 ORIGINAL ARTICLE Journal of Drugs in Dermatology

Effective and Safe Repeated Full-Face Treatments With AbobotulinumtoxinA, Hyaluronic Acid Filler, and Skin Boosting Hyaluronic Acid

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ABSTRACT

Background: It is important to study full-face aesthetic combination treatments to establish well-founded individual treatment plans.
Objective: To evaluate clinical outcome and perception of treatment with either abobotulinumtoxinA (ABO) or hyaluronic acid (HA) filler followed by repeated combined treatment with ABO, HA filler, and Restylane® Skinboosters (RSB).
Methods & Materials: This study was conducted at four sites in Sweden, France, and Brazil and included subjects aged 35-50 years with mild/moderate nasolabial folds and moderate/severe upper facial lines. Monotherapy was ≤125 s.U ABO in at least two upper facial indications with optional touch-up or ≤1 mL HA filler in nasolabial folds/cheeks. At months 6 and 12, both cohorts received ≤125 s.U. ABO in upper facial lines with optional touch-up, ≤2 mL HA filler in nasolabial folds/cheeks (and other facial areas as applicable), and ≤1 mL RSB. Assessments included global facial aesthetic appearance and improvement, first impression, perceived age, wrinkle severity, satisfaction questionnaires, and adverse events.
Results: Repeated full-face treatment with ABO, HA filler, and RSB was associated with better aesthetic outcome and higher levels of satisfaction than treatment with ABO or HA filler alone. However, even modest volumes of HA filler achieved good aesthetic outcomes and high satisfaction. Treatment of several indications was well tolerated.
Conclusion: Aesthetic improvement and subject satisfaction was high and increased with each treatment. All treatments were well tolerated. These data may be used as support when establishing individual treatment plans.

J Drugs Dermatol. 2019;18(7):682-689.

INTRODUCTION

Aesthetic treatment with either botulinum toxin type A (BoNT-A) or hyaluronic acid (HA) filler(s) is generally more common than combination treatment[1-4]; approximately one-third of patients receive a combination of injectable treatments.[5]

Upper facial aesthetic indications of BoNT-A include glabellar lines, lateral canthal lines, and horizontal forehead lines.[6-10] The marketing authorization for abobotulinumtoxinA (ABO) includes treatment of hyperfunctional facial lines in Brazil and moderate-to-severe glabellar lines and lateral canthal lines in many European countries including France and Sweden.

HA fillers are most commonly used for aesthetic soft-tissue augmentation of the mid and lower face.[11-16] Restylane® Skinboosters (RSB [Galderma Aesthetics, Sweden])[17-19] are used for skin rejuvenation and improved skin quality.

The objective of this study was to collect data on subjects receiving monotherapy with either ABO or HA filler followed by repeated combination treatment with ABO, HA filler, and RSB to provide guidance to practitioners for individual treatment plans. BoNT-A in up to three upper facial indications has not previously been studied in combination with HA filler and RSB.

