A Prospective, Open-Label Study of Hyaluronic Acid-Based Filler With Lidocaine (VYC-15L) Treatment for the Correction of Infraorbital Skin Depressions

Francois Niforos, MD,* Raj Acquilla, MBChB, MRCGP, MBCAM,† Patricia Ogilvie, MD, PhD,‡ Marva Safa, MD,§ Massimo Signorini, MD,‖ Lela Creutz, PhD,¶ Graeme Kerson, BSc,# and Michael Silberberg, MD, MBA#

BACKGROUND Infraorbital skin depressions are one of the most troublesome facial areas for aesthetically aware patients.

OBJECTIVE Evaluate effectiveness and safety of Juvéderm Volbella with Lidocaine (VYC-15L; Allergan plc, Dublin, Ireland) for correction of bilateral infraorbital depressions.

METHODS In this 12-month, prospective, uncontrolled, open-label study, subjects aged ≥18 years with infraorbital depressions rated ≥1 on the Allergan Infra-oRbital Scale (AIRS) received injections of VYC-15L with optional touch-up treatment on Day 14. The primary efficacy measure was ≥1 AIRS grade improvement from baseline at month 1.

RESULTS Of 80 subjects initially treated with VYC-15L, 75 (94%) completed the study. All injections were intentionally deep, most using multiple microbolus technique. At 1 month, 99.3% of eyes achieved ≥1 AIRS grade improvement. The responder rate (subjects with ≥1 AIRS grade improvement in both eyes) was 99% at month 1, 92% at month 6, and 54% at month 12. Most injection site reactions (e.g., bruising, redness, irregularities/bumps) were mild and resolved by day 14. Late-onset mild to moderate edema was observed in 11% of eyes at month 6% and 4% of eyes at month 12.

CONCLUSION VYC-15L is effective and safe for the treatment of infraorbital depressions, with effectiveness lasting up to 12 months.

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Infraorbital skin depressions (including tear troughs), which are often accompanied by dark circles under the eyes, can give a sad or fatigued look to the face.[1–4] The infraorbital area is one of the most troublesome facial areas and one of the areas patients are most likely to address first when seeking facial esthetic treatment.[5] Skin depressions in the infraorbital area are caused by the loss of inferior orbital fat volume in combination with malar fat ptosis, which disrupts the continuous plane of fat pads supporting the overlying structure of the cheek and midface.[4,6–10]

Hyaluronic acid dermal filler injections have been successfully used to correct volume loss in the infraorbital region.[11–16] This area has a unique anatomy compared with other parts of the face commonly treated with filler injections. The orbital rim is characterized by very thin tissue overlying bone, with skin

*Centre Chirurgical Niforos, Lyon, France; †The Gatehouse, Cheshire, United Kingdom; ‡SkinConcept, Munich, Germany; §La Jouvence, Neuchâtel, Switzerland; ‖Private Practice, Milan, Italy; ¶Peloton Advantage, Parsippany, New Jersey; #Allergan Plc, Marlow, United Kingdom

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that is often only a few millimeters thick.[16,17] As a result, superficial injections with hyaluronic acid fillers can cause long-lasting irregularities of contour (e.g., lumps and bumps) that are difficult to conceal.[17,18] Thus, most injectors have advocated a preference for deep injections in the infraorbital area (i.e., submuscular or preperiosteal) for optimal clinical outcomes.[4,16–22] The flow characteristics and viscosity of the filler may also contribute to clinical outcomes after infraorbital injections.[16,20]

Juvéderm Volbella with Lidocaine (VYC-15L; Allergan plc, Dublin, Ireland) is a hyaluronic acid–based filler that combines low– and high–molecular-weight hyaluronic acid to improve moldability (ease of modelling/shaping), improve ease of flow during injection, reduce swelling of the gel within the tissue, improve evenness of distribution within the tissue, and increase duration of effect.[23,24] All of these characteristics make VYC-15L an attractive candidate for treatment of the infraorbital area. This study evaluated the effectiveness and safety of VYC-15L treatment for the correction of bilateral infraorbital skin depressions.

