Journal of Cosmetics, Dermatological Sciences and Applications, 2023, 13, 1-15
https://www.scirp.org/journal/jcdsa
ISSN Online: 2161-4512
ISSN Print: 2161-4105

A Comprehensive Review of Long-Term Safety and Effectiveness of FACILLE Modified Sodium Hyaluronate Gel for Injection over 3 Years

Haw-Yueh Thong[1], Po-Jen Lin[2,3], Chieh-Chen Huang[1*]

[1]Department of Dermatology, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei
[2]College of Medicine, National Taiwan University, Taipei
[3]Bloomberg School of Public Health, John Hopkins University, Baltimore
Email: *M011971@ms.skh.org.tw

How to cite this paper: Thong, H.-Y., Lin, P.-J. and Huang, C.-C. (2023) A Comprehensive Review of Long-Term Safety and Effectiveness of FACILLE Modified Sodium Hyaluronate Gel for Injection over 3 Years. *Journal of Cosmetics, Dermatological Sciences and Applications*, **13**, 1-15.
https://doi.org/10.4236/jcdsa.2023.131001

Received: January 12, 2023
Accepted: March 12, 2023
Published: March 15, 2023

Abstract

FACILLE modified sodium hyaluronate gel was designed to be used for nasolabial fold (NLF) correction. However, no study has investigated the long-term safety and effectiveness of FACILLE. Thus, a retrospective study of 14 aesthetic clinics in China was conducted. This was the first large-scale, postmarketing study on FACILLE to evaluate the occurrence of adverse events (AEs) and provide essential information on the satisfaction of patients with FACILLE injections. This study recruited participants aged >18 years. FACILLE was injected into the NLFs on both sides of each participant's face. The primary endpoint for safety was systemic or severe AEs at an injection site. Effectiveness was assessed on the basis of the participants' subjective perceptions and satisfaction levels. Safety and effectiveness data were collected on the day of injection and at 2 weeks and 1, 3, 6, 9, 12, 18, 24, 30 and 36 months postinjection. In total, 1552 participants were enrolled (mean age, 29.1 years), and most of them (96.5%) were women. The mean injection volume was 1.39 ± 0.658 mL, and the average number of injections was 2.4 ± 1.68. AEs were reported by 205 participants (13.2%). All AEs occurred at local injection sites. No systemic or severe AEs were observed. Local pain was the most frequently reported AE regardless of the number of injections or the injection volume. Only eight AE cases were correlated with FACILLE administration, with two cases involving local allergic reactions. The participants self-reported that they perceived the procedure to have an effectiveness of ≥90% within 6 months postinjection although this percentage decreased substantially after 9 months. Their satisfaction level was >90% within 1 month postinjection but decreased gradually after 3 months. Our results indicate that the long-term safety of FACILLE injection is adequate. The high self-reported

perceived effectiveness and satisfaction levels indicate the considerable potential of FACILLE injections for correcting NLFs.

Keywords

Hyaluronic Acid, Nasolabial Folds, Dermal Implant, Aesthetics

1. Introduction

In the past decades, filler injections have become the preferred cosmetic solution for most patients and physicians. Filling properties allow a physician to obtain optimal results with minimal downtime and considerable longevity. Injection strategies are based on anatomical concepts, and they are aimed at maintaining results in the long term while ensuring patient safety. FACILLE modified sodium hyaluronate gel (Scivision Biotech, Kaohsiung, Taiwan) was designed to be injected into the middle and deep layers of the facial dermis to correct nasolabial folds (NLFs). A retrospective, open-label, and multicenter clinical study was conducted in China to evaluate the long-term safety and effectiveness of FACILLE modified sodium hyaluronate gel.

2. Materials and Methods

The present study was conducted at 14 aesthetic clinics in China. The inclusion period was from December 14, 2016, to May 7, 2017. Individuals were included if they were aged ≥18 years, had used or had the intention to use FACILLE modified sodium hyaluronate gel, and had agreed to participate and comply with the follow-up schedule of the present study. Individuals were excluded if they had a history of hypersensitivity or allergy to hyaluronic acid (HA) or any component of the gel or were affected by other circumstances that made them unsuitable for participation in the present study. FACILLE injections were administered to each participant on both NLF sides. The primary endpoint for safety was defined as the occurrence of adverse events (AEs) at an injection site (e.g., pain, swelling, bruising, nodules, local allergic reactions, pruritis, ecchymosis, or implant displacement), systemic AEs (e.g., systemic toxic reactions, systemic immunologic reactions, and vasovagal/neurocardiogenic syncope) or severe AEs (e.g., blindness or death). Effectiveness was assessed on the basis of the participants' subjective perceptions and satisfaction levels. Safety and effectiveness data were collected in person or through telephone interviews on the day of injection and at 2 weeks and 1, 3, 6, 9, 12, 18, 24, 30, and 36 months postinjection (**Appendix**). For continuous variables, the descriptive statistics included observed values, means, standard deviations, medians, and minimum and maximum values. Categorical variables were presented as frequency and percentage values. For the applicable safety variables, incidence values and 95% confidence intervals were calculated by applying the Clopper-Pearson exact probability method. We calculated the

