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ORIGINAL ARTICLE
Cosmetic

Long-term Safety and Effectiveness of Hyaluronic Acid Fillers Correcting Nasolabial Folds in Chinese Patients

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Background: Soft-tissue fillers, specifically hyaluronic acid fillers, can reduce many signs of aging by treating the associated loss of subcutaneous fat and midfacial contour deficiencies. The objective of this study was to investigate whether the effectiveness and safety of Belotero Volume Lidocaine (BVL) compared with Restylane (RES, control) is noninferior in the treatment of severe nasolabial folds (NLFs) in Chinese patients.

Methods: This was a prospective, randomized, controlled, split-face clinical study. Overall, 220 Chinese patients of both sexes with symmetrical NLFs of severe intensity (grade 4) on the Wrinkle Severity Rating Scale (WSRS) were treated with both fillers. Treatment outcomes were assessed by the WSRS, and other scales, at multiple time points up to 18 months postinjection. The co-primary effectiveness outcomes were based on the blinded evaluator ratings of NLFs according to the WSRS scale after 6 and 12 months. Adverse events were assessed during the whole study and patients' pain sensation at three time points after injection.

Results: Noninferiority of BVL versus control based on the WSRS was demonstrated at month 6 and month 12. Response rates were slightly higher for BVL than control at all time points, and BVL had a sustained effect until month 18. Pain sensation scores were significantly lower for BVL compared with control. The incidence rates of treatment-related AEs were low and very similar for both treatments.

Conclusions: This study demonstrates that BVL is a safe, long-lasting, and effective treatment to correct severe NLFs in Chinese patients while being noninferior to the control device. *(Plast Reconstr Surg Glob Open 2023; 11:e5423; doi: 10.1097/GOX.0000000000005423; Published online 20 November 2023.)*

INTRODUCTION

The aging process is a complex interplay of intrinsic and extrinsic factors across multiple layers of the face.[1]

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Received for publication May 25, 2023; accepted October 5, 2023.

DOI: 10.1097/GOX.0000000000005423

Facial aging is characterized by a combination of cutaneous alterations, including transverse forehead lines that can be accompanied by lowering of the eyebrows, increased prominence of the nasolabial folds (NLFs), and vertical rhytids in the perioral area.[2] Many of the signs of aging are due to the loss of subcutaneous fat, and thus, the use of soft-tissue fillers can help to create a more youthful appearance.[3] Among these, hyaluronic acid (HA) fillers are most commonly used due to their good performance and favorable safety profile.[4,5] To prevent the rapid degradation of HA and to prolong its persistence in the skin, various cross-linked HAs have been synthesized in the last two decades. The various HA preparations differ in molecule length and number of cross-links.

Belotero Volume Lidocaine (BVL) is a highly cross-linked HA that uses Cohesive Polydensified Matrix

Disclosure statements are at the end of this article, following the correspondence information.

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

technology to form a gel with tailored plasticity to lift deeper folds and volumize facial skin areas. It has a sodium hyaluronate gel content of 26 mg/mL of nonanimal origin in a physiological phosphate buffer and contains 0.3% of lidocaine hydrochloride.

Previous studies have shown BVL to be a safe and effective treatment in multiple facial indications.[6] However, there is little information existing on the clinical performance and safety of BVL in Chinese patients. Therefore, this clinical study evaluated the safety and effectiveness of BVL in comparison with Restylane (RES, control). RES is a viscous modified sodium hyaluronate gel (20 mg/mL) of nonanimal origin and a well-established HA filler in China, approved for the correction of NLFs.[6–8] A split-face study design was used to assess the effectiveness and safety of BVL and control and to investigate whether BVL is noninferior to control at 6 and 12 months post NLF treatment. The study design was comparable with previously conducted HA dermal filler studies in China.[9–12] In addition, the study allowed the first collection of safety data for the BVL product in Chinese patients. Only safety data on Belotero Balance Lidocaine (Merz Aesthetics), a China approved HA filler of the Belotero product family featuring Cohesive Polydensified Matrix technology but different to BVL in HA content and rheological properties, have been obtained previously.[12] This is important as Asian (Chinese) patients have unique, natural features compared with White patients, arising from differences in skin pathophysiology, mechanisms of aging, and unique facial structures between the ethnicities.[13]

Takeaways

Question: Is Belotero Volume Lidocaine (BVL) noninferior to the control (Restylane) for correction of severe nasolabial folds (NLFs) in Chinese patients?

Findings: This prospective, randomized controlled clinical study included 220 Chinese patients with severe NLFs who received BVL on one side and the control on the other. Response rates (according to Wrinkle Severity Rating Scale) at months 6 and 12 were similar for both products, demonstrating noninferiority of BVL.

Meaning: BVL is noninferior to the control. Both fillers are similarly effective and well-tolerated in Chinese patients.