Methods and Subjects

Study Design

This prospective, uncontrolled, single-arm, single-site, open-label study (NCT02176421) evaluated the effectiveness and safety of VYC-15L treatment for the correction of bilateral infraorbital skin depressions. The study was conducted at Dermscan, Lyon, France from May 2014 to July 2015. The protocol was reviewed and approved by an Independent Ethics Committee and was authorized by the French National Agency for Medicines and Health Products Safety (L'Agence Nationale de Sécurité du Médicament et des Produits de Santé [ANSM]). All subjects provided written informed consent.

Subjects

Eligible subjects were aged 18 years or older, desired correction of infraorbital skin depressions under both eyes, and were rated Grade 1 or higher on the Allergan Infra-oRbital Scale (AIRS) for each eye by the evaluating investigator at screening. The AIRS is a validated scale (Niforos F et al; er presented at the Anti-aging European Congress, October 24–25, 2014, Paris, France) that grades severity of skin crease and volume loss in the infraorbital area on a Scale of 0 to 5 (Figure 1). Subjects were to refrain from undergoing other antiwrinkle/volumizing treatments in the upper 2-thirds of the face (eyebrow to cheeks/cheekbones) for the study duration. Key exclusion criteria were: previous cosmetic facial procedures that could alter the appearance of the infraorbital area (e.g., treatment with dermal fillers, fat injections, or mesotherapy) anywhere in the face within 6 months before study entry; volumizing treatment of the midface within 12 months of the start of the study; and previous treatment with fillers or implants anywhere in the infraorbital area.

Treatment

Injections of VYC-15L were carried out by 4 European specialist injectors and were placed below the orbital rim and above the zygomatic region. The specialist injector determined the appropriate injection technique and volume of VYC-15L for each individual subject based on his/her clinical experience, the anatomy of subject's infraorbital area, the level of deformity, and the subject's clinical need. If optimum correction was not achieved after the initial treatment, an optional touch-up injection could be performed on day 14 by the same specialist injector. During all treatments, one of 2 French evaluating investigators (both were plastic surgeons) supervised clinical care.

Assessments

The primary end point was defined as a $\geq$1 AIRS grade improvement at 1 month. The evaluating investigators performed all AIRS assessments. Secondary end points included specialist injectors' ratings of ease of injection and ease of moldability of the product on a Scale from 0 to 10, evaluating investigators' and subjects' ratings of improvement with esthetic outcome on a Scale of 1 (very well improved) to 5 (worsened) using the Global