occurrence rate of AEs and its 95% confidence interval during each interview by using the Clopper-Pearson method. We evaluated the AE occurrence on the basis of the number of injections and injection volume. The participants who were given other aesthetic injectable products on or before the day of injection were discussed separately. Subjective perceptions and satisfaction levels were measured at various postinjection time points and when AEs occurred.

The postmarketing safety and efficacy surveillance of FACILLE did not affect the participants' medical care. The present study was conducted in compliance with the Good Clinical Practice (GCP) Guidelines for Market Research of the National Medical Products Administration (NMPA). The GCP Guidelines for Market Research of the NMPA is not a mandatory ethical approval framework for postmarketing studies; therefore, approval was not required for the present study. All information was disclosed voluntarily, and informed consent was obtained from all participants. The present study is registered with ClinicalTrials.gov (identifier: NCT05294562).

3. Results

3.1. Demographics

We recruited 1552 participants from 14 aesthetic clinics. Their mean and median ages were 29.1 and 28.0 years, respectively. The participants were aged between 18 and 62 years. Among the participants, 1498 (96.5%) were women, and 180 (11.6%) had had previous facial injections (Table 1). As of May 12, 2020, all participants had completed interviews on at least the day of injection and at 2 weeks and 1, 3, and 6 months postinjection. In total, 1547 (99.7%), 1539 (99.2%), 1533 (98.8%), 1532 (98.7%), 1519 (97.9%), and 1515 participants (97.6%) completed their interviews at 9, 12, 18, 24, 30, and 36 months postinjection, respectively.

Table 1. Demographics.

		N = 1552
Age (Years)	n	1539
	Mean (SD)	29.1 (7.23)
	Median (Years)	28.0
	Minimum (Years)	18
	Maximum (Years)	62
Gender		
Male	n (%)	54 (3.5)
Female	n (%)	1498 (96.5)
Previous facial injections		
Yes	n (%)	180 (11.6)
No	n (%)	1372 (88.4)

SD: Standard Deviation.

The loss to follow-up rate over 36 months was estimated to be 2.4%.

3.2. Details and Summary of the Injections

The mean and median FACILLE injection volumes were 1.39 ± 0.658 and 1.72 mL, respectively, for the 1552 participants, who received more than 2 mL of injections. The participants received an average of 2.4 ± 1.68 injections. A total of 459 (29.6%) participants received injections more than 3 times, and 101 (6.5%) received repeated injections over the follow-up period. A total of 508 participants used other products before, during, or after receiving FACILLE injections (Table 2); among these participants, 267 received type A botulinum toxin injections, 297 received sodium hyaluronate injections, and a small number received polymethyl methacrylate injections or underwent facial aesthetic laser treatments.

3.3. Long-Term Safety

AEs were reported by 205 (13.2%) of the 1552 participants. All AEs occurred at local injection sites, and no systemic or severe AEs were reported during the follow-up period. The most frequently reported AEs were local pain (11.0%), swelling (5.7%), and bruising (2.9%). Nodules, local allergic reactions, pruritis, ecchymosis, and implant displacement were rarely reported (Table 3).

The participants were classified by the number of injections that they received, and AEs were determined to have occurred in 1.7% of the participants who received a single injection (9/541). Local pain was the most frequently reported AE in this subgroup; the other AEs had an occurrence probability of <1%. For the participants who received two injections, their AE probability was higher, at 19.9% (55/277); local pain was the most frequently reported AE in this subgroup (15.5%, 43/277), and the other AEs had an occurrence probability of <8%. For the participants who received ≥3 injections, 29.0% developed AEs (133/459). Local pain and swelling were the two most frequently reported symptoms, and they were reported by 25.7% (118/459) and 13.9% (64/459) of the participants, respectively. The other AEs had a probability of occurrence of <1% (Table 4).