METHODS

Study Design

This was a prospective, multicenter, randomized, subject- and evaluator-blind, controlled, split-face clinical study. Overall, 220 Chinese patients of both sexes with symmetrical NLFs of severe intensity (grade 4) on the validated Wrinkle Severity Rating Scale (WSRS) were treated with both fillers. The randomization and allocation of the fillers to the side of the face was performed at baseline. The patients were followed up for 18 months.

The study was conducted at five study sites in accordance with EN ISO 14155/Chinese Good Clinical Practice, the Declaration of Helsinki, and local Chinese requirements. Regulatory authorities were notified and consulted as required. The study was approved by the ethics committees of the five participating hospitals [approval number of leading site (Shanghai Ninth People's Hospital): 沪九院伦审 2017-33].

Subject Selection

Patients of at least 18 years of age (upper age limit 75 years) with symmetrical NLFs (grade 4 on the WSRS) who desired correction of both NLFs, gave informed consent, understood the study procedures, and accepted the obligation not to receive any other procedures were included. Women of childbearing potential were required to use a highly effective method of birth control. Subjects were excluded if they had surgery, a permanent surgical implant, or a scar in either NLF. If a subject had previously been treated with a dermal filler in the NLF, they could be excluded, depending on the type of filler and when it was injected. Further, subjects who had recently received or planned to receive facial dermal therapies (eg, toxin treatment, laser treatment, microdermabrasion) were excluded. Subjects with medical conditions with the potential to interfere with the study or increase the risk of adverse events (AEs) (eg, known hypersensitivity to one of the components, history of severe allergies, hyper- or hypopigmentation) could not participate. In addition, nursing mothers and pregnant women were excluded. (**See table, Supplemental Digital Content 1**, which provides a list of inclusion and exclusion criteria. **http://links.lww.com/PRSGO/C882**.)

Treatment

Patients were randomized 1:1 to receive BVL (Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) in the left NLF and RES (Galderma, QMed AB, Uppsala, Sweden) in the right NLF, or RES in the left NLF and BVL in the right NLF (for further information on the randomization procedure refer to **Supplemental Digital Content 2**). BVL was injected using co-packaged 27G half-inch or 30G half-inch needles based on the investigator's choice, and the control was always injected using the co-packaged 30G half-inch needle. For injection-related pain management, subjects were offered ice or topical anesthetic cream. Per protocol, the same pain management treatment (none, ice, or topical anesthetic) had to be applied in the same volume on both NLFs. All China-approved international HA dermal fillers did not contain lidocaine at the time of the study. Therefore, BVL was compared against RES without lidocaine in the clinical investigation. (**See document, Supplemental Digital Content 2**, which shows the randomization procedure and additional statistical methods. **http://links.lww.com/PRSGO/C883**.)

Objectives and Assessments

The co-primary objectives of this study were to assess whether the effectiveness of BVL injected into severe

NLFs in Chinese patients is noninferior after 6 and 12 months compared with control, as assessed via the WSRS. The WSRS is a five-point numeric scale [ranging from 1 (absent) to 5 (extreme)] developed to objectively quantify the severity of lines and folds such as NLFs. The WSRS assessments were performed separately for the left and the right NLF by a blinded evaluator who had no access to subject files and who was blinded to the randomized treatment. At all visits, the same blinded evaluator performed the assessment to ensure consistency throughout the investigation.

Secondary objectives were to evaluate the noninferiority of BVL compared with control for injection in severe NLFs after 1, 3, 9, 15, and 18 months according to the WSRS, to assess noninferiority of BVL at 12 months compared with control at 6 months according to the WSRS, and to show a reduced pain sensation on the BVL side at baseline compared with control-treated side. Pain after injection was assessed by the subject for each side separately using an 11-point pain scale ranging from 0 (no pain) to 10 (extreme pain).

Other effectiveness variables included Global Aesthetic Improvement Scale (GAIS) scores [ranging from +3 (very much improved) to −3 (very much worse)], as assessed by the treating investigator, and Global Impression of Change Scale (GICS) scores [ranging from +3 (very much improved) to −3 (very much worse)], as assessed by the subject at months 1, 3, 6, 9, 12, 15, and 18.

Statistical Analyses

Statistical analyses were performed using SAS (version 9.4). Effectiveness analyses were based primarily on the per protocol set (PPS). The two co-primary effectiveness variables were analyzed using a repeated measures model (RMM) for binomial distributions, with the response rate on the WSRS as a dependent variable, and treatment, pooled investigational site, sex, and age group as independent variables. For the difference in proportions, a two-sided 95% confidence interval (CI) was calculated. To test the noninferiority of BVL compared with the control for the two co-primary effectiveness variables, a prespecified hierarchical testing procedure was applied. In both tests, the prespecified noninferiority margin was 10%. In a first step, noninferiority of BVL was tested at month 12. If noninferiority could be concluded for month 12, noninferiority was to be tested for month 6 in a second step. Noninferiority of BVL compared with control for month 6 or month 12 was concluded if the two-sided 95% CI for the difference in the proportion of responders lay completely within the predefined acceptance region for noninferiority (ie, above −10%).