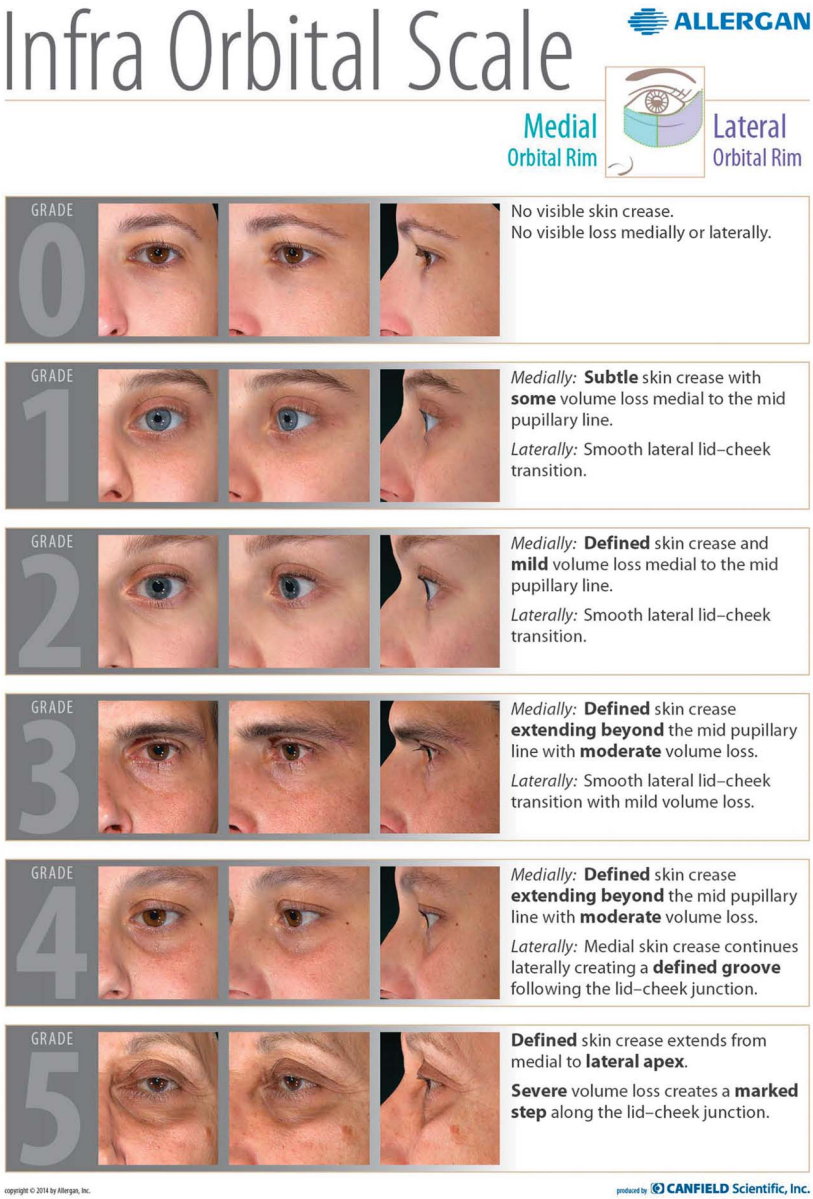

Figure 1. The Allergan Infra-oRbital Scale (AIRS). Reprinted with permission from Dermatol Surg 2017;43:684–691.

Aesthetic Improvement Scale (GAIS), and subjects' ratings on the Periorbital Aesthetic Appearance Questionnaire (PAAQ), a validated patient-reported outcome questionnaire with 9 questions rated on a Scale of 0 to 4 about the effects of overall eye appearance on the subject's perceptions of age, attractiveness, tired/sad appearance, and need to cover up eye appearance (e.g., with cosmetics or sunglasses) over the previous 7 days. Scores for the 3 PAAQ domains (psychological [5 questions], appearance [3 questions], and coping [1 question]) were also determined. Subjects were followed at days 1, 3, 7, and 14, with long-term follow-up at 1, 6, 9, and 12 months after the last injection.

Skin Quality Assessment

Skin hydration was measured in the injected zone (infraorbital area) under one eye and in a noninjected zone on the face (upper maxillary, near the ear) using the MoistureMeter D (Delfin Technologies Ltd., Kuopio, Finland) with the XS 5 (depth of effective measurement = 0.5 mm) and S 15 (depth of effective measurement = 1.5 mm) probes. An average of 3

acquisitions was used for each measurement. Skin elasticity was measured in the same regions using a MPA 580 Cutometer (Courage + Khazaka electronic GmbH, Cologne, Germany).

Safety Assessments

Adverse events (AEs) were recorded at all study visits. Evaluating investigators assessed the severity and duration of local injection site reactions (ISRs) at all study visits. Subjects reported local ISRs in diaries completed during the first 14 days after initial treatment and for 14 days after touch-up injection.

Statistical Analysis

A total of 80 subjects were recruited (assuming a 30% attrition rate) to achieve 90% power to detect at least a 1-point improvement in AIRS at month 1 with a 1-sided significance level of 0.05. The power calculation was based on the exact binomial test algorithm[25] as implemented by the POT0 procedure of the commercial software nQuery Advisor 6.0 (Statistical Solutions, Boston, MA). Descriptive statistics were provided by visit and as change between visits where applicable. All statistical tests were 2-sided with $\alpha = 0.05$.

Results

Subject Demographics and Baseline Characteristics

A total of 125 subjects were screened, and 80 subjects were enrolled and received initial treatment on day 0. On day 14, 62 (78%) of these subjects received touch-up injection under one or both eyes. Of the 80 treated subjects, 75 (94%) completed the study and 5 subjects discontinued (lost to follow-up, $n = 4$; serious AE unrelated to treatment, $n = 1$).

Most subjects were women (84%) and white (95%) (Table 1). Most eyes had baseline AIRS ratings of Grade 4 (54/152, 36%) or 3 (41/152, 27%). The remainder were rated at baseline as Grade 2 (33/152, 22%) or Grade 5 (24/152, 16%).

In total, 76 subjects were included in the 1-month effectiveness analysis (3 lost to follow-up; 1 excluded for protocol violation); subjects returned and were evaluated at 6 ($n = 75$), 9 ($n = 74$), and 12 months ($n = 75$) after initial treatment.