After the participants were classified by injection volume, AEs were reported in 13.7% of the participants who received ≤1 mL of FACILLE (130/952), 14.6% of those who received between 1 and 1.99 mL of injections of FACILLE (66/451), and 8.3% of those who received ≥2 mL of FACILLE (4/72). Local pain was the most frequently reported AE regardless of the injection volume (Table 5).

In terms of severity, almost all AEs were mild, with the exception of those of two cases involving moderate local allergic reactions (Table 6). Furthermore, eight AE cases were determined to be correlated with FACILLE administration; these cases involved nodules (two cases), local pain (two cases), local allergic reactions (two cases), pruritis (one case), and implant displacement (one case). The overall incidence of AEs correlated with FACILLE administration was 0.5% (8/1552; Table 7).

Table 2. Injection details and summary.

		All participants **(N = 1552)**	Received products other than FACILLE **(N = 508)**
Injection volume (ml)[a]	n	1475	
	Mean (SD)	1.39 (0.658)	
	Median	1.00	
	Minimum	0.4	
	Maximum	6.0	
Unknown	n (%)	77 (5.0)	
≤1	n (%)	952 (61.3)	
1 - ≤2	n (%)	451 (29.1)	
>2	n (%)	72 (4.6)	
Injection times[b]	n	1277	
	Mean (SD)	2.4 (1.68)	
	Median	2.0	
	Minimum	1	
	Maximum	12	
Unknown	n (%)	275 (17.7)	
1	n (%)	541 (34.9)	
2	n (%)	277 (17.8)	
3 or more	n (%)	459 (29.6)	
Injection Summary			
History injections	n (%)		165 (32.5)
Injection day of FACILLE	n (%)	1552 (100.0)	270 (53.1)
2 weeks post-injection	n (%)	10 (0.6)	14 (2.8)
1 month post-injection	n (%)	3 (0.2)	3 (0.6)
3 months post-injection	n (%)	9 (0.6)	30 (5.9)
6 months post-injection	n (%)	21 (1.4)	63 (12.4)
9 months post-injection	n (%)	20 (1.3)	64 (12.6)
12 months post-injection	n (%)	21 (1.4)	47 (9.3)
18 months post-injection	n (%)	10 (0.6)	32 (6.3)
24 months post-injection	n (%)	3 (0.2)	40 (7.9)
30 months post-injection	n (%)	0	34 (6.7)
36 months post-injection	n (%)	4 (0.3)	12 (2.4)

SD: Standard deviation. [a]Injection volume: Defined as the maximal injection volume at the same injection site. [b]Injection times: Defined as the maximal injection times at the same injection site.

Table 3. Summary of AEs.

AE type		All participants (N = 1552)	Received products other than FACILLE (N = 508)
Any	n (%)	205 (13.2)	20 (3.9)
	95% CI	(11.6, 15.0)	(2.4, 6.0)
Local	n (%)	205 (13.2)	20 (3.9)
	95% CI	(11.6, 15.0)	(2.4, 6.0)
Local pain	n (%)	171 (11.0)	16 (3.1)
	95% CI	(9.5, 12.7)	(1.8, 5.1)
Swelling	n (%)	88 (5.7)	8 (1.6)
	95% CI	(4.6, 6.9)	(0.7, 3.1)
Bruising	n (%)	45 (2.9)	2 (0.4)
	95% CI	(2.1, 3.9)	(0.0, 1.4)
Nodules	n (%)	4 (0.3)	1 (0.2)
	95% CI	(0.1, 0.7)	(0.0, 1.1)
Local allergic reaction	n (%)	2 (0.1)	0
	95% CI	(0.0, 0.5)	0
Pruritis	n (%)	1 (0.1)	0
	95% CI	(0.0, 0.4)	0
Ecchymosis	n (%)	1 (0.1)	0
	95% CI	(0.0, 0.4)	0
Implant displacement or bulge	n (%)	1 (0.1)	1 (0.2)
	95% CI	(0.0, 0.4)	(0.0, 1.1)
Others (*i.e.* local heat, acnes)	n (%)	3 (0.2)	2 (0.4)
	95% CI	(0.0, 0.6)	(0.0, 1.4)

Clopper-Pearson was applied to calculate 95% confidence interval.

Table 4. Summary of AEs by injection times.