All safety analyses were performed on the safety evaluation set (SES) and according to the actual treatment. For details on the definition of WSRS response, determination of the sample size, analysis methods for secondary effectiveness endpoints, and on safety analyses (**See Supplemental Digital Content 2, http://links.lww.com/PRSGO/C883**.).

RESULTS

Subject Disposition and Treatment Characteristics

At five investigational sites, 241 Chinese patients were screened in total. Of these, 220 subjects were randomized. Among those, 111 subjects were randomized to receive BVL in the left NLF and the control in the right NLF, and 109 subjects were randomized to receive the control in the left NLF and BVL in the right NLF. Overall, 201 subjects (91.4%) completed the study after 18 months, and 19 subjects (8.6%) discontinued the study prematurely. BVL was applied to all 220 randomized subjects via deep-dermal injection with the linear retrotracing technique. The control was applied to 219 subjects via mid-dermal injection with the linear threading technique and to one subject with the serial punctual injection technique. The linear retrotracing and linear threading techniques consist of inserting the needle to almost its entire length, keeping it closely parallel to the skin's plane and injecting the gel while slowly withdrawing it. Hence, a tunnel of filler is injected to efface the wrinkle. This technique is commonly used to address isolated creases such as NLFs as it means less pressure to the syringe and allows the threads of gel to be deposited more easily in the tissues.

The average injection volume of BVL was 1.08 ± 0.33 mL and the average volume of the control was 0.97 ± 0.27 mL. No overfilling was reported. The PPS included 206 subjects (Fig. 1).

All subjects in the PPS were Chinese, and most of them (91.3%) were female individuals. The mean age was 47.7 years (Table 1). For further details, **see table, Supplemental Digital Content 3**, which shows demographics and baseline characteristics. **http://links.lww.com/PRSGO/C884**.

Effectiveness

WSRS Response Rates at Months 6 and 12

Response rates at months 6 and 12 are shown in Table 2. At month 6, the WSRS response rates (response defined as ≥1-point improvement on the WSRS compared with screening) and associated 95% Pearson-Clopper CIs in the PPS were 89.9% (84.9%–93.8%) on the BVL-treated side and 85.4% (79.7%–90.0%) on the control side. The unadjusted difference in response rates was 4.5%.

At month 12, the WSRS response rates and associated 95% Pearson-Clopper CIs in the PPS were 80.2% (73.9%–85.6%) on the BVL-treated side and 75.0% (68.3%–81.0%) on the control side. The unadjusted difference in response rates was 5.2%.

Based on the RMM, the adjusted difference between the BVL and control sides at month 12 was 3.6%. The two-sided 95% CI (−1.1% to 8.3%) lay completely in the acceptance region for noninferiority (−10%, ∞), with the lower limit of the 95% CI being very close to zero. Similarly, the adjusted difference between the BVL and control sides at month 6 was 4.5% with a two-sided 95% CI (0.8%–8.1%). Noninferiority of BVL compared with control in the treatment of severe NLFs at month 6 and month 12 was thus demonstrated.

