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ORIGINAL ARTICLE
Cosmetic

A Multicenter Noninferiority Study Comparing Safety and Effectiveness of Hyaluronic Acid Fillers for Correction of Nasolabial Folds in Chinese Subjects

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Background: Hyaluronic acid fillers are the preferred choice for minimally invasive facial volume restoration. In this study, a split-face design was used to compare the effectiveness and safety results of Belotero Balance Lidocaine (BEL) and Restylane (RES, control) to investigate whether BEL is noninferior compared with RES in nasolabial fold (NLF) correction.

Methods: This was a prospective, controlled clinical study in Chinese subjects. Subjects with symmetrical moderate NLFs according to the Wrinkle Severity Rating Scale were randomized to receive BEL in one NLF and RES in the other. The primary objective was to investigate whether BEL is noninferior compared with RES after being injected mid-dermally in moderate NLFs after 6 months. Secondary objectives included responses at other visits and pain sensation. Treatment-emergent adverse events (TEAEs) were assessed.

Results: A total of 220 subjects were enrolled. The Wrinkle Severity Rating Scale response rates at month 6 were 62.9% for BEL versus 64.9% for RES, demonstrating noninferiority. The secondary endpoints supported this. Significantly reduced pain scores were observed for BEL versus RES. For both products, injection site nodule and bruising were the most frequent treatment-emergent adverse events at the injection site. All treatment-related treatment-emergent adverse events were mild.

Conclusions: The study showed that BEL is effective and well tolerated for correction of moderate NLFs in Chinese subjects. Noninferiority of BEL was demonstrated compared with RES, and regardless of applied pain treatment, a further reduction in injection pain was observed in BEL. *(Plast Reconstr Surg Glob Open 2023; 11:e4810; doi: 10.1097/GOX.0000000000004810; Published online 20 February 2023.)*

INTRODUCTION

Over the last few years, dermal fillers have become an integral part of cosmetic therapy, challenging the use of more invasive aesthetic surgical procedures. They provide volume restoration with minimal downtime, favorable safety profile, and rapid and reproducible results.[1] Soft tissue filler procedures are one of the top five cosmetic minimally invasive procedures with over 3.4 million procedures performed in 2020.[2] Currently, more than 200 injectable implants and volume enhancers are available internationally.[3]

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Received for publication April 12, 2022; accepted December 16, 2022.

DOI: 10.1097/GOX.0000000000004810

Disclosures: *Wenzhi Li is an employee of Beijing Anzhen Hospital, Beijing, PR China. He does not have any personal financial relationships with Merz Pharmaceuticals GmbH. Bi Li does not have any personal financial relationships with Merz Pharmaceuticals GmbH. Matthias Hofmann is an employee of Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany. Gudrun Klein is an employee Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany. Hongfu Xie does not have any personal financial relationships with Merz Pharmaceuticals GmbH. The study and this article were funded by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany.*

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Facial volume loss is an early sign of aging and is characterized by formation of wrinkles and folds, including exaggerated nasolabial folds (NLFs).[4] Facial fillers are widely used as a minimally invasive way to restore facial volume, and hyaluronic acid (HA) fillers have become the preferred choice due to natural appearance, a favorable safety profile, and relatively long-lasting effects.[5–8]

Treatment of NLFs with dermal fillers remains a major component of pivotal clinical studies in aesthetic clinical treatment. A meta-analysis has concluded that tissue fillers used for the treatment of the NLF area provide satisfactory and long-lasting improvement.[9]

Two HA fillers were investigated in this study, Belotero Balance Lidocaine (BEL) and Restylane (RES) as control. BEL is a sterile, nonpyrogenic, viscoelastic, colorless, transparent cross-linked sodium hyaluronate gel (22.5 mg/mL) of nonanimal origin in a physiological phosphate buffer and contains 0.3% of lidocaine hydrochloride.

Due to their distinct crosslinking technologies and formulations, BEL and RES exhibit differences in filling properties.[10,11] BEL is produced with the Cohesive Polydensified Matrix technology. A dynamic cross-linking process that comprises two sequential cross-linking steps resulting in a cohesive, homogeneous gel with zones of greater and lesser cross-linking density.[12] Gel parts with higher density refill and expand the tissue, whereas those with lower density diffuse into the fine pericellular tissue spaces. Cohesive Polydensified Matrix gel properties allow for a more homogeneous intradermal distribution of the material.[1,11,13–15]

RES is a clear, transparent, and viscous modified sodium hyaluronate gel (20 mg/mL) of nonanimal origin. It uses defined gel particle sizes, which are incorporated in a liquid phase to be injectable.[1,13,16]

The present study employed a split-face design to compare the effectiveness and safety results of BEL and RES and to investigate whether BEL is noninferior to the control device in corrective treatment of moderate NLFs, as assessed after 6 months according to the validated Wrinkle Severity Rating Scale (WSRS) in Chinese subjects.[17] RES was chosen as control device as it is a well-known filler for the treatment of NLFs and an established product in China. Furthermore, it has served as a control device in several split-face design studies in Asian and, especially, Chinese subjects.[18–23]

Takeaways

Question: Is the hyaluronic acid filler Belotero Balance Lidocaine (BEL) noninferior to a control (Restylane) for correction of moderate nasolabial folds in Chinese subjects?