AE type		Injection Time (s)			
		Unknown (N = 275)	Once (N = 541)	Twice (N = 277)	Thrice or more (N = 459)
Any	n (%)	8 (2.9)	9 (1.7)	55 (19.9)	133 (29.0)
	95% CI	(1.3, 5.7)	(0.8, 3.1)	(15.3, 25.0)	(24.9, 33.4)
Local	n (%)	8 (2.9)	9 (1.7)	55 (19.9)	133 (29.0)
	95% CI	(1.3, 5.7)	(0.8, 3.1)	(15.3, 25.0)	(24.9, 33.4)

Continued

Local pain	n (%)	3 (1.1)	7 (1.3)	43 (15.5)	118 (25.7)
	95% CI	(0.2, 3.2)	(0.5, 2.6)	(11.5, 20.3)	(21.8, 30.0)
Swelling	n (%)	1 (0.4)	1 (0.2)	22 (7.9)	64 (13.9)
	95% CI	(0.0, 2.0)	(0.0, 1.0)	(5.0, 11.8)	(10.9, 17.5)
Bruising	n (%)	0	1 (0.2)	12 (4.3)	32 (7.0)
	95% CI	(0.0, 1.3)	(0.0, 1.0)	(2.3, 7.4)	(4.8, 9.7)
Nodules	n (%)	2 (0.7)	0	1 (0.4)	1 (0.2)
	95% CI	(0.1, 2.6)	(0.0, 0.7)	(0.0, 2.0)	(0.0, 1.2)
Local allergic reaction	n (%)	1 (0.4)	0	0	1 (0.2)
	95% CI	(0.0, 2.0)	(0.0, 0.7)	(0.0, 1.3)	(0.0, 1.2)
Pruritis	n (%)	1 (0.4)	0	0	0
	95% CI	(0.0, 2.0)	(0.0, 0.7)	(0.0, 1.3)	(0.0, 0.8)
Ecchymosis	n (%)	0	0	0	1 (0.2)
	95% CI	(0.0, 1.3)	(0.0, 0.7)	(0.0, 1.3)	(0.0, 1.2)
Implant displacement or bulge	n (%)	1 (0.4)	0	0	0
	95% CI	(0.0, 2.0)	(0.0, 0.7)	(0.0, 1.3)	(0.0, 0.8)
Others (*i.e.* local heat, acnes)	n (%)	0	0	0	3 (0.7)
	95% CI	(0.0, 1.3)	(0.0, 0.7)	(0.0, 1.3)	(0.1, 1.9)

Clopper-Pearson was applied to calculate 95% confidence interval.

Table 5. Summary of AEs by injection volume.

AE type		Injection Volume (ml)			
		Unknown (N = 77)	**≤1 (N = 952)**	**>1 - ≤2 (N = 451)**	**>2 (N = 72)**
Any	n (%)	3 (3.9)	130 (13.7)	66 (14.6)	6 (8.3)
	95% CI	(0.8, 11.0)	(11.5, 16.0)	(11.5, 18.2)	(3.1, 17.3)
Local	n (%)	3 (3.9)	130 (13.7)	66 (14.6)	6 (8.3)
	95% CI	(0.8, 11.0)	(11.5, 16.0)	(11.5, 18.2)	(3.1, 17.3)
Local pain	n (%)	2 (2.6)	112 (11.8)	53 (11.8)	4 (5.6)
	95% CI	(0.3, 9.1)	(9.8, 14.0)	(8.9, 15.1)	(1.5, 13.6)
Swelling	n (%)	1 (1.3)	54 (5.7)	33 (7.3)	0
	95% CI	(0.0, 7.0)	(4.3, 7.3)	(5.1, 10.1)	(0.0, 5.0)
Bruising	n (%)	0	19 (2.0)	25 (5.5)	1 (1.4)
	95% CI	(0.0, 4.7)	(1.2, 3.1)	(3.6, 8.1)	(0.0, 7.5)
Nodules	n (%)	1 (1.3)	1 (0.1)	1 (0.2)	1 (1.4)
	95% CI	(0.0, 7.0)	(0.0, 0.6)	(0.0, 1.2)	(0.0, 7.5)

Continued

Local allergic reaction	n (%)	0	1 (0.1)	1 (0.2)	0
	95% CI	(0.0, 4.7)	(0.0, 0.6)	(0.0, 1.2)	(0.0, 5.0)
Pruritis	n (%)	0	1 (0.1)	0	0
	95% CI	(0.0, 4.7)	(0.0, 0.6)	(0.0, 0.8)	(0.0, 5.0)
Ecchymosis	n (%)	0	0	1 (0.2)	0
	95% CI	(0.0, 4.7)	(0.0, 0.4)	(0.0, 1.2)	(0.0, 5.0)
Implant displacement or bulge	n (%)	0	0	0	1 (1.4)
	95% CI	(0.0, 4.7)	(0.0, 0.4)	(0.0, 0.8)	(0.0, 7.5)
Others (*i.e.* local heat, acnes)	n (%)	0	0	3 (0.7)	0
	95% CI	(0.0, 4.7)	(0.0, 0.4)	(0.1, 1.9)	(0.0, 5.0)

Clopper-Pearson was applied to calculate 95% confidence interval.