METHODS

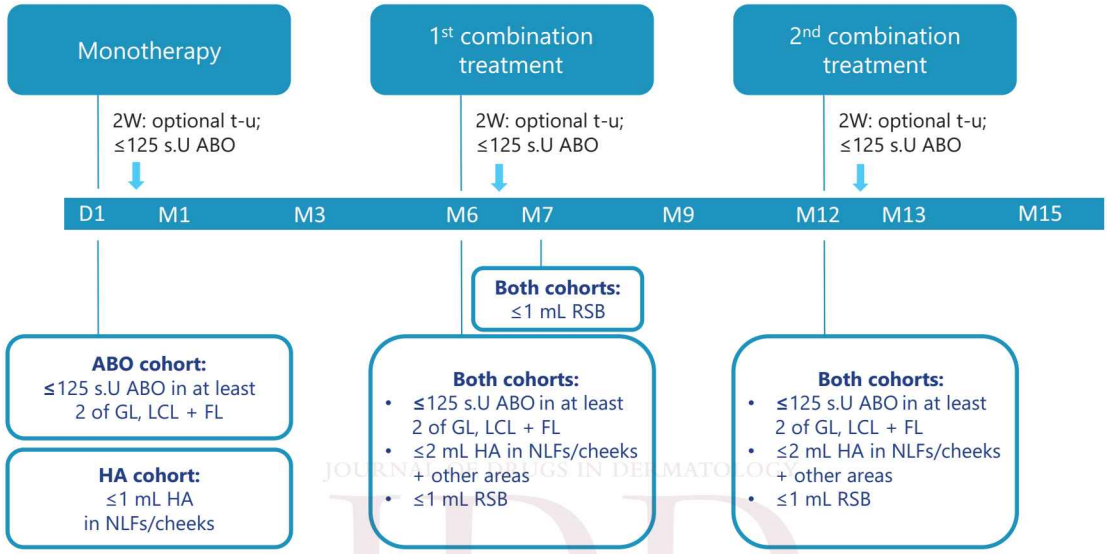
Study Design

This was an 18-month study conducted at four sites in Sweden, France, and Brazil (Figure 1). ABO cohort data up to 6 months have been published.[20] The study protocol was approved by independent Ethics Committees and conformed to the Declaration of Helsinki, Good Clinical Practice, and local regulations.

Eligibility Criteria

Subjects between 35 and 50 years who provided signed in-

FIGURE 1. Study design and treatments. D: Day, M: Month, T-u: Touch-up, W: Weeks.



formed consent and had mild-to-moderate nasolabial folds[21] and moderate-to-severe upper facial lines at maximum contraction[22] were eligible for the study.

Key exclusion criteria included (1) apparent facial sagging, (2) facial procedures eliciting an active dermal response during the preceding 6 months, or BoNT-A, HA or collagen treatment within the preceding 12 months, (3) treatment with non-collagen or non-HA product, or facial surgery, (4) history of dysphagia, neuromuscular junctional disorders, signs of compensatory frontalis muscle activity or eyelid ptosis, known hypersensitivity to BoNT-A, HA, lidocaine hydrochloride or other amide-type anesthetics, or history of autoimmune disease, (5) inflammation, active skin disease, scarred, or damaged facial skin.

Treatment Procedure

Injections were performed in accordance with the Instructions for Use (HA fillers and RSB) and Summary of Product Characteristics (ABO) that were valid at the time. Local anesthesia was used by decision of the Investigators.

Monotherapy

ABO cohort: Subjects received up to 125 s.U ABO (Azzalure®/Dysport® [Ipsen Biopharm Limited, UK]) intramuscularly in at least two upper facial indications. Recommended doses were 50 s.U in 5 injection points for glabellar lines, 60 s.U (30 s.U/side) in 3 injection points/side for lateral canthal lines, and 20-60 s.U in 4-6 injection points for forehead lines. Optional touch-up was allowed after 2 weeks.

HA cohort: Subjects were injected in nasolabial folds and/or cheeks with ≤1 mL of either OBT™ or NASHA™ fillers (Galderma Aesthetics, Sweden). OBT fillers were Restylane Refyne and/or Restylane Defyne; NASHA fillers were Restylane Lidocaine and/or Restylane Lyft Lidocaine. Needle/cannula and injection method were at the Investigator's discretion. No touch-up was allowed.

Combination Treatment

At months 6 and 12, subjects in both cohorts received up to 125 s.U ABO in at least two upper facial indications, ≤2 mL HA filler in nasolabial folds and/or cheeks (and other areas as applicable), and ≤1 mL Restylane Skinboosters Vital Lidocaine (Europe)/Restylane Skinboosters Vital (Brazil) (Figure 1). Touch-up with ABO was allowed after 2 weeks. Each subject received either OBT or NASHA filler during the study. A second RSB treatment (≤1 mL) was given at month 7.

Efficacy Assessments

Subject photographs were taken one month after each treatment (months 1, 7, and 13). Global aesthetic facial appearance was assessed by blinded evaluators by comparing photographs from months 1 and 7, as well as from month 13.

Subject photographs were also used for blinded evaluation of perceived age and first impression regarding social skills, academic performance, dating success, occupational success, attractiveness, financial success, relationship success, and athletic success, using a 10-grade scale. Overall first impression was the sum of the scores from all categories, with a maximum score of 80.

Aesthetic improvement compared to baseline was assessed using the 5-grade Global Aesthetic Improvement Scale (GAIS).[23]

Blinded evaluators used photographs, while subjects and Investigators did the assessment during the medical appointment. Wrinkle severity assessment of upper facial indications at rest and at maximum contraction was assessed by Investigators using a validated 5-grade scale.[22]

Subject and Investigator satisfaction was assessed using questionnaires.

Safety Assessment

Methods for collecting safety data included assessment of adverse events (AEs).