Findings: This randomized, split-face study enrolled 220 Chinese subjects who received BEL in one nasolabial fold and the control in the other. Wrinkle Severity Rating Scale response rates were similar for both products, demonstrating noninferiority of BEL.

Meaning: BEL is effective and well tolerated for correction of moderate nasolabial folds in Chinese subjects, and noninferior to the Restylane.

METHODS

Study Design

This was a prospective, randomized, multicenter, controlled, clinical study performed in China with a subject- and evaluator-blinded, split-face design. BEL was injected into the NLF on one side of a subject's face and RES into the contralateral NLF. Subjects were treated once and underwent five follow-up visits after 1, 3, 6, 9, and 12 months.

The study was performed at three study sites in China, from November 2017 to July 2019 and conducted in accordance with the Chinese Good Clinical Practice, EN ISO 14155, the Declaration of Helsinki, and local Chinese requirements governing medical research and experimentation on humans. The study was approved by the ethics committees of the three participating hospitals [approval number of leading site (Beijing Anzhen hospital): (2017) 器伦审第[6]号]. Written informed consent was obtained from all subjects.

Subject Selection

Subjects over 18 years of age with symmetrical, moderate NLFs (grade 3 on the WSRS) were recruited. Subjects were excluded if they had ever received surgery or previous dermal filler treatment (excluding HA) in the NLF, had a permanent surgical implant or scar in the NLF, or had received HA filler in the NLF within the past 12 months. (**See table 1, Supplemental Digital Content 1**, which shows the inclusion criteria and exclusion criteria. **http://links.lww.com/PRSGO/C384**.)

Treatment

Subjects were randomized 1:1 to receive BEL (Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) in the right NLF and RES (Galderma, QMed AB, Uppsala, Sweden) in the left NLF or vice versa. BEL and RES were injected by trained treating investigators into the mid-dermal plane using the linear retrotracing/threading technique. BEL was injected using 27G half-inch or 30G half-inch needles based on the investigator's judgement. RES was injected with 30G half-inch needles. Subjects received approximately equal amounts of each filler per side, but there was not a standardized amount given for each subject. For injection-related pain management, subjects were offered ice or topical anesthetic cream. Per protocol, the same pain management regime (none, ice, or topical anesthetic) had to be applied on both injection sides

At the time of the study conduct, all in China-approved international HA dermal fillers did not contain lidocaine. Therefore, BEL was compared against RES without lidocaine in this clinical study.

Objectives and Assessments

The primary objective was to investigate whether BEL is noninferior to RES in correcting moderate NLFs after 6 months, according to the WSRS, in Chinese subjects. The WSRS was assessed live by an independent blinded

evaluator and was performed separately for the left and right NLF. The five-point WSRS ranges from +1 (no visible fold) to +5 (extremely deep and long folds). Response was defined as greater than or equal to one-point improvement compared with screening. (**See table 2, Supplemental Digital Content 2,** which shows the WSRS. **http://links.lww.com/PRSGO/C385**.)

Secondary objectives were to demonstrate noninferiority of BEL versus RES for mid-dermal injection in moderate NFLs after 1, 3, 9, and 12 months, according to the WSRS and to show a reduced pain sensation on the BEL-treated side compared with the RES-treated side (immediately after injection, after 15 minutes, and after 30 minutes). 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 outcomes included differences in response rates at months 1, 3, 6, 9, and 12 according to the seven-point Global Aesthetic Improvement Scale (GAIS) and the seven-point Global Impression of Change Scale (GICS). Both scales range from +3 (very much improved) to −3 (very much worse). The GAIS was evaluated by the investigator, and the GICS was assessed by the subject. Response was defined by a score of greater than or equal to +1 (at least "improved") for both. Mean pain sensation scores and the difference in scores between BEL and RES at each visit were also evaluated. Treatment-emergent adverse events (TEAEs) were assessed to evaluate potential complications and side-effects.

