# Eight-Year Postmarket Safety Surveillance of Delayed Complications With a Flexible Lip Filler

Hyaluronic Acid (HA)-based dermal fillers are the most popular aesthetic fillers because of their safety profile.[1,2] However, adverse events (AEs) still occur, which are generally characterized as early (<14 days post-treatment) or delayed-onset (≥14 days post-treatment).[1] Delayed-onset AEs are the focus of this communication because they tend to be related to the patient immunologic response to the product rather than the injection technique and can appear months to years after treatment.[1,2]

Restylane Kysse ($HA_{KYS}$) is an HA filler manufactured using Galderma's (Uppsala, Sweden) XpresHAn technology (Optimal Balance Technology, ex-USA) that offers a balance of flexibility and support (G′) for lip augmentation.[3] $HA_{KYS}$ was introduced in Europe in 2010 (marketed as Emervel Lips until December 2015) and FDA-approved in 2020 for lip augmentation and upper perioral rhytids.[3] The safety of $HA_{KYS}$ was evaluated in 4 clinical studies conducted in Europe and the United States, involving 319 subjects with postinjection follow-up ranging from 2 months to 1 year.

In this study, we present the global postmarket safety experience for $HA_{KYS}$ from 2011 to 2019, with a focus on delayed-onset events, including nodules and inflammatory events, such as hypersensitivity reactions and granulomas.

## Methods

Data were gathered from AE reporting during postmarketing safety surveillance (PMS) between January 2011 and September 2019 for $HA_{KYS}$ (8 years). Sources include spontaneous health care provider or consumer reports, the literature, and health authorities. All AEs were coded using the Medical Dictionary for Regulatory Activities Preferred Terms (MedDRA PT), and medical professionals assessed the relationship to products based on the cumulative case information.

Complaint reports without a clear time to onset or <14 days were excluded (early onset). Delayed-onset events were categorized based on MedDRA PT coding: granulomas ("granuloma" and "foreign body"), nodules ("mass," "nodule," "papule," and "induration"), and hypersensitivity ("hypersensitivity" and "inflammation"). Nodules were further categorized into "noninflammatory" and "inflammatory" based on the event descriptions; they were considered inflammatory if the description included tenderness, swelling/inflammation, pain, or irritation. Hypersensitivity reactions were categorized as such if the description included diffuse facial swelling in all injected areas, or acute and persistent facial swelling. Some cases of inflammatory nodules were also categorized as hypersensitivity reactions depending on the descriptions. Granulomas were categorized only if they were histologically confirmed. The total number of single-use syringes sold worldwide during the search period was used for calculating postmarket AE reporting frequencies.

## Results

From 557 spontaneous complaint reports for $HA_{KYS}$ (reporting frequency 0.05%), 239 (42.9%) were coded as potential events of interest. However, we identified only 94 (16.8%) as delayed-onset, giving a reporting frequency of 0.008% during the period of 2011 to 2019. Most (89/94; 94.7%) were reported between 2015 and 2019, which is the timeframe most (92%) units were sold.

Nodules were the most reported delayed event of interest (71/94, 76%; reporting frequency 0.006%). There were 36 events categorized as inflammatory nodules (38%; reporting frequency 0.003%), 35 noninflammatory nodules (37%; reporting frequency 0.003%), 22 hypersensitivity reactions (23%; reporting frequency 0.002%), and 1 histologically confirmed granuloma (1%; reporting frequency 0.0001%).

Twenty-three reports included degree of severity: 39.1% (9/23) were mild, 43.4% (10/23) moderate, and 17.4% (4/23) severe (1 inflammatory nodule, 2 noninflammatory nodules, and 1 case of hypersensitivity). For the events with reported outcomes (61/94), 31.1% (19/61) had resolved or were resolving at the time of reporting. Most events (84/94) had a defined time to onset ranging from 2 weeks to 2 years, and of these, 75% (63/84) occurred between 2 weeks and 4 months.