Statistical Methods

Two analysis populations were defined for the study. The safety population included all subjects who were injected in at least one nasolabial fold/cheek (HA cohort) or one injection point (ABO cohort). The intention-to-treat population was the primary population for efficacy analyses and included all subjects who were injected in both nasolabial folds/cheeks or at least two upper facial indications.

Statistical analyses and the randomization list were done using SAS® version 9.4. Analyses of global facial aesthetic appearance, wrinkle severity, and GAIS were done using 95% confidence intervals. The aim was to show that global facial aesthetic appearance was superior at month 7 compared to month 1, with the 95% confidence interval above 50%. First impression was presented descriptively and using Wilcoxon signed-rank test. Perceived age assessments were presented descriptively and with paired t-test. Satisfaction questionnaires were analyzed descriptively.

RESULTS

Figure 2 shows subject disposition. Sixty-five subjects were randomized to monotherapy with either ABO (n=32) or HA filler (n=33). Table 1 and Table 2 show demographic and baseline data. Injection data are presented in Table 3 to Table 5.

Efficacy

Global Facial Aesthetic Appearance

One month after first combination treatment (month 7), most subjects (ABO cohort: 67%; HA cohort: 94%) had a superior global facial aesthetic appearance compared with after monotherapy (month 1; Figure 3). When the evaluators compared photographs from months 1, 7, and 13, the best result was obtained at month 13 (one month after the second combination treatment [60% of subjects]), followed by first combination treatment (36%) and monotherapy (4%), both cohorts combined (Figure 4).

FIGURE 2. Subject disposition. [a]Nasolabial folds not assessed as mild/moderate (n=3), signs/symptoms of eyelid ptosis/compensatory frontalis muscle activity (n=1), active skin disease, inflammation, or related conditions (n=1). [b]AE (headache). [c]Treatment with prohibited procedure before (n=1) or during (n=1) the study, consent withdrawal (n=1). [d]Safety analyses after first combined treatment did not include subjects withdrawn before month 6. [e]Safety analyses after second combined treatment did not include subjects withdrawn before month 12.

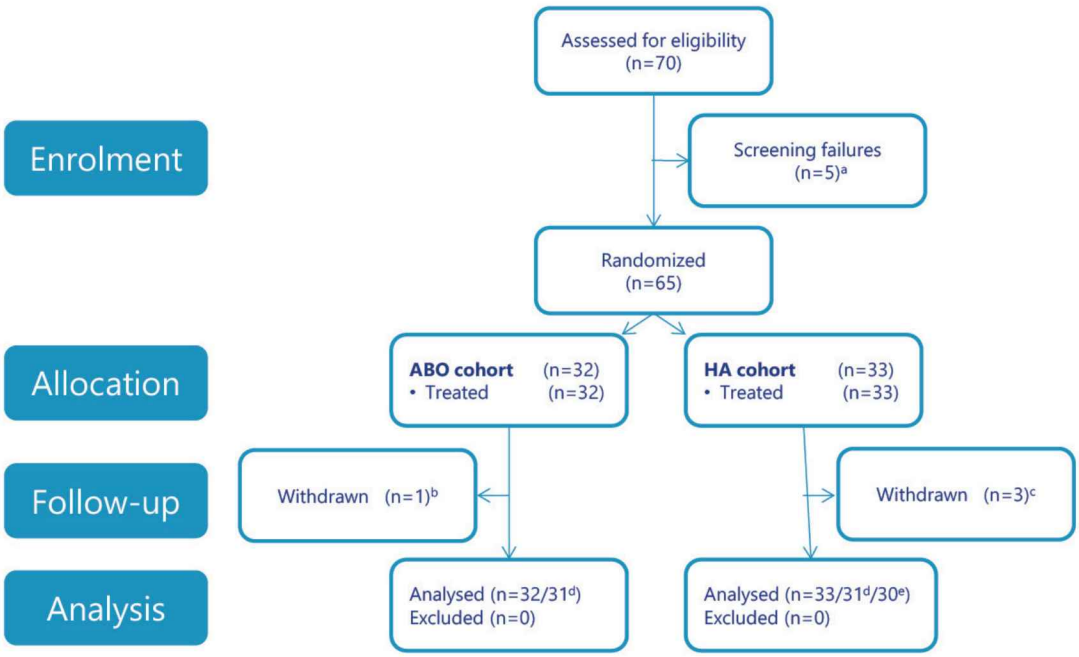


TABLE 1.

