Post Marketing Study of Safety and Efficacy of Crystalys, a Calcium Hydroxyapatite Based Filler for Facial Soft Tissue Augmentation

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Objective: In this post marketing study our primary objective was to assess the safety of Crystalys, a new calcium hydroxyapatite based filler, in subjects who received sub-dermal or deep-dermal injections for facial soft tissue augmentation. The secondary objective was to evaluate the performance of Crystalys within six months of injection.

Methods: Crystalys was injected to 173 patients, age ranging from 27-72 years, with a variety of facial aesthetic conditions, most common being pronounced nasolabial folds. On average, patients were injected with 3.4ml of Crystalys. After obtaining informed consent form, the subjects were evaluated for adverse events (AEs) and efficacy using three different performance methods.

Results: Safety – 173 patients were evaluated for adverse events. No severe, serious or long-lasting AEs were reported or recorded by patients or physicians. In addition, all events were self-resolving. All reported AEs are common when treated with all injectable fillers. The AEs reported were: Ecchymosis, Edema, Erythema and Pain. Efficacy – efficacy ratings were performed on a subset of 59 patients using the Lemperle Rating Scale (LRS) and the Global Aesthetic Improvement Scale (GAIS) validated clinical scales. In addition, a 5-point Likert scale User Satisfaction Questionnaire was filled out by 72 patients. Crystalys dermal implant demonstrated excellent efficacy results, using both the LRS and GAIS scales, and by user satisfaction ratings. All scales indicated an overall improvement in treated facial areas, coupled with markedly high patient satisfaction scores.

Conclusions: Our results clearly show that Crystalys, a new calcium hydroxyapatite based filler, is safe and effective. No significant risks were associated with Crystalys administration and an unequivocally low risk-to-benefit ratio was established. Crystalys showed an excellent safety profile and high satisfaction rate, making it a highly suitable biodegradable filler.

Introduction

Dermal fillers are widely used for restoration of soft tissue augmentation. These fillers can be classified according to the duration of the effect (temporary, semi-permanent and permanent) or according to the mechanism of action (replacement fillers or stimulatory fillers) (1). The ideal characteristics of soft-tissue filling material include filler longevity, biocompatibility, non-migratory, low AE and risk-to-benefit profile at a reasonable cost-to-benefit ratio (2). Calcium hydroxyapatite (CaHA) based fillers comply with these desired characteristics.

Hydroxyapatites are a class of chemical compounds that share the chemical formula $Ca_{10}(PO_4)_6(OH)_2$ and vary, among other properties, in their biological behavior. Macroporous ceramic hydroxyapatite (10µm-500µm) are osteoconductive, and support ingrowth of fibrous and vascular tissue. CaHA metabolites are calcium and phosphate ions, both normally found in the body. Studies of implants containing CaHA, both *in vitro* and *in vivo*, showed minimal or no inflammatory response, foreign body or giant cell granulomatous reaction, and no systemic toxicity (3-5).

CaHA is the primary component of bone and dents, it is biocompatible and used in medicine for more than two decades. One of the first clinical applications of CaHA in a particle form was as onlay grafts for bone regeneration and in dentistry (2). CaHA is used in orthopedic surgery as bone cement and it has been shown to be effective in contouring of cranial vault irregularities and craniofacial trauma surgery (6-8). CaHA has also been used as a bulking agent in urinary incontinence (9) and for treatment of vesicoureteral reflux (10).

CaHA is also used for velopalatal insufficiency (11) and glottal insufficiency (vocal fold augmentation) (12), and for vertebral augmentation, showing good safety profile (13).

CaHA is used in the dermal filler market for more than 10 years. Crystalys, a new calcium hydroxyapatite based filler, is a sterile, latex-free, non-pyrogenic, semi-solid, cohesive, sub-dermal, injectable implant, whose main component is synthetic CaHA. The semi-solid nature of CaHA-based dermal fillers is created by suspending CaHA microspheres of 25–45 micron diameter in a gel carrier that consists primarily of phosphate buffer and glycerin. The gel structure is formed by the addition of a small amount of carboxymethylcellulose (2). CaHA microspheres form scaffold for ingrowth by fibroblasts, which gradually replace the carrier gel. As the fibroblasts grow, they generate collagen fibers, which anchor the microspheres in place (3, 14, 15). CaHA is biodegradable, following the same metabolic pathway as bone debris resulting from common bone fractures. After 2–3 months the carboxymethylcellulose is fully absorbed and replaced by collagen. Finally, a gradual breakdown of the particles occurs until complete phagocytosis is achieved (2). CaHA is highly viscous and is injected into the deep dermis or, for volume restoration, at or below the dermal subcutaneous junction (16).