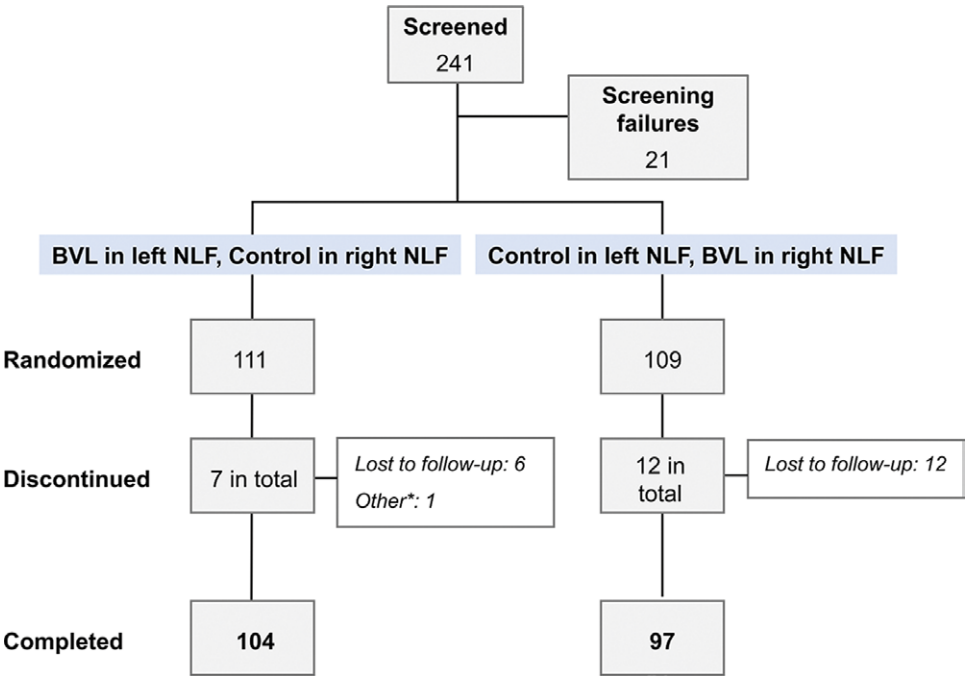

Fig. 1. Flow chart of patients included in the study. *One patient refused to visit the hospital for the final visit due to the COVID-19 pandemic.

Table 1. Demographics and Baseline Characteristics

	PPS Total (N = 206)
Sex, n (%)	
Male	18 (8.7)
Female	188 (91.3)
Age (y)	
Mean ± SD	47.7 ± 9.15
Age category, n (%)	
<45 years	72 (35.0)
45-54 years	88 (42.7)
>54 years	46 (22.3)
Race, n (%)	
Asian (Chinese)	206 (100.0)
BMI (kg/m²)	
Mean ± SD	22.59 ± 2.858

BMI, body mass index; N, number of patients in population; n, number of patients with nonmissing observation.

WSRS Response Rates at Months 1, 3, 9, 15, and 18

The unadjusted differences in response rates between the two treatments at months 1, 3, 9, 15, and 18 ranged between 0.5% and 8.3% (Table 3) and were thus all greater than zero, similar to the unadjusted differences in response rates observed at month 6 and month 12 (Fig. 2). A positive difference indicated a better response rate for BVL than the control. Moreover, at all visits (months 1, 3, 6, 9, 12, 15, 18), the lower limits of the associated two-sided 95% CIs ranged between −2.4% (month 1) and 3.5% (month 15). These findings consistently indicate that BVL is noninferior to control in the treatment of severe NLFs over the entire 18-month follow-up period. Photographs of the treatment results in female and male patients up to 18 months are shown in Figure 3. Detailed information on WSRS ratings of patients presented in Figure 3 can be found in Supplemental Digital

Table 2. Response Rates and Differences in Response Rates on the WSRS (≥1-point Improvement) at Months 6 and 12, as Assessed by a Blinded Evaluator – PPS

	BVL (N = 206)		Control (N = 206)		Unadjusted Difference in Response Rates*	Adjusted Difference BVL-control in Response Rates
Month	n/ Nobs	% [95% CI]†	n/ Nobs	% [95% CI]†	% [95% CI]	% [95% CI]
6	179/199	89.9 [84.9–93.8]	170/199	85.4 [79.7–90.0]	4.5 [0.8–8.3]	4.5 [0.8–8.1]‡
12	154/192	80.2 [73.9–85.6]	144/192	75.0 [68.3–81.0]	5.2 [-0.1 to 10.6]	3.6 [-1.1 to 8.3]§

*Estimates based on LSMEANS from an RMM including treatment as the only independent variable.
†Two-sided 95% Pearson-Clopper CI for the response rate.
‡Estimates based on LSMEANS from an RMM including treatment, study site and sex as independent variables.
§Estimates based on LSMEANS from a RMM including treatment, pooled investigational site, sex and age group as independent variables.
LSMEANS, least-squares means; N, number of patients in population; n, number of patients with response; Nobs, total number of patients with WSRS value for the respectively treated side of the face at respective visit.

Table 3. Response Rates and Differences in Response Rates on the WSRS (≥1-point Improvement) Over Time (Secondary Endpoints), as Assessed by a Blinded Evaluator – PPS (OC)

	BVL (N = 206)		Control (N = 206)		Unadjusted Difference in Response Rates‡
Visit*	n/Nobs	% [95% CI]†	n/Nobs	% [95% CI]†	% [95% CI]
Month 1	194/205	94.6 [90.6, 97.3]	193/205	94.1 [90.0, 96.9]	0.5 [−2.4, 3.4]
Month 3	187/202	92.6 [88.0, 95.8]	184/202	91.1 [86.3, 94.6]	1.5 [−0.2, 3.2]
Month 9	170/197	86.3 [80.7, 90.8]	164/197	83.2 [77.3, 88.2]	3.0 [−1.2, 7.2]
Month 15	146/193	75.6 [69.0, 81.5]	130/193	67.4 [60.3, 73.9]	8.3 [3.5, 13.1]
Month 18	133/199	66.8 [59.8, 73.3]	125/199	62.8 [55.7, 69.5]	4.0 [−1.9, 9.9]

*Results for months 6 and 12 (primary endpoints) are provided in Table 2, above.
†Two-sided 95% Pearson-Clopper CI for the response rates.
‡Estimates based on LSMEANS from an RMM, including treatment as the only independent variable.
LSMEANS, least-squares means; N, number of patients in population; n, number of patients with response; Nobs, total number of patients with WSRS value for the respectively treated side of the face at the respective visit; PPS, per protocol set; RMM, repeated measures model; WSRS, Wrinkle Severity Rating Scale.