Statistical Analyses

Effectiveness analyses were performed on the per protocol set (PPS). The primary variable (difference in response rates between BEL- and RES-treated side at month 6 as assessed by the independent blinded evaluator according to the WSRS) was analyzed using a repeated measures model (RMM) for binomial distribution. Independent variables were defined as treatment, study site, and gender. Compound symmetry was selected for the covariance matrix of responses between both sides. Identity link was applied to model the probability of a response. The treatment difference in response rates and the associated two-sided 95% CI were based on LSMeans.[24] The prespecified noninferiority margin was 10% as commonly used in noninferiority studies in aesthetics medicine.[19]

The unadjusted difference in response rates was estimated using a similar RMM but with treatment as the only independent variable. The two-sided 95% Newcombe-Wilson CIs for paired data[25] were also provided. (**See document, Supplemental Digital Content 3**, which shows additional statistical methods and sample size estimation. **http://links.lww.com/PRSGO/C386**.)

Safety analyses were performed for the safety analysis set (SES, all subjects exposed to treatments). TEAEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 22.0).

RESULTS

Subject Disposition and Treatment Characteristics

Subjects participated in the study between November 2017 and July 2019. Of the 237 screened subjects, 220 subjects were enrolled. Overall, 209 subjects (95.0%) completed the study, whereas 11 subjects (5.0%) discontinued

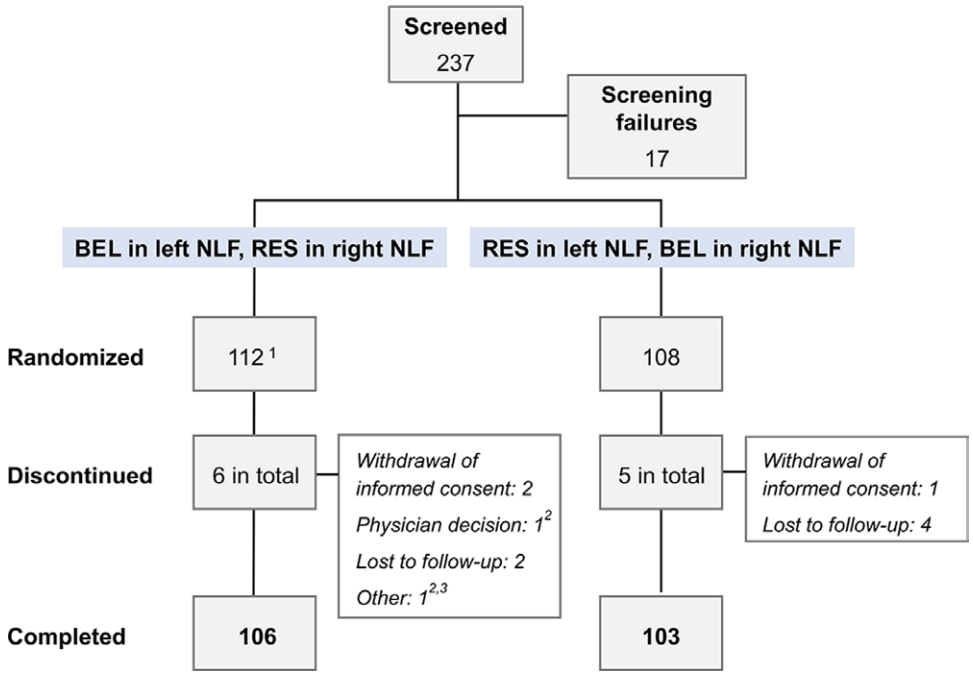

Fig. 1. Flow chart of subjects included in the study. 1, Two of these subjects were randomized but not treated. 2, Subject was randomized but not treated. 3, Investigator became aware after the randomization that the subject met an exclusion criterion.

prematurely (Fig. 1). The SES included 218 subjects and the PPS 205 subjects.

For the PPS, all subjects were of Chinese origin and most (95.6%) were women. The mean age was 43.4 years (Table 1). BEL and RES were applied with linear retrotracing/ threading technique into the mid-dermis. The mean injection volume of BEL was 1.22 ± 0.40 mL and the mean volume of RES was 1.05 ± 0.31 mL. No overfilling occurred.

Effectiveness

WSRS Response Rates at Month 6

Effectiveness analyses were performed on the PPS. For the primary endpoint, the response rates at month 6 based on WSRS assessment (≥1 point improvement compared with screening) as determined by the blinded evaluator were 62.9% on the BEL-treated side versus 64.9% on the RES-treated side (Table 2). The unadjusted difference in response rates was -2.0%. The confirmatory primary effectiveness analysis based on an RMM for binomial distributions accounted for potential confounding effects of study site and gender. The adjusted treatment difference in response rates was -0.6% [CI = (-1.3%; 0.1%)]. The lower limit of the two-sided 95% CI was greater than the noninferiority limit of -10%, demonstrating noninferiority of BEL versus RES in the treatment of moderate NLFs.