TABLE 1. Demographic and Baseline Characteristics

	N = 80
Age, mean ± SEM (range), yrs	46 ± 1 (21–69)
Sex, *n* (%)	
Women	67 (84)
Men	13 (16)
Race, *n* (%)	
White	76 (95)
Black	1 (1)
Other	3 (4)
Fitzpatrick skin type, *n* (%)	
I	1 (1)
II	11 (14)
III	47 (59)
IV	19 (24)
V	2 (3)
Current smoker, *n* (%)	
Yes	21 (26)
No	59 (74)

SEM, standard error of the mean.

Injection Parameters

Table 2 summarizes key injection parameters. All injections were intentionally deep. The most common injection technique was multiple microbolus for both initial (81%) and touch-up treatments (78%). The average number of needle punctures per eye was 4.9 for initial treatment and 3.9 for touch-up treatment. The mean volume of VYC-15L injected per eye was 0.5 mL for initial treatment (day 0), 0.30 mL for touch-up (day 14), and 0.79 mL in total for initial + touch-up. All subjects were injected with 30-gauge, half-inch needles, except one subject for whom smaller 32-gauge needles were used in addition during the initial treatment. After the initial and touch-up injections, 62% and 42% of subjects, respectively, were massaged with arnica or a cosmetic cream.

The specialist injectors gave high ratings for ease of VYC-15L injection and moldability. Scores ranged from 9 to 10 on a Scale of 0 to 10 for the initial and touch-up injections (Table 2).

TABLE 2. Injection Parameters

	Day 0	*Touch-Up, Day 14*
No. of subjects injected	80	62
No. of eyes injected	160	118
No. of punctures per eye		
Mean ± SEM (range)	4.9 ± 0.1 (1–8)	3.9 ± 0.2 (1–8)
Injection technique, % of eyes		
Multiple microbolus	81	78
Multiple microbolus + retrograde tunnelling/threading	19	15
Retrograde tunnelling/threading	0	4
Single bolus	0	3
Depth of injection, % of eyes		
Intentionally deep*	100	100
Volume injected per eye, mL		
Mean ± SEM (range)	0.50 ± 0.02 (0.2–1.0)	0.30 ± 0.03 (0.0–1.0)
Total (initial + touch-up)		
Mean ± SEM (range)	0.79 ± 0.04 (0.2–2.0)	
Ease of injection†		
Mean ± SEM (range)	9.8 ± 0.0 (9–10)	10.0 ± 0.0 (10–10)
Ease of moldability†		
Mean ± SEM (range)	9.8 ± 0.0 (9–10)	10.0 ± 0.0 (9–10)

*All injections were intentionally deep (submuscular/preperiosteal), with none being intentionally subcutaneous.
†Scale of 0 (most difficult) to 10 (easiest).
SEM, standard error of the mean.

Effectiveness

At 1 month, 99.3% of eyes (147/148 eyes) achieved the primary end point of ≥1 grade AIRS improvement and 87.8% of eyes attained a ≥2 grade improvement (Figure 2A). The responder rate (percentage of subjects with ≥1 grade improvement in both eyes) was 99% at month 1, 92% at month 6, and 54% at month 12 (Figure 2B).

AIRS scores were significantly lower versus baseline at all time points ($p < .001$, Figure 3). Mean (±standard error of the mean [SEM]) AIRS scores decreased from 3.45 ± 0.08 at baseline to 1.63 ± 0.10 immediately after the initial injection and remained relatively stable until the touch-up injection on day 14. The touch-up injection decreased the mean ± SEM AIRS score to 1.0 ± 0.10, which remained stable at 1 month.

At 1 month, investigators rated 100% of eyes as "improved," "well improved," or "very well improved" using the GAIS, with 59% of eyes rated improved or better at month 12 (Figure 4). Similarly, at 1 month, subjects rated 96% of their eyes as "improved," "well improved," or "very well improved," with 64% of eyes rated improved or better at month 12 (Figure 4). Subjects' mean PAAQ scores (i.e., lower scores) indicated significant improvement from baseline in the effects of overall eye appearance at all post-treatment time points ($p < .0001$) (Figure 5A). Results for the psychological, appearance, and coping domains of the PAAQ were similar (Figure 5B). Figure 6 shows representative images of subjects treated with VYC-15L.

