**b**). One month after fillers injection: 12.0 mm at left side treated with Ial System Duo (**c**), 12.2 mm at right side treated with Belotero Basic/Balance (**d**). Three months after the procedure: 12.0 mm at left side treated with Ial System Duo (**e**), 12.2 mm at right side treated with Belotero Basic/Balance (**f**). Six months after the procedure: 11.8 mm at left side treated with Hal system (**g**), 12.1 mm at right side treated with Belotero Basic/Balance (**h**)

Balance 8.2 ± 1.9 vs. Ial System Duo 8.4 ± 1.6 Student's t test $p = 0.5485$); 3 months (Belotero Basic/Balance 8.4 ± 1.5 Ial System Duo 8.5 ± 1.5 Student's t test $p = 0.7212$); and 6 months (Belotero Basic/Balance 8.2 ± 1.6 vs. Ial System Duo 8.4 ± 1.3 Student's t test $p = 0.5845$). No significant differences were observed between physician satisfaction with Ial System Duo and Belotero Basic/Balance at the various time points of observation: 1 month (Belotero Basic/Balance 8.6 ± 1.2 vs. Ial System Duo 8.6 ± 1.2 Student's t test $p = 0.8807$); 3 months (Belotero Basic/Balance 8.6 ± 1.1 vs. Ial System Duo 8.7 ± 1.1 Student's t test $p = 0.7447$); and 6 months (Belotero Basic/Balance 8.3 ± 1.4 vs. Ial System Duo 8.5 ± 1.2 Student's t test $p = 0.3653$).

Adverse Events

As a result of treatments, 61 subjects (93.8%) experienced at least 1 expected adverse event in the area treated with Belotero Basic/Balance and 60 (92.3%) in the area treated with Ial System Duo (Fisher's test, $p = 1.000$). The most frequent expected adverse events during the injection procedure were temporary pain and redness. The pain was more frequent during the first injection in the areas treated with Belotero Basic/Balance (60/65 subjects, 92.3%) than Ial System Duo (52/65 subjects, 80.0%; Chi-squared $p = 0.0048$) and at the additional injection (touch-up) at 1-month follow-up (Belotero Basic/Balance 8/11, 72.7% vs. Ial System Duo 8/10, 80.0% Fisher's test, $p = 1$). At the first injection, 50 subjects in each group referred to the pain as slight or moderate (76.9%). No significant difference was observed for the redness at first injection (Belotero Basic/Balance 46/65, 70.8% vs. Ial System Duo 47/65, 72.3%, Fisher's test, $p = 1$) and at 1 month (Belotero Basic/Balance 10/11, 90.9% vs. 9/10, 90.0%, Fisher's test, $p = 1$). The presence of ecchymosis was more frequent following Ial System Duo than Belotero Basic/Balance at the 14-day follow-up (Belotero Basic/Balance 16/64, 24.0% vs. Ial System Duo 26/64, 40.6%, Fisher's test $p = 0.0896$).

During the study, two unexpected adverse events unrelated to the investigation medical devices were recorded: one labyrinthitis (vestibular neuritis) and a threatened miscarriage. The subject with the threatened miscarriage reported that she was not pregnant when she enrolled in the study. No other serious adverse events were reported during this clinical investigation.

Discussions

The present study has confirmed the efficacy of Ial System Duo for the correction of nasolabial wrinkles, with effects visible at 3 months and 6 months compared to baseline, with the permanence of the two products up to 9.5 months, as previously described [12, 13]. In the current study however, the effects of Ial System Duo were compared with the Belotero Basic/Balance, a HA filler with a cohesive polydensified matrix for the long-term duration of the filling effect. Although both products gave substantial positive results, clinicians attributed a higher quantitative WSRS score to areas treated with Ial System Duo at 3 months (33.3% of subjects were assessed as having an improvement of the WSRS greater than or equal to 2 points in the treated areas with Ial System Duo, while only 20.6% have improved by 2 points in the areas treated with Belotero Basic/Balance). Similar results were found with regard to the clinician evaluation score, using the GAIS: After 3 months, 46.0% of subjects treated with Ial System Duo presented a marked improvement compared to Belotero Basic/Balance (39.7%). The analysis per single subject showed that the side of the face after 3 months with the most noticeable improvement on the WSRS scale was the side treated with Ial System Duo: 14.3% had WSRS scores higher than Belotero Basic/Balance. This result was confirmed after 6 months when 20.3% of the subjects treated with Ial System Duo had scores higher than Belotero Basic/Balance. The global judgment on the subject expressed by the GAIS scale has not favored one product more than another, except after 6 months when for 7 subjects (11.9%) the side treated with Ial System Duo was again preferred. The observed increased frequency of ecchymosis between the Ial System Duo treatment compared to the Belotero treatment, albeit not significant, indeed requires further research.

Analysis of facial skin thickness has been previously investigated with in vitro histometric measurements, or by in vivo modalities with the aid of the Harpenden caliper, micrometer screw or radiographic technology [22], showing a variability according to different ethnic groups and ages. However for this study's purposes, it was more important to evaluate the variation of skin thickness in the nasolabial folds treated with Belotero Basic/Balance or Ial System Duo fillers than to establish an absolute value of the soft tissue thickness of the study population. The subjective evaluation of the treatment is an important limitation of this study. Ideally, it should be replaced by a more objective methodology. Future studies using high-resolution 3D imaging systems would allow for a more accurate and objective evaluation.

Diagnostic ultrasound (US) is a useful tool for noninvasive imaging of the skin and subcutaneous tissue [23] and has proven to be a reliable, widely diffuse, useful and economical tool to identify the extension, the site and the amount of the dermal filler injected into the soft tissues [24, 25]. Our study confirms the leading role of US as a diagnostic tool to follow up on filler effects in terms of soft

thickness variation of facial soft tissues, in a reproducible way and not operator dependent, the persistence of the filler effects when measuring and documenting with sonographic images taken at fixed facial points, the skin thickness. It was possible for all subjects to observe and record volume modifications when comparing baseline skin thickness to post-treatment dermal thickness as in increased value, to progressively decrease until the last follow-up measurement.

The permanence time of the two products injected was about 9.5 months (277 vs. 285 days on average) in the nasolabial folds treated, respectively, with Belotero Basic/Balance and Ial System Duo, and was not significant. Subjects were satisfied with both products administered as shown in the numeric scale 1–10. Pain occurred in 92.3% of the areas treated with Belotero Basic/Balance versus 80.0% with Ial System Duo. With regard to the product safety, a case of labyrinthitis and a case of threatened miscarriage were registered; both resolved positively and were clearly not attributable to the administration of the products.

Conclusions

The current study shows that the Ial System Duo achieves long-term permanence in the skin (more than 9 months), similar to Belotero Basic/Balance, and that clinicians seem to prefer results achieved with Ial System Duo. Both Ial System Duo and Belotero Basic/Balance have good safety profiles.

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