Content 4. **(See table, Supplemental Digital Content 4,** which shows Wrinkle Severity Rating Scale values. **http://links.lww.com/PRSGO/C885**.)

WSRS Response Rates of BVL at 12 Months versus Control at 6 Months

The unadjusted difference in response rates between the two treatments and associated two-sided 95% CI was −3.8% (−9.4% to 1.9%) in the PPS. The lower CI limit was greater than −10%, thus indicating noninferiority.

Pain Sensation

The sum in pain sensation over all three time points (immediately, 15 minutes and 30 minutes after injection) was assessed from 0 points (no pain at all three time points) and 30 points (extreme pain at all three time points). In the PPS, the mean sum in pain sensation was more than 50% lower for the lidocaine containing BVL-treated side (3.5 points) compared with the nonlidocaine control side (8.2 points). The mean within-subject difference in sum in pain sensation between the two treatments was -4.7 points (95% CI = −5.2 to −4.2). A two-sided paired *t* test indicated a statistically significantly reduced sum in pain sensation ($P < 0.0001$) at the BVL-treated side compared with the control side. This was independent of the type of injection pain management applied ($P < 0.05$ for each of the three subgroups; Table 4).

Other Effectiveness Endpoints

For both treatments, the response rates determined by the treating investigators (GAIS score ≥ 1, at least "improved") were greater than 78% at months 1, 3, 6, and 9. At month 12, response rates were 70.1% for BVL and 62.4% for the control, and at month 18 they were 62.8% and 52.3%, respectively (Fig. 4A).

GICS response rates, as evaluated by the patients (GICS score ≥ 1, at least "improved"), showed a similar trend to the GAIS, with greater than 72% for both treatments at months 1, 3, 6 and 9. At month 12, response rates were 62.4% for BVL and 59.8% for the control, and at month 18 they were 58.3% and 49.2%, respectively (Fig. 4B).

Safety

Among the 220 patients in the SES, who were all exposed to both treatments, 124 patients (56.4%) reported at least one treatment-emergent adverse event (TEAE). Four patients (1.8%) reported at least one TEAE affecting the local injection sites treated with BVL, and two patients (0.9%) reported at least one TEAE affecting the local injection site treated with control. Three patients (1.4%) reported at least one treatment-related TEAE. This included two local injection site treatment-related TEAEs for BVL in two patients (0.9%) (injection site bruising and nasal pruritus) and one local injection site treatment-related TEAE for control in one patient (0.5%) (therapeutic embolization; Table 5). Furthermore, two treatment-related TEAEs occurring outside either of the two local injection sites in one subject (0.5%; abscess and erythema) were reported. Due to the split-face study design, it was not possible to assess if these TEAEs were related to BVL or control. All treatment-related