Skin Quality

Baseline skin moisture levels were higher in the infraorbital area (mean ± SEM: XS 5 = 51.6 ± 0.7; S 15 = 41.1 ± 0.8) compared with the control non-injected zone (XS 5 = 32.5 ± 0.8; S 15 = 24.1 ± 0.8). Skin moisture readings with both probes significantly increased from baseline in the injected zone at day 14 (before touch-up), but not in the noninjected zone (Figure 7). With the XS 5 probe, the difference in skin moisture increase between injected and noninjected

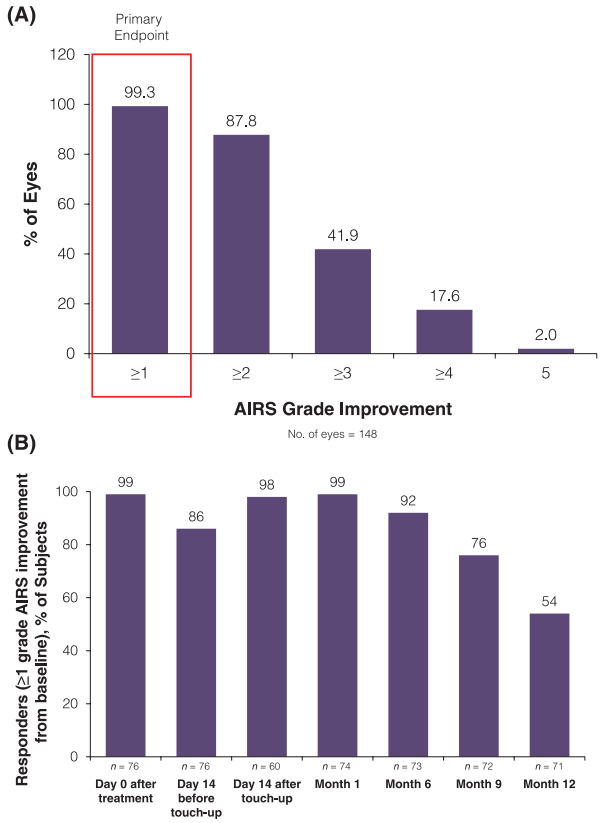

Figure 2. (A) Proportion of eyes with ≥1 grade AIRS improvement from baseline to month 1 and (B) responder rates (percentage of subjects with ≥1 grade AIRS improvement from baseline) over 12 months after treatment with VYC-15L in the infraorbital area. AIRS, Allergan Infra-oRbital Scale.

zones was statistically significant at day 14 ($p = .002$), month 1 ($p < .0001$), and month 6 ($p < .05$), but not at month 9 and month 12, consistent with a gradual progressive disappearance of the product. Cutometer readings showed that the change from baseline in

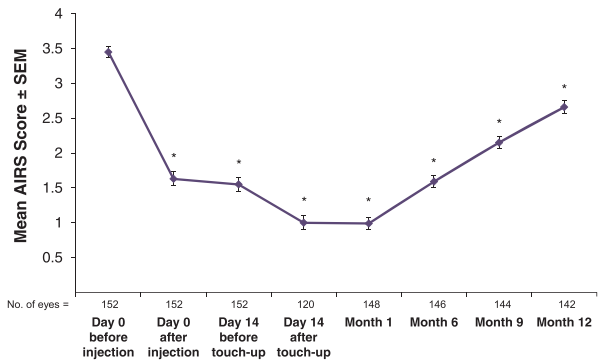

Figure 3. Mean AIRS scores over 12 months after treatment with VYC-15L in the infraorbital area. AIRS, Allergan Infra-oRbital Scale; SEM, standard error of the mean. *$p < 0.001$ versus baseline.