Demographic and Baseline Data		
	ABO cohort (N=32)	HA cohort (N=33)
Age, mean (range)	43.9 (35-50)	44.8 (36-50)
Sex, n (%)		
Female	31 (96.9)	32 (97.0)
Male	1 (3.1)	1 (3.0)
Fitzpatrick skin type[24], n (%)		
I	1 (3.1)	1 (3.0)
II	10 (31.3)	8 (24.2)
III	14 (43.8)	19 (57.6)
IV	3 (9.4)	3 (9.1)
V	4 (12.5)	2 (6.1)
VI	--	--

%=(n/N)*100

GAIS

According to blinded evaluators, 70% of subjects in the ABO cohort and 61% in the HA cohort were improved on the GAIS after monotherapy. After first and second combination treatment, 90% and 88% of subjects were improved, respectively, both cohorts combined. GAIS assessments by subjects and Investigators showed improvement for 88-100% of subjects after monotherapy and for 94-100% of subjects after both combination treatments (Figure 5).

Wrinkle Severity

Responders to treatment were defined as subjects with at least 1-grade improvement of upper facial lines. In general, more subjects were responders at maximum contraction than at rest, except forehead lines, for which more subjects were responders at rest than at maximum contraction. A majority of subjects were responders at 1 month after each treatment (month 1, month 7, and month 13). Six months after the treatments (month 6, month 12, and month 18), the effect had generally subsided. However, more subjects were responders at month 12 than at month 6, and also at month 18 than at month 12, except for lateral canthal lines at rest (Figure 6).

First Impression

Overall first impression was similar between monotherapy and combination treatments; mean scores ranged from 42.4 to 44.6 during the study, both cohorts combined.

Perceived Age

Subjects were perceived to look younger after first and second combination treatment compared to after monotherapy, mean difference was -1.3 years (P-0.007) and -2.0 years (P<0.001), respectively, both cohorts combined. Also, most subjects were assessed as looking younger after the second combination treatment than after the first; mean difference was -0.9 years with P=0.043, both cohorts combined.

TABLE 2.

Wrinkle Severity[22] at Baseline					
		ABO cohort (N=32)		HA cohort (N=33)	
		At rest n (%)	At max contraction n (%)	At rest n (%)	At max contraction n (%)
GL	No GL	2 (6.3)	--	1 (3.0)	--
	Mild GL	21 (65.6)	--	21 (63.6)	--
	Moderate GL	8 (25.0)	14 (43.8)	9 (27.3)	15 (45.5)
	Severe GL	1 (3.1)	18 (56.3)	2 (6.1)	18 (54.5)
	Very severe GL	--	--	--	--
LCL	No LCL	2 (6.3)	--	1 (3.0)	--
	Mild LCL	21 (65.6)	--	21 (63.6)	--
	Moderate LCL	8 (25.0)	14 (43.8)	9 (27.3)	15 (45.5)
	Severe LCL	1 (3.1)	18 (56.3)	2 (6.1)	18 (54.5)
	Very severe LCL	--	--	--	--
FL	No FL	2 (6.3)	--	1 (3.0)	--
	Mild FL	21 (65.6)	--	21 (63.6)	--
	Moderate FL	8 (25.0)	14 (43.8)	9 (27.3)	15 (45.5)
	Severe FL	1 (3.1)	18 (56.3)	2 (6.1)	18 (54.5)
	Very severe FL	--	--	--	--

%=(n/N)*100

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines

TABLE 3.

Injection Information Baseline			
	ABO cohort (N=32)		HA cohort (N=33)
ABO dose (s.U), mean (range)			
GL	Baseline (n=32)	47.5 (30.0-58.0)	
	Touch-up (n=11)	16.4 (6.00-26.0)	
LCL	Baseline (n=32)	33.9 (20.0-50.0)	
	Touch-up (n=13)	14.5 (1.50-22.0)	
FL	Baseline (n=27)	29.2 (7.50-60.0)	
	Touch-up (n=4)	10.6 (1.00-20.0)	
HA filler volume mL, mean (range)			
NLFs (n=33)			0.87 (0.40-1.00)
Cheeks (n=9)			0.44 (0.20-0.60)

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines

TABLE 4.