Table 1. Demographics and Baseline Characteristics

	PPS Total (N = 205)
Sex, n (%)	
Men	9 (4.4)
Women	196 (95.6)
Age (y)	
Mean ± SD	43.4 ± 9.46
Age category, n (%)	
<45 years	109 (53.2)
45–54 years	72 (35.1)
>54 years	24 (11.7)
Race, n (%)	
Asian	205 (100)
Body mass index (kg/m²)	
Mean ± SD	22.55 ± 2.99
Fitzpatrick skin type, n (%)	
Type I or II	0
Type III	84 (41.0)
Type IV	121 (59.0)
Type V or VI	0

n, number of subjects with nonmissing observation; N, number of subjects in population.

In addition, an explorative subgroup analysis was conducted on subjects treated with more than 1.5 mL BEL to assess a potential impact on the slightly higher injection volume used for BEL during the study compared with RES. The treatment difference in response rates was -1.8% [95% CI: (-4.3%, 0.8%)] and similarly low as in the primary analysis.

WSRS Response Rates at Months 1, 3, 9, and 12

The secondary endpoint data corroborate the results for the primary endpoint (Fig. 2). The unadjusted differences in WSRS response rates between the two treatments at months 1, 3, 9, and 12 ranged between 1.0% and 0.5%. Moreover, at all visits, the limits of associated two-sided 95% CIs indicate expected treatment differences to be less than 4% (Table 3). Photographs of the treatment results in two representative subjects are shown in Supplemental Digital Content 4. (**See figure, Supplemental Digital Content 4,** which shows subject photographs. **http://links.lww.com/PRSGO/C387**.)

Pain Sensation

The mean sum in pain sensation over the three assessment time points (immediately after injection, after 15 min, after 30 min) was assessed as a secondary effectiveness outcome. The average pain sensation from lidocaine containing BEL injections was greater than 50% lower than the pain from RES injections. The mean within-subject difference in sum in pain sensation between the two treatments was −4.7 points [95% CI= (−5.4, −4.0)], indicating a statistically significantly reduction ($P < 0.0001$) for BEL versus RES. This pain reduction was independent of the type of injection pain management applied (Table 4).

At each time point, the mean pain sensation score (independent of type of pain management) was significantly lower for BEL compared with RES (Fig. 3A). Generally, the mean treatment difference in pain score was most pronounced immediately after injection, with an estimate of −2.4 (95% CI= [−2.7, −2.0]), showing that the pain sensation assessed immediately after injection was lower for BEL than RES. Moreover, the 95% CIs for the mean treatment differences lay completely below zero at all time points, indicating statistical significance. Of note, this did not only apply for the total sample but also for each of the three subgroups defined by type of injection pain management applied (none, ice, or topical anesthetic cream) (Fig. 3B).

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

BEL (N=205)		Control (RES) (N=205)		Unadjusted Difference in Response Rates*	Adjusted Difference BEL-RES in Response Rates†	Newcombe-Wilson CI
n	% [95% CI] ‡	n	% [95% CI] ‡	% [95% CI]	% [95% CI]	[95% CI]
129	62.9 [55.9–69.6]	133	64.9 [57.9–71.4]	−2.0 [−4.3 to 0.4]	−0.6 [−1.3 to 0.1]	[−4.5 to 0.6]

*Estimates based on LSMEANS from an RMM including treatment as only independent variable.
†Estimates based on LSMEANS from an RMM including treatment, study site, and gender as independent variables.
‡Two-sided 95% Pearson-Clopper CI for the response rate.
LSMEANS, least-squares means; n, number of subjects with nonmissing observation; N, number of subjects in population.