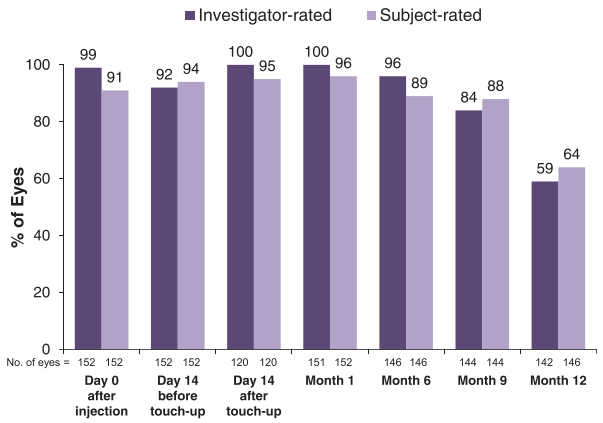

Figure 4. Percentage of eyes rated by investigators and subjects as improved, well improved, or very well improved using the GAIS. GAIS, Global Aesthetic Improvement Scale.

elasticity (Ur/Ue) was significantly higher in the injected compared with the control noninjected zone at day 14, month 1, month 9, and month 12 ($p < .05$).

Safety

The incidence of ISRs reported by subjects in diaries is shown in Figure 8. The vast majority of the ISRs

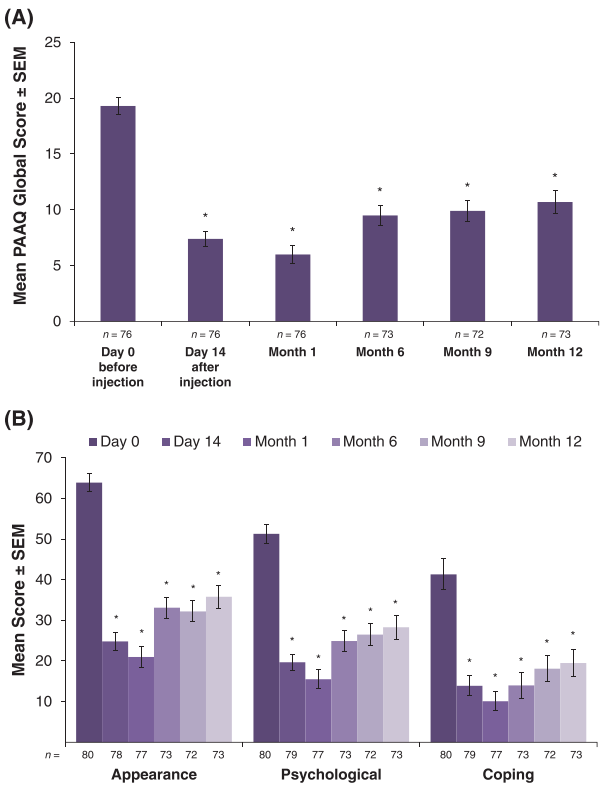

Figure 5. Mean subject-reported (A) total and (B) subdomain PAAQ scores. PAAQ, Periorbital Aesthetic Appearance Questionnaire. *$p < 0.0001$ versus baseline.

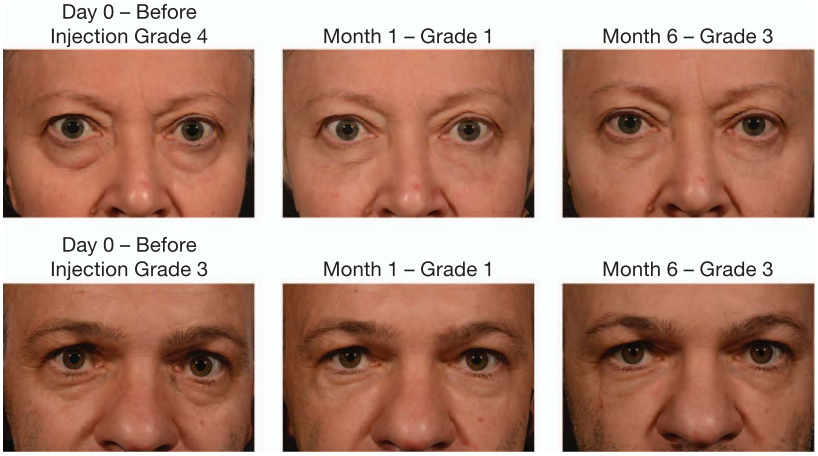

Figure 6. Representative photographs of a 62-year-old woman (top row) and a 46-year-old man (bottom row) treated with VYC-15L in the infraorbital area.

were judged mild or moderate by the subjects. Subjects reported severe ISRs of bruising (3% of eyes), irregularities/bumps (3%), redness (2%), edema (2%), and pain (1%). None of the ISRs were rated severe by the investigators. Most ISRs were resolved by day 14 before the touch-up injection. ISRs after the touch-up injection were similar to those reported after the initial treatment, but at numerically lower rates.