Injection Information: First Combined Treatment (Month 6)				
	ABO cohort (N=31)		HA cohort (N=31)	Both (N=62)
ABO dose (s.U), mean (range)				
GL	Month 6 (n=31[a]/31[b])	49.3 (32.0-64.0)	51.5 (40.0-64.0)	50.4 (32.0-64.0)
	Touch-up (n=12[a]/9[b])	19.6 (6.0-30.0)	30.2 (18.0-50.0)	24.1 (6.0-50.0)
LCL	Month 6 (n=30[a]/31[b])	38.1 (20.0-56.0)	37.7 (24.0-58.0)	37.9 (20.0-58.0)
	Touch-up (n=10[a]/9[b])	17.7 (12.0-30.0)	19.0 (8.0-40.0)	18.3 (8.0-40.0)
FL	Month 6 (n=28[a]/23[b])	28.8 (9.0-54.0)	30.3 (8.0-46.0)	29.5 (8.0-54.0)
	Touch-up (n=6[a]/5[b])	23.0 (10.0-40.0)	23.4 (2.0-40.0)	23.2 (2.0-40.0)
HA filler volume mL, mean (range)				
NLFs (n=31[a]/29[b])		0.71 (0.40-1.30)	0.61 (0.20-1.20)	0.66 (0.20-1.30)
Cheeks (n=24[a]/24[b])		0.77 (0.20-1.30)	0.73 (0.40-1.20)	0.75 (0.20-1.30)
Other[c] (n=29[a]/31[b])		0.67 (0.20-1.60)	0.78 (0.10-2.00)	0.72 (0.10-2.00)
HA filler volume mL, mean (range)				
Month 6 (n=31[a]/31[b])		0.95 (0.50-1.00)	0.95 (0.50-1.00)	0.95 (0.50-1.00)
Month 7 (n=29[a]/31[b])		0.94 (0.50-1.00)	0.97 (0.50-1.00)	0.96 (0.50-1.00)

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines
[a]ABO cohort
[b]HA cohort
[c]Marionette lines, oral commissures, tear troughs, lips, jaw line, nose area, chin, eye area, forehead, perioral lines, mental crease, glabella, mouth corners, pre-jowls.

TABLE 5.

Injection Information: Second Combined Treatment (Month 12)				
	ABO cohort (N=31)		HA cohort (N=29)	Both (N=60)
ABO dose (s.U), mean (range)				
GL	Month 12 (n=30[a]/29[b])	46.0 (25.0-64.0)	49.2 (32.0-58.0)	47.6 (25.0-64.0)
	Touch-up (n=11[a]/7[b])	20.3 (3.0-40.0)	17.1 (10.0-24.0)	19.1 (3.0-40.0)
LCL	Month 12 (n=29[a]/29[b])	41.0 (25.0-60.0)	38.7 (28.0-60.0)	39.8 (25.0-60.0)
	Touch-up (n=9[a]/7[b])	14.6 (3.0-16.0)	21.4 (16.0-30.0)	17.6 (3.0-30.0)
FL	Month 12 (n=25[a]/18[b])	29.1 (10.0-40.0)	28.0 (8.0-40.0)	28.7 (8.0-40.0)
	Touch-up (n=5[a]/5[b])	24.0 (10.0-40.0)	31.6 (18-60.0)	27.8 (10.0-60.0)
HA filler volume mL, mean (range)				
NLFs (n=28[a]/26[b])		0.51 (0.20-1.00)	0.50 (0.20-1.00)	0.51 (0.20-1.00)
Cheeks (n=29[a]/25[b])		0.82 (0.30-1.60)	0.89 (0.30-2.00)	0.85 (0.30-2.00)
Other[c] (n=27[a]/22[b])		0.73 (0.20-1.80)	0.63 (0.20-1.50)	0.69 (0.20-1.80)
RSB volume mL, mean (range)				
Month 12 (n=30[a]/29[b])		0.95 (0.50-1.00)	0.94 (0.40-1.00)	0.94 (0.40-1.00)

GL: Glabellar lines; LCL: Lateral canthal lines; FL: Forehead lines
[a]ABO cohort
[b]HA cohort
[c]Oral commissures, marionette lines, mouth corners, lips, jaw line, chin, tear troughs, perioral lines, forehead, eye area, nose area, glabella, mental crease, pre-jowl, medium cheek, low cheek, mid face.

FIGURE 3. Subjects with superior global facial aesthetic appearance after first combination treatment than after monotherapy. Since the confidence interval was above the predetermined limit (50%; dashed line) in the HA cohort and in both cohorts combined, it was shown that with 95% confidence, the majority of subjects in the underlying populations had a superior facial aesthetic appearance after combination treatment than after monotherapy.