Crystalys is marketed in Israel from September 2011 for facial soft tissue augmentation. We recently conducted a post marketing study of safety and efficacy of Crystalys among 173 patients. This article summarizes its results.

Methods

A retrospective study was conducted on patients injected with Crystalys between July 2012 and December 2013. This study was designed as a postmarket, two-center study, comprised of both retrospective and prospective elements. Retrospective element: Safety and performance data were collected from all the available medical charts of Crystalys-treated patients that contained sufficient data for analysis (n=173). In addition, telephone interviews were conducted to capture information that may not have been noted in their medical files. Prospective element: After providing informed, signed consent, photographs of a subset of 59 patients treated within six months of initiation of this study and with a "before" photo in their medical file, were either captured or taken from patient medical files and assessed by the investigators using the Lemperle Rating Scale (LRS) and the Global Aesthetic Improvement Scale (GAIS). In addition, the 5-point Likert scale User Satisfaction Questionnaire was filled out by 72 patients.

Patients ranged in age from 27 to 72 years. Patients follow up ranged between one month to more than 6 month, the time from treatment is indicated in table 1. To be eligible for inclusion, subjects were required to be at least 18 of age, to be treated with Crystalys, and to provide informed consent after being counseled about the study protocol. This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the ICH Harmonized Tripartite Guideline for GCP. The protocol and informed consent forms (ICFs) for this study were reviewed and approved by our Institutional Review Board (IRB).

Table 1. Demographics Characteristics - Time from treatment to follow up

Time from treatment (months)	Number (%) of patients
1-2	28 (16%)
3-4	18 (10%)
5-6	19 (11%)
>6	108 (62%)

Areas treated

Several facial areas were treated with Crystalys, the most commonly treated site was the nasolabial folds (95 patients). Other treated areas included the Marionette lines, cheek bones, mouth corners, jaw lines and others (Table 2). Note, that some patients underwent treatment in multiple regions.

Table 2. Facial treatment areas

Injection site*	Number of patients*
Nasolabial folds	95
Marionette lines	42
Cheek bones	30
Mouth corners	55
Jaw line	3
Other	17
* Some patients were treated at multiple sites	

Number of Crystalys injections per patient

Mean and median injected volume of Crystalys per patient were 3.4 ml and 3.0 ml, respectively. The maximum volume injected to a single patient in one session was 8 ml whereas the minimum was 1 ml. Injection volume per patient was determined by the physician according to the depth of the fold and the number of treated areas. The maximum injection volume for a single patient in multiple sessions was 14 ml.

Patient's safety evaluation

Safety was evaluated by the incidence and duration of local and systemic AEs. Patients answered a questionnaire on a telephone call, or in the follow up visit at the clinic, and any AEs noted by the patients were recorded. Descriptive tables summarize the AEs reported, the severity and duration of the events.

Patient's effectiveness and satisfaction evaluation

The effectiveness was evaluated on a subset of patients that were treated during the 6 months period that preceded the initiation of this analysis and for whom both pre- and post-treatment photos were available. These 59 patients were scored by Physicians using the LRS (Table 3) and GAIS (Table 4) scales by comparing post-treatment outcomes to baseline. LRS scores were statistically analyzed using paired Student's *t*-test. GAIS scores were statistically analyzed using Kolmogorov-Smirnov test for two null hypotheses: (1) the treatments resulted in "no change", and (2) the treatments resulted in merely "improved". For all statistical analysis, a *p*-value of <0.05 was considered statistically significant.

In addition, 72 patients filled out the 5-point Likert Scale User Satisfaction Questionnaire (see Table 7 for details of this questionnaire).