By investigators' assessments, some AEs were not detectable until the month 6 visit. Late-onset mild to moderate edemas, which mostly appeared after month 1, were observed by the evaluating investigator under 17 (11%) eyes at month 6, of which only 10 were noticed by the subjects. Investigators observed edema under 8 (5%) eyes at month 9, and 6 (4%) eyes at month 12. At month 12, 4 (5%) subjects reported edema (2 subjects under one eye and 2 subjects under both eyes); this edema was mild in 4 of 6 eyes and moderate in 2 of 6 eyes. The mean ± SEM volume injected was greater for subjects with edema (1.02 ± 0.10 mL) compared with subjects who did not develop edema (0.76 ± 0.38 mL). However, the study was not powered or designed to detect relationships between volume injected and edema.

A mild Tyndall effect (refractive phenomenon giving the skin a grey/blue color resulting from a volume of gel readily visible under thin skin) was observed by the evaluating investigator at month 6 in 3 subjects (4%).

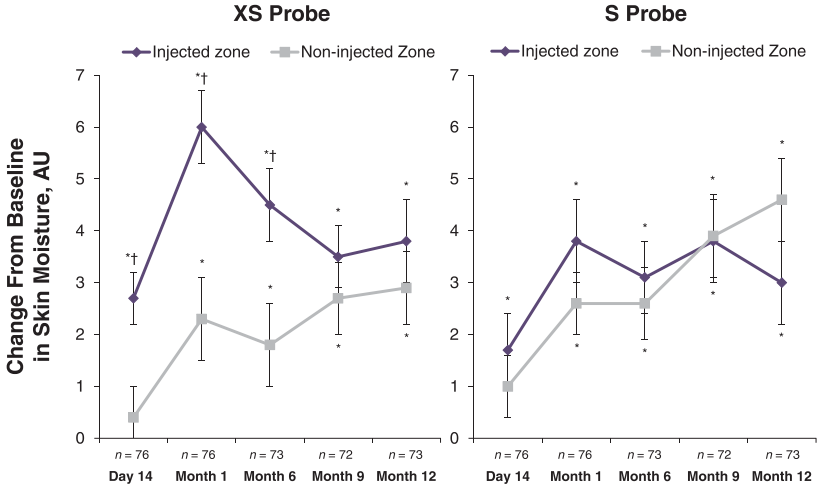

Figure 7. Change from baseline in skin moisture measurements in the infraorbital area after injection with VYC-15L and in a noninjected facial zone in the upper maxillary area. Moisture measurements were taken with the MoistureMeter D using the XS 5 probe and the S 15 probe. AU, arbitrary units. *$p < 0.05$ versus baseline. †$p < 0.05$ versus noninjected zone.

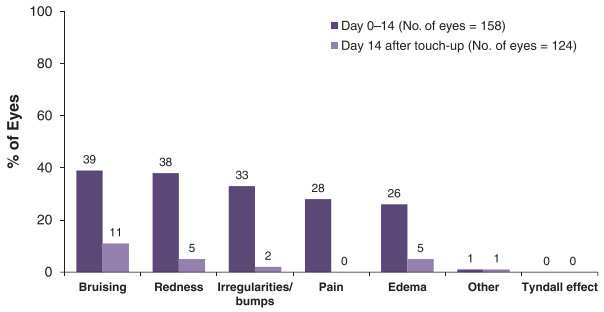

Figure 8. Incidence of ISRs reported by subjects in diaries after initial injection of VYC-15L in the infraorbital area. ISR, injection site reaction.

None of the subjects noticed this effect. No ISRs of lumps or indurations were reported by the investigators after day 14. One serious AE was reported (uterine leiomyoma) that was not related to treatment.

Discussion

VYC-15L injected in the infraorbital area was effective for the correction of infraorbital skin depressions with results lasting up to 12 months. Aesthetic improvements in appearance were noted by high percentages of subjects and investigators throughout the course of the study. Injections in the infraorbital area performed by specialist injectors were safe with only expected, primarily mild to moderate local ISRs. The injectors were also very satisfied with the ease of use and the moldability of VYC-15L.