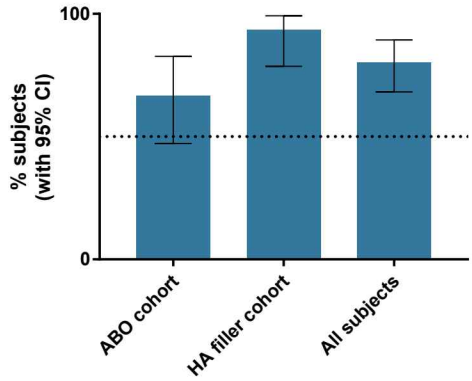
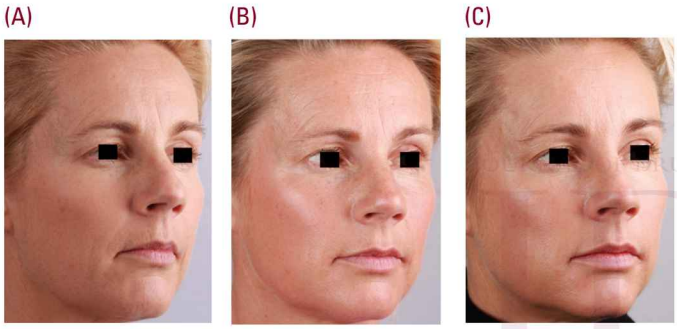


FIGURE 4. Subject photographs. Female subject, age 45, with no previous facial procedures. The subject provided signed consent to that photographs of her face could be used publicly for scientific purposes. (A) One month after monotherapy with: 51 + 8 s.U ABO in glabellar lines, 29 + 10 s.U in lateral canthal lines, and 11 s.U in forehead lines. (B) One month after first combination treatment with: 48 s.U ABO in glabellar lines, 23 s.U in lateral canthal lines, and 11 s.U in forehead lines; 1.90 mL HA filler in nasolabial folds, lips, cheeks, nose tip and pre-mental crease; 1 mL RSB in lower face. (C) One month after second combination treatment with: 50 s.U ABO in glabellar lines and 25 s.U in lateral canthal lines; 2.0 mL HA filler in nasolabial folds, cheeks, lips, tear troughs, pre-mental crease and upper eyelids; 1 mL RSB in upper and lower face.



Subject and Investigator Satisfaction Questionnaire

At baseline, approximately one-third of subjects were satisfied with their facial appearance. The proportion of satisfied subjects increased from baseline/month 1 to month 7 and month 13 (Figure 7a). Satisfaction with skin quality parameters improved from baseline to month 7 and month 13 (Figure 7b). At all timepoints, more than 90% of subjects stated they would do the treatment again and recommend treatment to a friend.

Investigator satisfaction with overall facial aesthetic outcome was high after monotherapy (ABO cohort: 84%; HA cohort: 67%) and after both combination treatments (98-100%, both cohorts combined).

Safety

Monotherapy

Ten subjects (15%, both cohorts combined) had 12 treatment-related AEs of mild or moderate intensity. None were serious; most resolved within 2 weeks. Headache was most common in the ABO cohort, affecting 3 subjects, and injection-site bruising in the HA cohort, also affecting 3 subjects.

First combination treatment

Twenty-eight subjects (45%) had 45 treatment-related AEs of mild or moderate intensity; most resolved within 1 week; none were serious. Injection-site bruising after HA filler or RSB injection was most commonly reported, affecting 13 subjects. Headache was most common in the ABO cohort, reported for 2 subjects.

FIGURE 5. GAIS score improvement compared to baseline. *Somewhat, much, or very much improved.

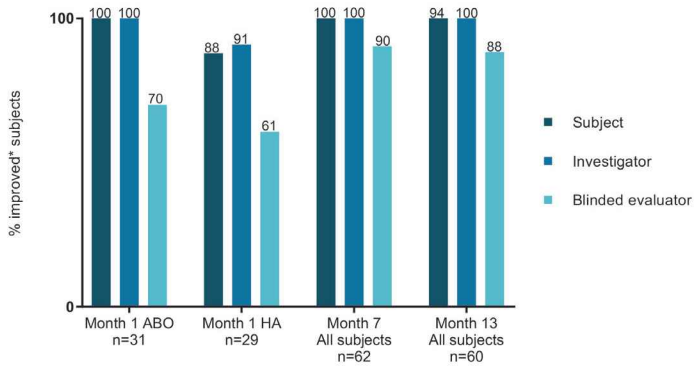


FIGURE 6. Improvement of wrinkle severity of upper facial lines. (A) At rest. (B) At maximum contraction. *Improvement month 18 compared to month 12: $P<0.05$.