Table 3. Lemperle Rating Scale (LRS)

Classification	Description
5	Very deep wrinkle, redundant fold.
4	Deep wrinkle, well-defined edges.
3	Moderately deep wrinkle.
2	Shallow wrinkles.
1	Just perceptible wrinkle
0	No wrinkle

Table 4. Global Aesthetic Improvement Scale (GAIS)

Rating	Description
Very Much Improved	Optimal cosmetic result for the implant in this patient.
Much Improved	Marked improvement in appearance from initial condition, but not completely optimal for this patient. A touch-up would slightly improve the result.
Improved	Obvious improvement in appearance from initial condition, but a touch-up or re-treatment is indicated.
No Change	The appearance is essentially the same as the original condition.
Worse	The appearance is worse than the original condition.

Results

Safety

Hydoxytite injection was well tolerated by all patients. No serious AEs were reported by patients or physicians during the study, or were collected from patients' files. All reported AEs were standard, local injection site reactions, with most being mild, short-term and self-resolving. No AEs were considered device-related. The following side effects, which are common in dermal fillers in general and in CaHA-based dermal fillers in particular, were not reported: granulomas, allergic reaction, nodule, pruritus, erosion, necrosis or infection. Table 5 details the AEs that were potentially attributed to the treatment.

Table 5. Frequency of related Treatment-Emergent AEs

Adverse Event	Number (%) of patients
Ecchymosis	73 (42%)
Edema	121 (70%)
Erythema	39 (23%)
Pain	7 (4%)

The most common side effects reported were Edema (70% of patients) and Ecchymosis (42% of patients). Edema mean duration was 5.5 days while erythema mean duration was 4.1 days; pain mean duration was 7.1 days and the mean duration of ecchymosis was 6.9 days following treatment with Crystalys. All AEs resolved without any medical intervention.

Efficacy rating by treating physicians and by patients

1. Performance Evaluation Using LRS. Efficacy ratings, using LRS, were performed on a subset of 59 patients. A significant clinical improvement was observed in the vast majority (70/84 assessed sites) of Crystalys-treated facial regions, when compared to baseline. Apart from four reports of inferior outcomes, the remaining regions were deemed equivalent to baseline conditions. Table 6 summarizes performance as per LRS scores. Statistical analysis was performed on the LRS results using paired *t*-test. Crystalys induced a significant improvement in facial contours.

2. Performance Evaluation Using GAIS. The same subset of 59 patients was also rated using GAIS. The GAIS scores analysis demonstrate clinical effectiveness of the dermal filler as 31% of the patients (18 out of 59) were "much improved", 58% (34) were "improved" and only 12% (7) showed "no change" following treatment compared with baseline. These data were statistically analyzed using Kolmogorov-Smirnov test for two null hypotheses: (1) the treatments resulted in "no change" (*p*-value<1e-6), and (2) the treatments resulted in merely "improved" (*p*-value=0.008). Both these hypotheses were rejected (*p*-value<0.05) leading to the conclusion that Crystalys induced a substantial improvement ("much improved") in treated facial sites.

3. Performance Evaluation Using the 5-point Likert Scale User Satisfaction Questionnaire Performance was also evaluated using 5-point Likert Scale User Satisfaction Questionnaire, which was answered by 72 patients. A high user satisfaction was reported for all questions posed in the user satisfaction questionnaire, with mean ratings >4 for all questions. Overall satisfaction exceeded 4.4, and likeliness to repeat similar treatment as well as recommendation regarding the treatment to others exceeded 4.5 (Table 7).

Table 7. Performance as per User Satisfaction

Question	Mean score*
Being treated with Crystalys injections was beneficial to me.	4.138
I am happy with the look and feel of my face after having had this treatment.	4.201
Overall, I am satisfied with having had this treatment.	4.444
Overall, the treatment outcome meets my expectations.	4.145
I would be likely to return to the clinic to receive additional treatment with this product.	4.513
I would recommend treatment with this product to others.	4.569

* Score scale: 1 – Strongly disagree; 2 – Disagree; 3 – Neither agree or disagree; 4 – Agree; 5 – Strongly Agree

Table 6. Performance as per LRS Scores

Injection site	Number of patients				*p*-value[2]
	Total[1]	Superior	Equivalent	Inferior	
Nasolabial folds	34	29	3	2	$1e^{-7}$
Marionette lines	14	10	2	2	0.005
Cheek bones	14	12	2	0	$2e^{-5}$
Mouth corners	20	19	1	0	$1e^{-9}$
Jaw line	2	0	2	0	/

[1] Some patients were injected at multiple sites

[2] For the null hypothesis that there was no improvement in LRS scores upon treatment.