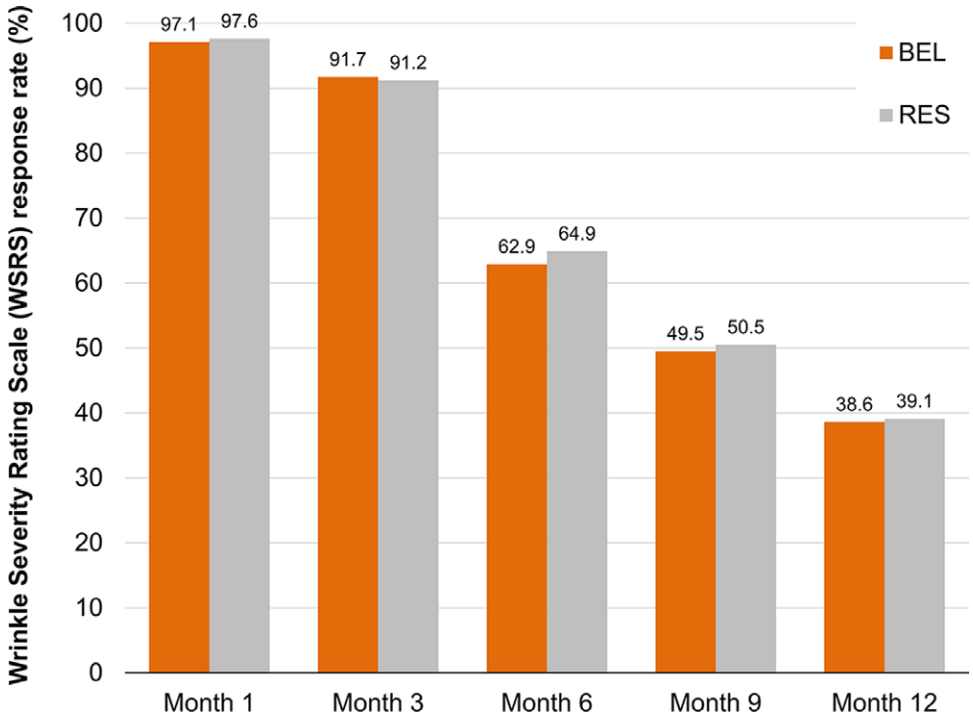

Fig. 2. Response rates (≥1-point improvement) according to the WSRS over time (PPS).The numbers of subjects with WSRS results for the respectively treated side of the face at the respective visit time points are provided in Table 2 and Table 3.

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

	BEL (N= 205)		Control (RES) (N = 205)		Unadjusted Difference in Response Rates†
Visit*	n	% [95% CI]	n	% [95% CI]‡	% [95% CI]
Month 1	199	97.1 [93.7–98.9]	200	97.6 [94.4–99.2]	−0.5 [−1.4 to 0.5]
Month 3	188	91.7 [87.1–95.1]	187	91.2 [86.5–94.7]	0.5 [−1.6 to 2.6]
Month 9	100	49.5 [42.4–56.6]	102	50.5 [43.4–57.6]	−1.0 [−3.7 to 1.8]
Month 12	78	38.6 [31.9–45.7]	79	39.1 [32.3–46.2]	−0.5 [−3.4, 2.4]

*Note that results for month 6 (primary end point) are provided in Table 2 above.
†Estimates based on LSMEANS from an RMM including treatment as only independent variable.
‡Two-sided 95% Pearson-Clopper CI for the response rates.
LSMEANS, least-squares means; n, number of subjects with nonmissing observation; N, number of subjects in population.

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

	BEL (N= 205)		Control (RES) (N= 205)		Difference	
Type of Injection Pain Management*	n	Mean ± SD	n	Mean ± SD	Mean [95% CI]†	*P*‡
Total	205	4.1 ± 4.09	205	8.8 ± 5.76	−4.7 [−5.4 to −4.0]	<0.0001
None	75	6.0 ± 4.32	75	11.0 ± 5.78	−5.0 [−6.2 to −3.9]	<0.0001
Ice	52	4.1 ± 3.93	52	10.1 ± 4.58	−6.0 [−7.4 to −4.7]	<0.0001
Topical anesthetic cream	78	2.4 ± 3.10	78	5.8 ± 5.19	−3.4 [−4.7 to −2.2]	<0.0001

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, a maximum sum score of 30 was possible. The sum score of pain sensation was calculated as the sum of the pain sensation scores assessed immediately, 15 minutes, and 30 minutes after injection.
*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 subjects with nonmissing observation; N, number of subjects in population.

Other Effectiveness Endpoints

For both treatments, the investigators assessed the GAIS as at least "improved" in more than 84% of subjects at months 1, 3, and 6. By month 12, response rates were still 55.0% and 62.9% for BEL and RES, respectively (Fig. 4A).

GICS response rates indicated that subjects were satisfied with treatment results and showed a similar trend to the GAIS. Over 72% of subjects rated their overall appearance on the GICS as at least "improved" for both treatments at months 1, 3, and 6. By month 12, response rates were around 58% for both treatments (Fig. 4B).