Treatments of these AEs were documented in most cases (66/94; 70%). Although treatment varied on a case-by-case basis, most noninflammatory nodules were treated with hyaluronidase, whereas inflammatory nodules were treated with some combination of hyaluronidase, antihistamines, corticosteroids, anti-inflammatories, and antibiotics. Hypersensitivity reactions were typically treated with some combination of corticosteroids, anti-inflammatories, and antihistamines. The granuloma was treated with hyaluronidase and corticosteroids.

## Discussion

Although delayed-onset (≥14 days post-treatment) nodules and inflammatory events are rare in clinical practice, in this postmarketing safety review, they occurred in ~17% of cases reported between 2011 and 2019, with most being reported after 2014. These events were typically mild and moderate with a time to onset of 4 months or less. Interventions for these events were documented in most cases and were typically consistent with current consensus guidelines.[1,2]

The relative frequency of the delayed-onset events of interest (0.008%) in this review is similar to the frequency of delayed events reported for the XpresHAn range of HA fillers between 2011 and 2015 (28 events; 0.003%) and agrees with previous findings from clinical trials.[3,4] These estimated frequencies are relatively low compared with other reports in the literature,[5] but comparison is difficult considering

differences in data collection and frequency calculations. However, it is important to note that because PMS relies on self-reporting, AE frequencies are underestimated because of underreporting, so the AE rates are likely higher than those estimated in this report. Nevertheless, our data demonstrate a low incidence of delayed-onset nodules, hypersensitivity, and granulomas reported during PMS after treatment with $HA_{KYS}$.

## Conclusions

$HA_{KYS}$ has a favorable safety profile based on the relatively low incidences of delayed-onset nodules, hypersensitivity, and granulomas reported during postmarketing surveillance between 2011 and 2019. These data support its recent FDA-approval and continued use for lip augmentation and upper perioral rhytides.

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# Acoustic Shockwave Therapy as an Adjunct to Picosecond Laser for Multicolored Tattoo Removal

Tattoo removal is one of the most common cosmetic dermatologic procedures. Laser treatment remains the gold standard, which uses selective photothermolysis to selectively destroy pigment. A standard treatment regimen can include 7 to 10 sessions with a single laser pass. A major limiting factor is the development of tattoo whitening, which is due to the creation of steam vacuoles within the epidermis and dermis from rapid heating of tattoo particles. Although superficial vacuoles may dissipate more quickly, deep dermal vacuoles can persist for up to 48 hours, which prevents additional laser penetration—a phenomenon known as shielding. Although multiple-pass methods using the R20 protocol or the perfluorodecalin (PFD) patch can enhance tattoo removal through improved epidermal clearance, they may have limited effects deeper in the dermis.[1]

The use of acoustic shockwave (ASW) therapy as a novel adjunct to laser tattoo removal was first reported in 2017 to 2018.[2,3] More recently, a prospective clinical trial found a significant increase in tattoo clearance using 3 to 5 laser passes in combination with ASW compared to laser monotherapy.[4] With this technology, shockwaves are electromagnetically generated using a ferromagnetic projectile within the device handpiece, which is then accelerated by an electromagnet at the applicator end. This leads to production and propagation of a pulse. When the kinetic energy is transferred to the applicator head, an ASW is generated to propagate the skin, which can cause dispersion and destruction of dermal vacuoles to allow for multiple laser passes in a single treatment session.

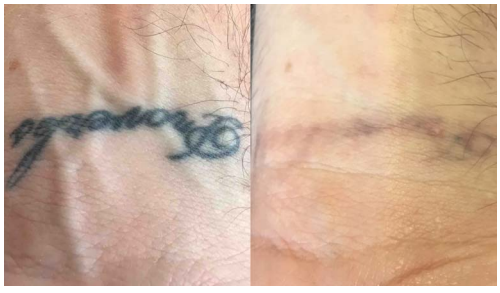

**Figure 1.** Black tattoo on the left wrist of a patient with FST 3. There were 484 pulses/cm$^2$ delivered during the first treatment session with 51% to 75% improvement. After 4 treatment sessions and 1,934 total pulses/cm$^2$, there was 76% to 99% overall improvement. FST, Fitzpatrick skin type.