Fig. 1 shows representative outcome of Crystalys treatment of a 51-year-old female patient before treatment, immediately after treatment, two weeks after treatment and 4 months after treatment. The patient was injected in the nasolabial folds, marionette lines, and cheek bones with a total of 5ml Crystalys.

Discussion

Crystalys, a CaHA based filler, is a new product in the biodegradable, subcutaneous and deep dermal fillers market. Crystalys is marketed in a box containing 2 ready-to-use 1.25ml syringes. It is our impression that Crystalys is easy to use, safe, reasonably-priced and effective.

Safety results of Crystalys treatment are excellent. No severe, serious or long-lasting AEs were reported or recorded by patients or physicians. In addition, there were no records of any measures taken to resolve AEs, indicating that all AEs were self-resolving. All reported AEs are common when treated with all injectable fillers, including collagen and hyaluronic acid. In most cases the AEs resolved within 4-7 days. The AEs reported are typical injection site reactions, of no relation to the administered product, and were of standard durations. There were no reports of granulomas, ecchymosis, allergic reaction, nodule, pruritus, erosion, necrosis or infection.

Post treatment, patients were advised to gently compress the injection site with an ice pack in order to reduce swelling and redness.

Crystalys efficacy was demonstrated upon comparison of post-treatment to baseline photographs, with significant improvements observed in the majority of evaluated cases in both LRS and GAIS scores. User satisfaction ratings were high, exceeding 4, for overall satisfaction. In summary, no significant risks were associated with Crystalys administration and an unequivocally low risk-to-benefit ratio was established. Crystalys was shown to be both safe and effective for soft tissue augmentation of facial regions.

CaHA is known to stimulate fibroblasts to produce collagen fibers (3). The mechanism of action, as seen in our study, is divided to two stages. At the first stage the microspheres suspended in the carrier gel generate immediate augmentation. As the carrier gel is absorbed in the body, a slight reduction in volume is seen in some of the patients. At the second stage, collagen fibers are built, filling the injected areas and providing volume. The overall results are excellent, as determined using three different methods of performance evaluation.

Crystalys treatment has all the desired characteristics of dermal fillers. It is biodegradable, yet long lasting, safe, easy to use, and cost-effective. The CaHA microspheres do not migrate, and harmonically merge with the tissue, giving glowing, natural look. All in all, this new filler is highly suited for soft tissue augmentation.

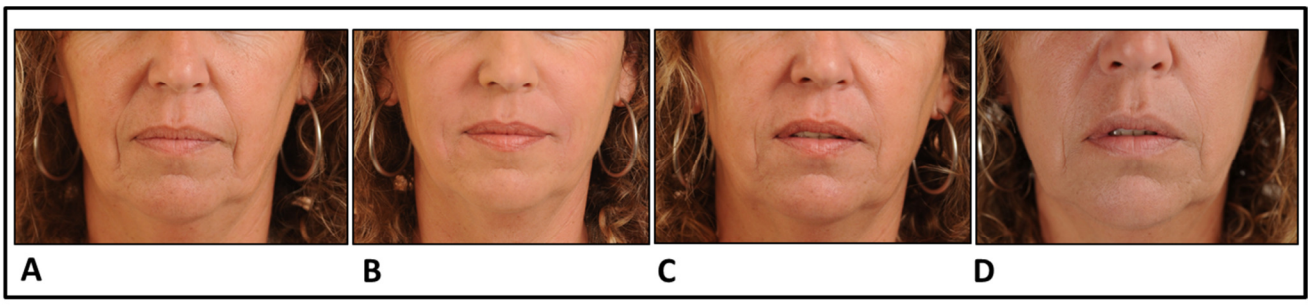

Figure 1. Photograph of a 51 year-old female patient at four time points. (A) Before treatment. (B) Immediately after treatment. (C) Two weeks after treatment. (D) Six months after treatment. Patient was injected in the nasolabial folds (1ml at each side), marionette lines (1ml at each side), and cheek bones (0.5ml at each side).

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