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

	Local Injection Site, BEL		Local Injection Site, RES		Nonlocal Injection Site	
MedDRA System Organ Class Preferred Term	**n* (%)**	**m**	**n* (%)**	**m**	**n† (%)**	**m**
Subjects with at least one related TEAE, number of related TEAEs	24 (11.0)	30	26 (11.9)	34	2 (0.9)	2
General disorders and administration site conditions	23 (10.6)	29	25 (11.5)	33	0 (0.0)	0
Injection site nodule	13 (6.0)	13	18 (8.3)	18	0 (0.0)	0
Injection site bruising	15 (6.9)	15	12 (5.5)	12	0 (0.0)	0
Injection site pruritus	1 (0.5)	1	2 (0.9)	2	0 (0.0)	0
Injection site rash	0 (0.0)	0	1 (0.5)	1	0 (0.0)	0
Hepatobiliary disorders	0 (0.0)	0	0 (0.0)	0	2 (0.9)	2
Hepatic function abnormal	0 (0.0)	0	0 (0.0)	0	1 (0.5)	1
Hyperbilirubinaemia	0 (0.0)	0	0 (0.0)	0	1 (0.5)	1
Product issues	1 (0.5)	1	1 (0.5)	1	0 (0.0)	0
Device dislocation	1 (0.5)	1	1 (0.5)	1	0 (0.0)	0

*Subjects with TEAEs affecting the local injection site treated with the respective filler. TEAEs affecting both local injection sites were considered for both treatments.
†Subjects with TEAEs not affecting either of the two local injection sites.
MedDRA, Medical Dictionary for Regulatory Activities, n, number of subjects with at least one respective TEAE; SES, safety evaluation set; TEAE, treatment-emergent adverse event.

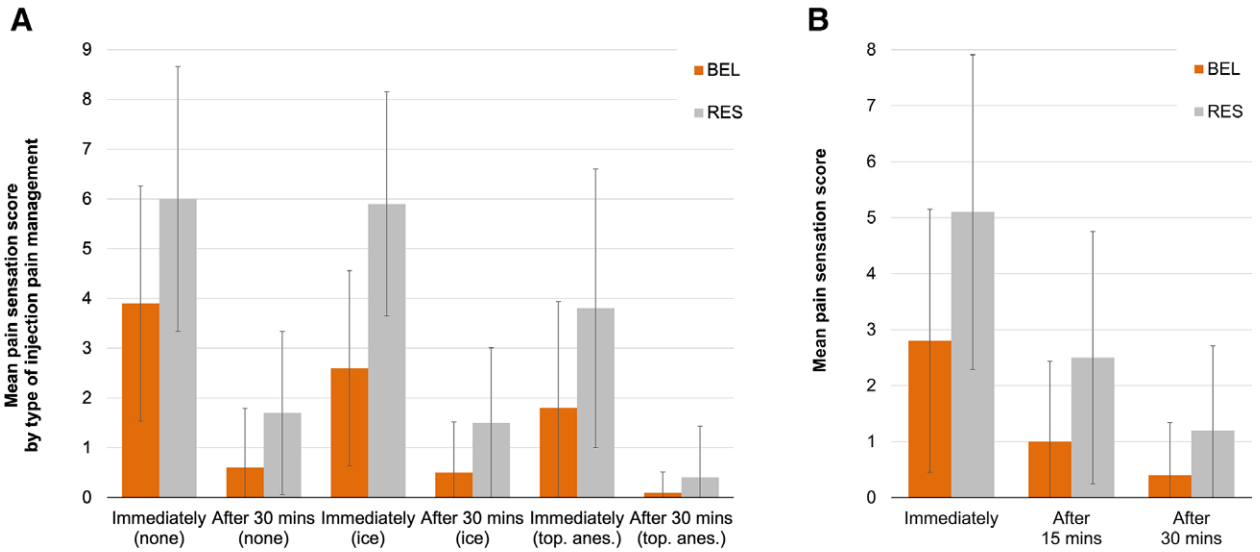

Fig. 3. Mean pain sensation scores. A, By time points and by treatment (PPS; n=205 subjects for each group and time point), with error bars showing SD. B, By type of injection pain management, time points and treatment (PPS; n=75 subjects with no pain treatment, 52 subjects with ice and 78 subjects with topical anesthetic cream), with error bars showing SD. Pain was assessed on an 11-point scale, ranging from 0 (no pain) to 10 (extreme pain). n, number of subjects with nonmissing observation; top. anes, topical anesthetic cream.

Safety

Among the 218 subjects (SES), 99 subjects (45.4%) reported at least one TEAE. Most subjects [82 (37.6%)] experienced TEAEs of mild intensity followed by TEAEs of moderate intensity (16 subjects; 7.3%). Only one subject (0.5%) experienced a nonrelated TEAE of severe intensity. Eight subjects (3.7%) reported a total of 10 serious TEAEs, none of which were treatment-related or affected a local injection site. No subject died and no TEAE led to study discontinuation. No vascular events, allergic reactions, or overfilling were reported.