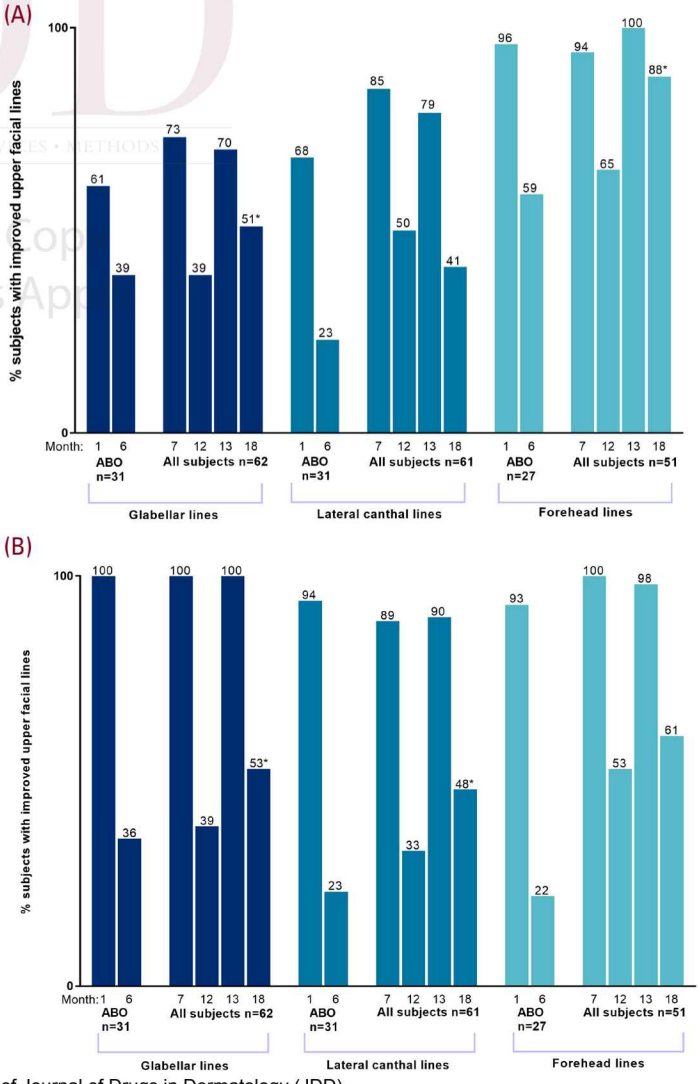
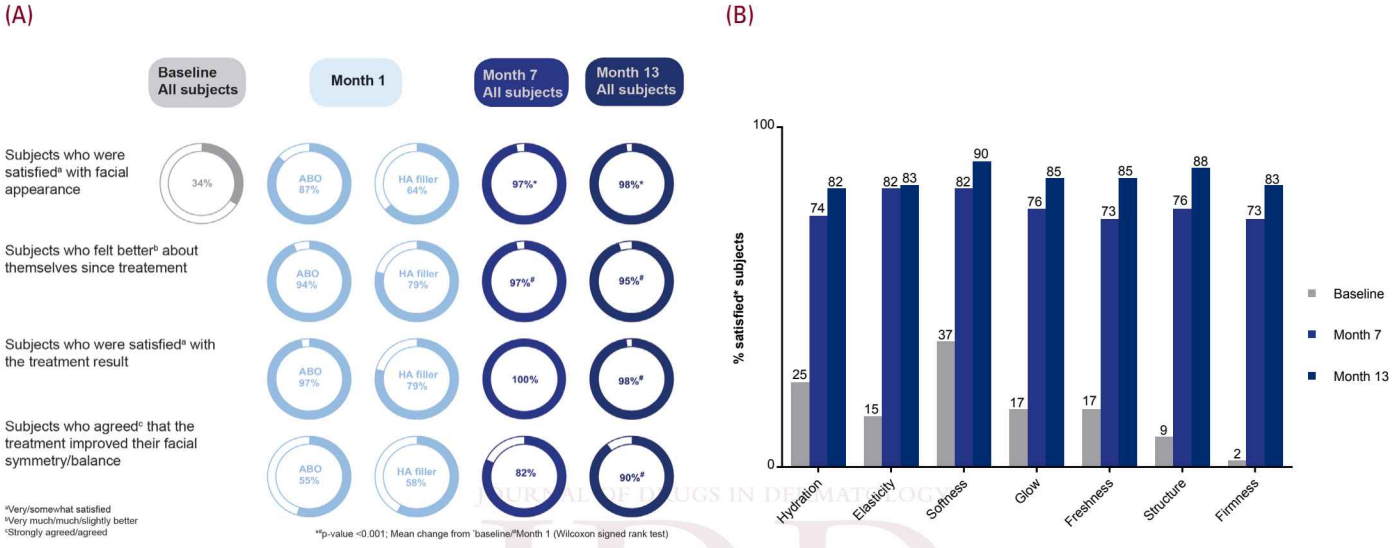


FIGURE 7. Subject satisfaction. *Somewhat/very satisfied.