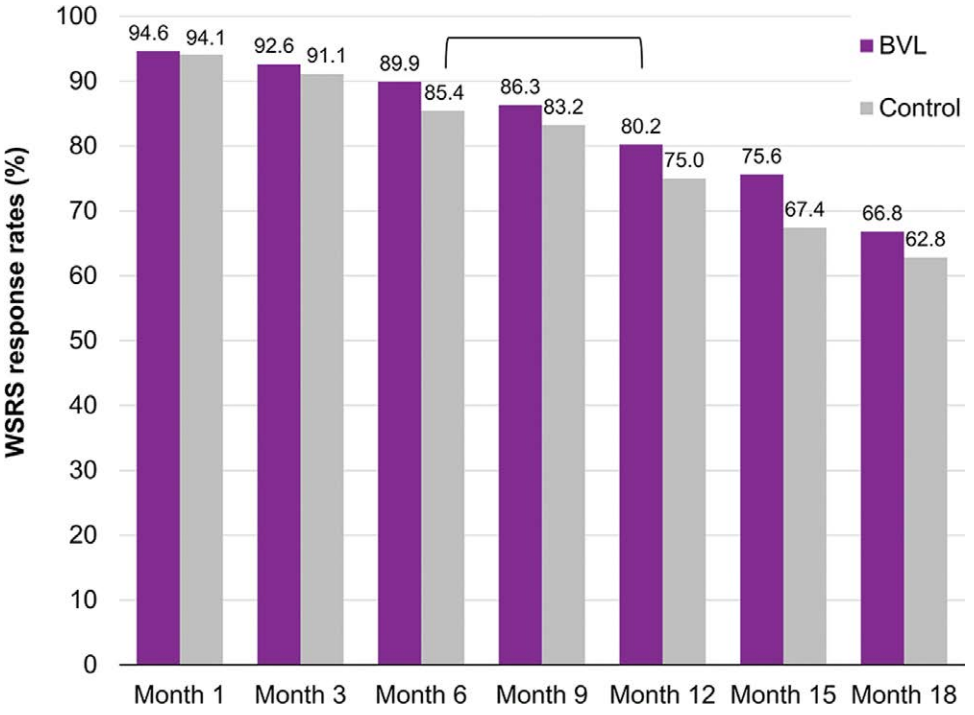

Fig. 2. Response rates (≥1-point improvement) according to the WSRS over time (PPS). The numbers of patients with WSRS results for the respectively treated side of the face at the respective visit time points are provided in Tables 2 and 3. The bracket shows the comparison of WSRS response rates of BVL at 12 months vs control at 6 months.

TEAEs were of mild or moderate intensity and were recovered before month 18. Eleven subjects (5.0%) reported at least one serious TEAE. None of the serious TEAEs affected either of the two local injection sites, and no serious TEAE was related to treatment. No TEAE leading to discontinuation and no TEAE leading to death occurred. In addition, no allergic reactions and no overfilling were reported.

DISCUSSION

The aim of this study was to provide data for the Chinese population on the effectiveness and safety of BVL in the treatment of severe NLFs and to show noninferiority to the established filler RES. Demographic data were comparable with previously conducted studies in Chinese patients for the treatment of NLFs with HA dermal fillers.[9–12]

BVL treatment was statistically noninferior to control at month 6 and month 12, and thus, the primary objective was successfully met. Moreover, WSRS responder rates as assessed by the blinded evaluators were numerically higher for subjects treated with BVL at all other time points over the 18-month follow-up period. The observed response rates were in line with previous studies conducted for HA dermal fillers in the NLF indication in China with similar effectiveness endpoints for noninferiority.[10,14] Further published studies comparing HA fillers with and without lidocaine for NLF correction suggested comparable effectiveness in terms of reducing the severity of wrinkles.[15–17]

In line with the WSRS response rates, the GAIS response rates assessed by the investigators and the GICS response rates assessed by the patients were numerically higher for BVL compared with control. The comparison was particularly noteworthy at month 18, where the GAIS and GICS response rates were much higher for BVL and were more comparable to the control at month 12. This shows that BVL resulted in desirable aesthetic perception of patients and treating investigators. Those results are consistent with data of an earlier split-face study comparing Modélis Shape (former name of Belotero Volume) versus Juvéderm Voluma in cheek treatment. In this study, a long-term duration of the volumizing effect was maintained up to month 18, and grades on the GAIS scale were higher for Belotero Volume compared with Juvéderm Voluma.[18] In a similar study investigating Juvéderm Volift (incorporating lidocaine) for use in NLFs in Chinese patients, the GAIS score and pain sensation score of Volift were comparable to BVL in the present study.[19]

In contrast to control, BVL contains 0.3% of lidocaine HCl added as an ancillary substance to reduce patients' pain during injection. HA fillers containing the local anesthetic lidocaine are designed to reduce injection pain and procedural time by combining anesthesia and treatment, as well as to promote recovery with minimal additional risk.[15,20,21] The mean sum in pain sensation over the three assessment time points from injections with BVL was on average more than 50% lower than pain from injections with control. Similar findings were revealed in previous studies comparing HA fillers with and without lidocaine for NLF correction.[15,16,22]