A total of 34 subjects (15.6%) reported 45 treatment-related TEAEs. For the RES-treated side, 34 treatment-related local injection site TEAEs were reported in 26 subjects (11.9%). For the BEL-treated side, 30 treatment-related local injection site TEAEs were reported in 24 subjects (11.0%). For both treatments, injection site nodule and injection site bruising were the most frequently reported treatment-related local injection site TEAEs (Table 5). All injection site nodules were assessed by the investigator as mild, only palpable, and not visible. In addition, all injection site nodules resolved. Other treatment-related local injection site TEAEs with low incidence rates were injection site pruritus, injection site rash and device dislocation. Only two treatment-related nonlocal injection site TEAEs were reported, for two subjects: abnormal hepatic function based on one elevated µGT value (twice the normal range) and hyperbilirubinaemia in a subject

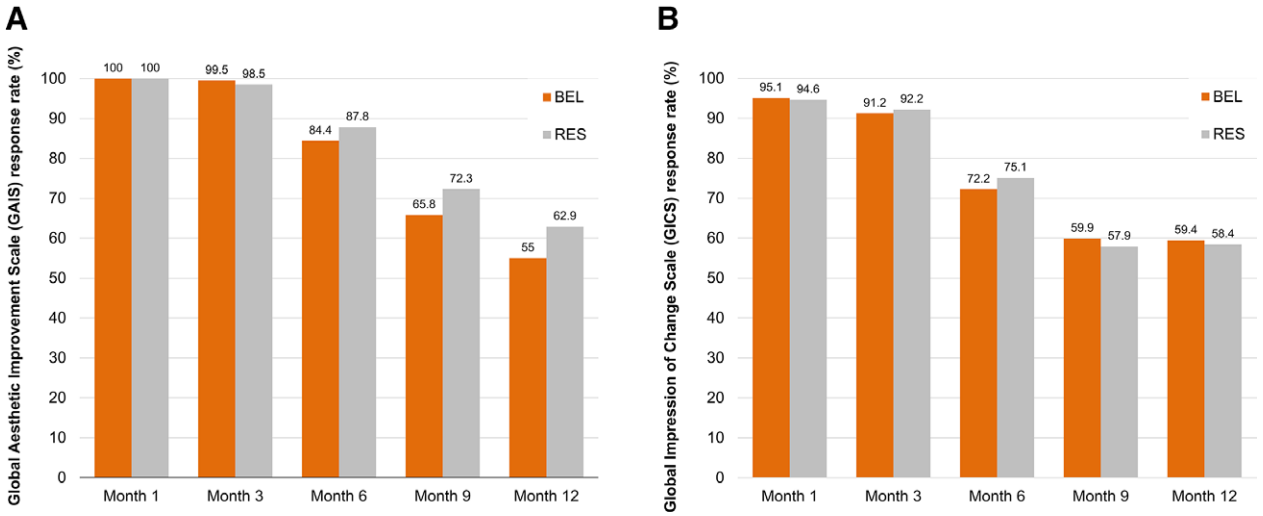

Fig. 4. Response rate score of at least "improved" over time for GAIS and GICS, as assessed by (A) the investigator for GAIS and (B), by the subjects for GICS.

who had shown increased bilirubin values already at screening. All treatment-related (including local injection site and nonlocal injection site) TEAEs were mild and all resolved, apart from hyperbilirubinemia which was ongoing at the end of the study.

DISCUSSION

The aim of this randomized, split-face comparison study was to provide data for the Chinese population on the effectiveness and safety of BEL in the treatment of moderate NLFs and to show noninferiority to the established approved RES filler in this indication.

A split-face design was used in many previous clinical studies in the NLF indication in China.[19–23] RES was used as control device of similar effectiveness compared with BEL, with the exception that BEL contains 0.3% lidocaine to reduce injection pain.

The study was performed exclusively in China. All subjects in this study were of Chinese origin and most were women. The demographic data were comparable to published studies in Chinese subjects for treatment of NLFs with HA fillers.[19,22,23]

The primary effectiveness variable in this study was the difference in response rates between the BEL- and RES-treated side at month 6, as assessed by the blinded evaluator according to the WSRS. Noninferiority of BEL versus RES was successfully demonstrated. The WSRS response rates at month 6 (≥1-point improvement compared with screening) were 62.9% on the BEL-treated side and 64.9% on the RES- treated side. The adjusted difference in response rates from the confirmatory primary analysis was –0.6% [95% CI = (–1.3% to 0.1%)]. This is in line with previous studies conducted with HA fillers for NLF correction in China featuring similar effectiveness endpoints for noninferiority.[20,22] The current study's WSRS response rate for the comparator (64.9%) is also in line with previous trials. While one previous study of RES for NLF correction in Chinese subjects reported WSRS responder rates of 95.5% at 6 months postinjection,[19] two other studies reported response rates of 52.2% and 64.0% at 24 weeks and 6 months, respectively.[21,23] An explorative subgroup analysis of subjects treated with more than 1.5 mL BEL showed that the treatment difference in response rates was –1.8% (95% CI: [–4.3% to 0.8%]) and similarly low as in the primary analysis.