Second combination treatment

Nineteen subjects (31%) had 36 treatment-related AEs of mild or moderate intensity, most resolved within two weeks; none were serious. All but one treatment-related AE were related to HA filler and/or RSB injection. Injection-site bruising was most commonly reported, affecting 14 subjects.

DISCUSSION

We previously conducted a study where ABO was administered in glabellar lines only (Cartier et al, *accepted for publication Dermatologic Surgery 2019*). The present study was designed similarly, but with ABO administered also in lateral canthal lines and forehead lines.

As in our previous study (Cartier et al, *accepted for publication Dermatologic Surgery 2019*), overall aesthetic outcomes were more beneficial after combination treatment than after monotherapy. The first combination treatment achieved a superior global facial aesthetic appearance over monotherapy in most subjects. Global aesthetic appearance increased further with the second combination treatment. Thus, cumulative treatments over time resulted in better aesthetic outcomes.

Most subjects had GAIS score improvement throughout the study (61-90%) according to blinded evaluators. Subject/Investigator assessments showed improvement for 94-100% of subjects after both combination treatments and after monotherapy with ABO, and for 88-91% of subjects after monotherapy with HA filler.

Combination treatments achieved higher subject and Investigator satisfaction than monotherapy. This is in line with results after combination treatment in another study where higher mean ABO doses and HA filler volumes were injected.[1] It should be noted though, that combination treatments were administered after monotherapy in our study.

The volume of HA filler at monotherapy was restricted to maximum 1 mL to reflect what was considered feasible for the majority of new aesthetic patients. Although the Investigators assessed that most subjects (76%) would have benefited from having additional filler volume, most subjects (64%) in the HA filler cohort were satisfied with the treatment results after monotherapy and Investigators were satisfied with the overall facial aesthetic outcome for 67% of the subjects.

Subject satisfaction with treatment and skin quality improved over time, suggesting that the addition of Skinbooster was effective for improving skin quality, although the assessment could be influenced by all products included in the combination treatments.

The wrinkle severity of upper facial lines improved at least 1-grade 1 month after treatment for a majority of subjects, both at rest and at maximum contraction. Improvement was generally higher at maximum contraction than at rest, except for forehead lines for which improvement at rest was comparatively high, also at six months after treatment. By reducing muscle movement while maintaining some muscle activity, botulinum toxins have potential to reduce also static wrinkles with natural looking results. Wrinkle severity improvement data for glabellar lines were in line with previous results (Cartier et al, *accepted for publication Dermatologic Surgery 2019*).

Both single and combination treatments were well tolerated. Most treatment-related AEs resolved spontaneously, and all were of mild-to-moderate intensity. The most frequently reported AE was injection-site bruising, an anticipated reaction to the study treatments.

This study was limited by the restricted volumes of HA filler, set to reflect a real-life scenario where subjects often have limited resources. Also, since combination treatments were administered in sequence following monotherapy, potential confounding effects on clinical outcome should be considered.

Efficacy results from this and from our previous study (Cartier et al, *accepted for publication Dermatologic Surgery 2019*) underline the benefit of establishing treatment plans based on patients' individual treatment goals.

CONCLUSIONS

Treatment of several indications with HA products and ABO was effective and well tolerated. Combination treatment with ABO, HA filler, and RSB, administered in sequence after monotherapy, resulted in more beneficial aesthetic outcomes than monotherapy alone.

DISCLOSURES

Galderma funded the study and provided the study products. H. Cartier, P. Bergentz, C. Siega, and F. Camozzato have no other conflicts of interest to declare; P. Hedén is a consultant for Allergan, Galderma, and Teoxane; D. Hexsel is a consultant for Galderma and Merz; C. Skoglund, C. Edwartz, and M. Norberg are employed by Galderma; P. Kestemont is a consultant for Allergan, Filorga, Galderma, Teoxane, Universkin, and Vivacy.

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