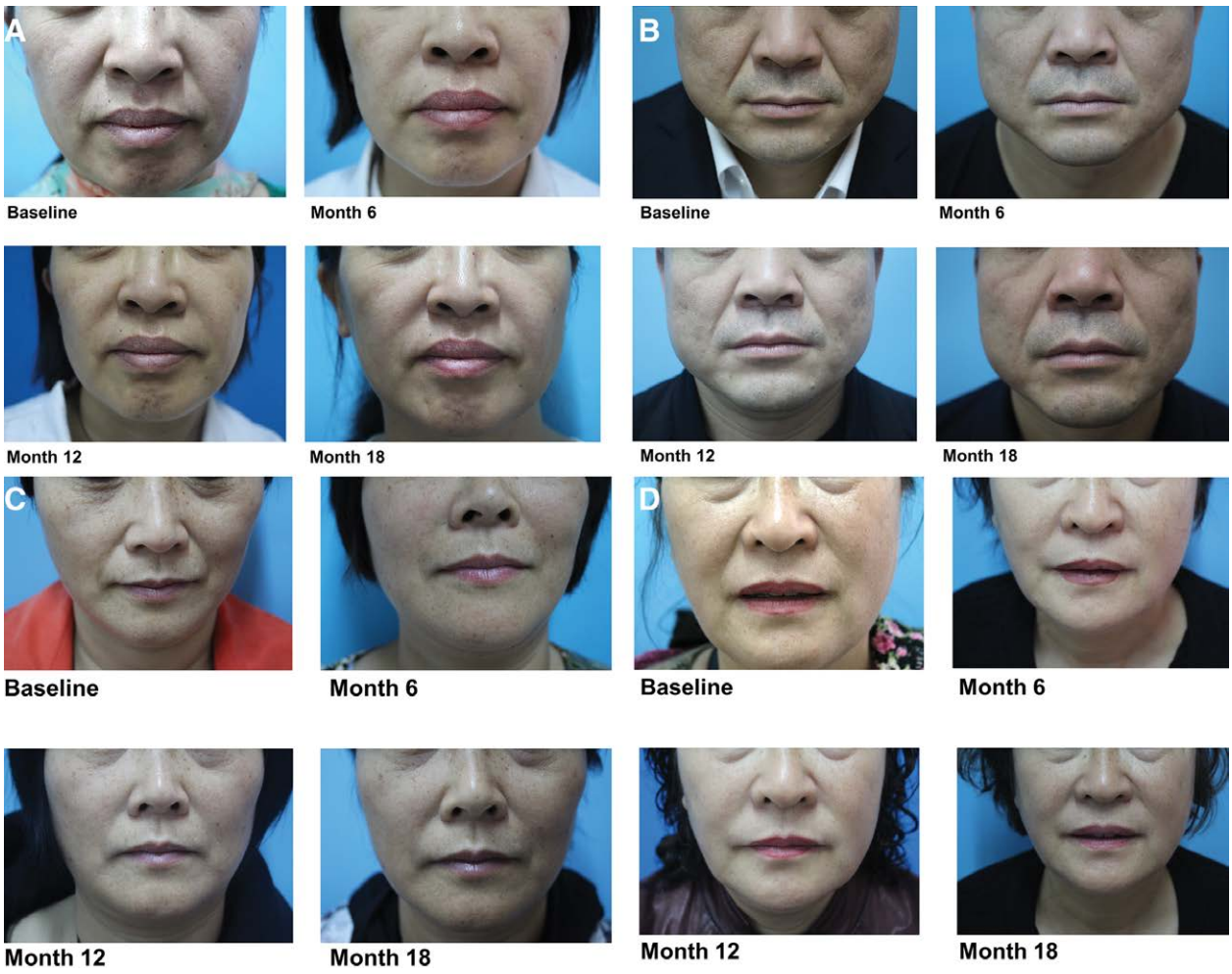

Fig. 3. Results of representative study patients, from baseline (pretreatment) to month 18. A, Female patient, 49 years old, who was treated with BVL in the left NLF and with control in the right NLF at baseline. B, Male patient, 41 years old, who was treated with BVL in the right NLF and with control in the left NLF at baseline. C, Female patient, 51 years old, who was treated with BVL in the right NLF and with control in the left NLF at baseline. D, Female patient, 56 years old, who was treated with BVL in the right NLF and with control in the left NLF at baseline.

Table 4. Mean Sum Score of Pain Sensation and Mean Difference in Sum of Pain Sensation, by Treatment and Type of Injection Site Pain Management – PPS

	BVL (N = 206)		Control (N = 206)		Difference (%)	
Type of Injection Pain Management*	n	Mean ± SD	n	Mean ± SD	Mean [95% CI]†	P‡
Total	206	3.5 ± 3.22	206	8.2 ± 4.59	−4.7 [−5.2 to −4.2]	<0.0001
None	132	3.5 ± 3.12	132	8.6 ± 4.87	−5.1 [−5.8 to −4.4]	<0.0001
Ice	58	3.6 ± 3.49	58	7.7 ± 3.72	−4.2 [−5.0 to −3.4]	<0.0001
Topical anesthetic cream	16	3.3 ± 3.24	16	6.4 ± 4.73	−3.1 [−5.5 to −0.6]	0.0183

Pain was assessed on an 11-point scale, ranging from 0 (no pain) to 10 (extreme pain). As pain was assessed at three time points (immediately, 15 minutes, and 30 minutes after injection), a maximum sum score of 30 was possible.
*The same treatment was applied for both injection sites.
†95% CI as two-sided 95% for difference in paired means between the two treatments.
‡*P* value for a two-sided paired *t* test for the mean difference in sum in pain sensation between the two treatments.
N, number of patients in population; n, number of patients with nonmissing observation; PPS, per protocol set.