The secondary effectiveness outcomes corroborated the primary results: The course of the WSRS response rates (≥1-point improvement from baseline) over the 12-month follow-up period was very similar for the BEL-treated and the comparator treated sides, with the point estimate for the treatment difference at months 1, 3, 9, and 12 ranging between –1.0% and 0.5% and all associated 95% CIs lying completely above –4.0. The findings indicate that BEL was noninferior to the comparator for treatment of moderate NLFs at all time points during the study period. At month 12, the WSRS response rates were 39.1% for BEL, compared with 38.6% for the comparator. The observed WSRS data from both treatments were in line with a clinical study comparing RES to Restylane Lyft in Chinese subjects.[21]

In the current study, the subjects' pain sensation after injection and its difference between the treatments suggest significantly reduced injection pain for BEL versus RES irrespective of any topical pain management. The difference in pain score between the treatments was most pronounced immediately after injection. Obviously, the lidocaine content in BEL was the main determining factor in the pain reduction. Pain is the major complaint of subjects receiving dermal filler injections.[26–28] Therefore, HA fillers containing lidocaine have been developed to reduce injection pain and procedural time, and to promote recovery with minimal additional risk.[27,29]

The current study's findings are in line with published data from a split-face trial in the United States (NCT03319719) which revealed significantly reduced pain

for the NLF side treated with HA filler with lidocaine compared with HA without lidocaine. The greatest difference in pain was observed at the time of injection and it gradually decreases over 60 minutes. Nevertheless, a difference greater than 50% was observed between the two treatment sides at each time point.[28] Similar findings were revealed in overseas and Asian studies comparing HA fillers with and without lidocaine for NLF correction.[26–28,30–32] It has also been shown that the use of topical anesthesia does not affect the difference in pain scores between HA fillers with and without lidocaine,[33] which was corroborated in the current study.

Published studies comparing HA fillers with and without lidocaine for NLF correction suggest comparable effectiveness for reducing the severity of wrinkles.[26–28,30–32] It has been reported that lidocaine can be easily dissolved in HA gel without altering its concentration and properties, thus enabling the filler to effectively reduce procedural pain while not compromising effectiveness.[30]

In addition to WSRS improvements compared with baseline and favorable results regarding pain sensation for BEL versus the control, the current study's GAIS- and GICS-based response rate results indicate that both investigators and subjects perceived improvements throughout the follow-up period. Results were similar between BEL and the control at all time points. Thus, the GAIS and GICS outcomes consistently support the primary and secondary effectiveness outcomes. This is in line with published studies comparing HA fillers with and without lidocaine, which showed no relevant differences between the two types in terms of GAIS and/or GICS ratings.[27,29,34]

BEL and RES were well tolerated and safe, with no meaningful differences in the safety profile. The majority of treatment-related TEAEs occurred at the injection sites and the most frequent events were injection site nodules and bruising. The reported incidence rates of nodules in the current study were lower than in a previous study in China with similar HA fillers.[23] The comparable TEAE rates between the two products is in line with literature showing that the addition of lidocaine to HA fillers is safe and beneficial.[26,31,32]

In conclusion, the noninferiority of BEL was demonstrated in comparison to RES, and even further significant reduction in injection pain was documented for BEL regardless of the type of injection pain management applied (none, ice, or topical anesthetic cream) to the subjects' prior injection. The study showed that BEL is an effective and well-tolerated treatment for correction of moderate NLFs in a Chinese population.

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ACKNOWLEDGMENTS

The authors would like to thank the Chinese study sites in Beijing (2x) and Changsha, PRC; the Merz study team (A. Blum, N. Henke, K. Müller, N. Wegener), B. Wang and Q. Wu at Tigermed; and D. Mueller and A.M. Waldron at Cerner Enviza, Munich, Germany, for medical writing assistance.

Trial registry name: Chinese clinical trial registry (ChiCTR)
Registration identification number: ChiCTR2200058113
Date registered: 30 Mar 2022
Registry URL: http://www.chictr.org.cn/enIndex.aspx

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