Response rates in the current study were very high, with 99% of eyes reaching the primary end point of ≥1 grade AIRS improvement at month 1% and 88% of eyes attaining a ≥2 grade improvement. The ≥1 grade AIRS improvement was durable, with 92% of subjects maintaining the response in both eyes at month 6. These response rates are higher than those reported in a single-arm study (n = 49) of infraorbital treatment with cohesive polydensified matrix hyaluronic acid.[11] That study, which assessed effectiveness using a 5-point validated infraorbital scale,[26] reported that approximately three quarters of the subjects had at least a 1-point improvement across both eyes at month 2 (76%) and month 6 (74%).[11]

Injection of VYC-15L significantly increased skin water content in the infraorbital area compared with a noninjected skin zone used as a control. The XS 5 probe of the MoistureMeter was better placed to measure moisture in the infraorbital area compared with the deeper penetration of the S 15 probe. Cutometer readings showed that skin elasticity also significantly improved in the injected versus noninjected control area, with increases lasting through 12 months. Previous studies have reported similar increases in hydration and elasticity after injection of hyaluronic acid–based fillers in other facial areas.[27,28] The increases in moisture and elasticity may contribute to the subject- and investigator-perceived improvements in appearance after injection as measured by the GAIS and to the lessening of the negative effects of overall eye appearance after injection as measured by subjects on the PAAQ.

The safety profile of VYC-15L injection in the infraorbital area was similar to previous infraorbital studies with other hyaluronic acid based fillers.[29,30] AEs reported in the current and previous studies were those typically associated with injection of soft tissue fillers, including transient mild to moderate erythemas, bruising, and edemas, with no investigator-reported severe AEs.[11–14,16,17,19,20,22,30,31] Late-onset mild to moderate edema was observed in 13% of subjects at month 6, which is consistent with other reported rates (range, 3%–24%) of late-onset or prolonged edema after infraorbital injection of hyaluronic acid gel fillers.[11,17,32] Unlike many other reports in the literature, this study had AEs independently assessed by evaluating investigators, rather than by injectors. Most cases of late-onset edema in the current study were mild and not bothersome to the subjects, such that 59% of the edemas reported by investigators at 6 months were not noticed by the subjects. Late-onset edemas in this study may be associated with higher injection volumes, supporting findings in other studies.[29,33]

The importance of injection technique in the treatment of the infraorbital area cannot be overstated. All injections administered in this study were intentionally deep (submuscular/preperiosteal). Although injecting deeply reduces the risk for edema,[13,16] filler displacement from deeper to more superficial planes may cause edema nonetheless. However, injecting deeply can also

help to avoid the Tyndall effect.[34] Performing injections in very small volumes (e.g., serial microaliquots) as opposed to bolus injections that require massaging and/or molding is another important consideration in reducing risk for edema.[11] In the present study, most injections were administered using the multiple microbolus technique, with an average of 4.9 needle punctures per eye.

This study was designed to provide further clarity to physicians with regard to injecting VYC-15L in the infraorbital area. Within the study it was important to permit the specialist injectors to inject as they would in their normal practice to reflect best clinical guidance. A specialist contract research organization performed the standardized skin quality measurements, an increasingly important consideration for esthetic practitioners. Therefore, a limitation of the study may be that the environment was not that of a typical practitioner's clinic. Another consideration is that the malar region is often treated before direct treatment into the infraorbital area. Treatment of the malar region may indirectly lead to improvements in the infraorbital region.

Conclusions

Injection of VYC-15L in the infraorbital area was effective and safe in the correction of infraorbital skin depressions. Results lasted up to 12 months and impressions of esthetic improvements in appearance by subjects and investigators remained high throughout 12 months of follow-up. Improvements in moisture levels of treated infraorbital areas may have contributed to perceptions of improved esthetic appearance. Only expected local ISRs were observed. The incidence of delayed edema in this study was consistent with that reported for infraorbital injections with other hyaluronic acid gel fillers. Use of appropriate injection technique is imperative for optimizing effectiveness and safety of infraorbital treatment with hyaluronic acid-based fillers.

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Address correspondence and reprint requests to: Francois Niforos, MD, Centre Chirurgical Niforos, 55 Boulevard des Belges, Lyon 69006, France, or e-mail: fniforos@niforos.fr