In terms of safety, the incidence rates of treatment-related TEAEs and local injection site TEAEs were low and very similar for both treatments. All local injection site TEAEs and all treatment-related TEAEs were recovered by month 18. These findings are in line with a systematic review and meta-analysis suggesting that lidocaine containing HA fillers displayed similar rates of AEs when compared with HA alone, with most adverse reactions being mild.[23]

As a limitation of the split-face study design, it was not possible to assess if treatment-related TEAEs occurring

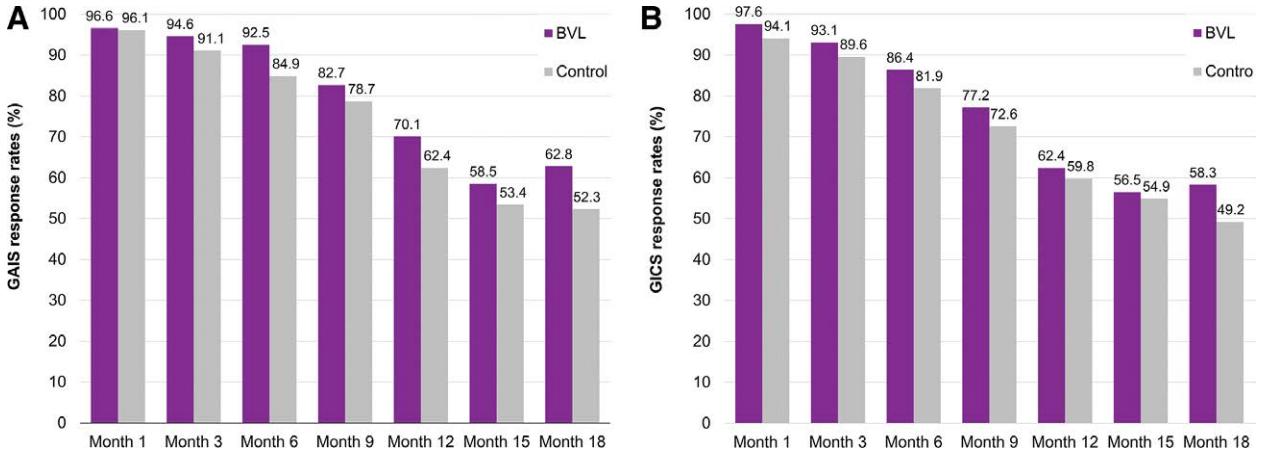

Fig. 4. Response rates with score of at least "improved" over time (PPS) as assessed by (A) GAIS (investigator) and (B) GICS (patient).

Table 5. Summary of Patients with Treatment-related TEAEs and Number of Treatment-related TEAEs (SES)

MedDRA System Organ Class Preferred Term	Local Injection Site, BVL		Local Injection Site, Control		Nonlocal Injection Site	
	n (%)	m	n (%)	m	N* (%)	m
Patients with at least one related TEAE, number of related TEAEs	2 (0.9)	2	1 (0.5)	1	1 (0.5)	2
General disorders and administration site conditions	1 (0.5)	1	0	0	0	0
Injection site bruising	1 (0.5)	1	0	0	0	0
Infections and infestations	0	0	0	0	1 (0.5)	1
Abscess	0	0	0	0	1 (0.5)	1
Respiratory, thoracic and mediastinal disorders	1 (0.5)	1	0	0	0	0
Nasal pruritus	1 (0.5)	1	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0	1 (0.5)	1
Erythema	0	0	0	0	1 (0.5)	1
Surgical and medical procedures	0	0	1 (0.5)	1	0	0
Therapeutic embolization	0	0	1 (0.5)	1	0	0

*Patients with TEAEs not affecting either of the two local injection sites.
m, number of TEAEs; MedDRA, Medical Dictionary for Regulatory Activities, n, number of patients with at least one respective TEAE.

outside either of the two local injection sites were related to BVL or control.

CONCLUSIONS

In conclusion, this clinical study clearly demonstrated noninferiority of BVL compared with control in correcting severe NLFs in Chinese patients for up to 18 months. BVL showed a safety profile comparable to the control, and injection-related pain was significantly lower for BVL than for control, independently of the applied pain management regime.

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DISCLOSURES

Matthias Hofmann is an employee of Merz Aesthetics GmbH, Frankfurt am Main, Germany and a former employee of Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany. Gudrun Klein is an employee of Merz Therapeutics GmbH, Frankfurt am Main, Germany and a former employee of Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany. Qingfeng Li does not have any personal financial relationships with Merz Pharmaceuticals GmbH. All the other authors have no financial interests to declare in relation to the content of this article. This study was supported by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.

ACKNOWLEDGMENTS

The authors thank the Chinese study sites in Shanghai (2x), Hangzhou, Nanjing and Xi´An, PRC, B. Wang, and Z. Hao at Tigermed, Beijing, PRC, the Merz study team (A. Blum, N. Henke, K. Müller, N. Wegener), and D. Müller, K. Wißmiller, and A.-M. Waldron at Cerner Enviza (formerly Kantar Health), Munich, Germany, for medical writing assistance.

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