Table 6. Severity of AEs.

AE type **AE severity**		**All participants** **(N = 1552)**
Any	n (%)	205 (13.2)
Local pain	n (%)	171 (11.0)
Mild	n (%)	171 (11.0)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0
Swelling	n (%)	88 (5.7)
Mild	n (%)	88 (5.7)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0
Bruising	n (%)	45 (2.9)
Mild	n (%)	45 (2.9)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0
Nodules	n (%)	4 (0.3)
Mild	n (%)	4 (0.3)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0

Continued

Local allergic reaction	n (%)	2 (0.1)
Mild	n (%)	0
Moderate	n (%)	2 (0.1)
Severe	n (%)	0
Extremely severe	n (%)	0
Pruritis	n (%)	1 (0.1)
Mild	n (%)	1 (0.1)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0
Ecchymosis	n (%)	1 (0.1)
Mild	n (%)	1 (0.1)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0
Implant displacement or bulge	n (%)	1 (0.1)
Mild	n (%)	1 (0.1)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0
Others (*i.e.* local heat, acnes)	n (%)	3 (0.2)
Mild	n (%)	3 (0.2)
Moderate	n (%)	0
Severe	n (%)	0
Extremely severe	n (%)	0

If one participant had the same AE for several times, it was counted only once and the most severe episode was counted. Mild: defined as no treatment required. Moderate: defined as treatment required or led to at least 1 day of hospitalization. Severe: defined as ICU treatment required or led to at least 7 days of hospitalization. Extremely severe: defined as death, life-threatening, or conditions leading to permanent disability.

Table 7. Summary of AEs correlated with FACILLE administration.

AE type		All participants (N = 1552)
Total	n (%)	8 (0.5)
	95% CI	(0.2, 1.0)

Continued

Nodules	n (%)	2 (0.1)
	95% CI	(0.0, 0.5)
Local pain	n (%)	2 (0.1)
	95% CI	(0.0, 0.5)
Local allergic reaction	n (%)	2 (0.1)
	95% CI	(0.0, 0.5)
Pruritis	n (%)	1 (0.1)
	95% CI	(0.0, 0.4)
Implant displacement or bulge	n (%)	1 (0.1)
	95% CI	(0.0, 0.4)

3.4. Effectiveness

The participants' perception of the effectiveness of the treatment was the highest on the day of injection (97.7%), and it was ≥90% within 6 months postinjection. However, their perception of the injection's effectiveness decreased substantially after 9 months (Table 8).

The percentage of participants with a satisfaction level of *very satisfied* or *satisfied* on the day of injection was 95.1% and remained at >90% within 1 month postinjection. Over the course of 3 months, their satisfaction level decreased gradually.

Notably, the participants who developed AEs during the follow-up period exhibited satisfaction levels similar to those of the participants who did not develop AEs (Table 9).

4. Discussion

Since the 1970s, HA has been widely applied in ophthalmology and orthopedics [1]. Animal- and bacteria-sourced HA are structurally identical to the HA produced in the human body. Because of its nonantigenic, nonallergic, and biodegradable characteristics and its excellent biocompatibility, HA is a commonly used material in the aesthetic field [2]. Allergic reactions to HA injections are rare, and such reactions are most likely caused by the trace protein components that are formed while HA injections are being prepared [3].

In the present study, all reported AEs following FACILLE administration were local. Acute-onset reactions, such as local pain, swelling, and bruising, were predominant and mainly occurred on the day of injection. Chronic-onset reactions (e.g., nodules, local allergic reactions, and implant displacement) were rare, and they tended to occur 2 weeks after FACILLE injection. Almost all of the AEs were mild and could be managed conservatively; however, two cases involving moderate local allergic reactions required antiallergic medications to be administered. One participant with an allergic reaction received dexamethasone with

Table 8. Subjective effectiveness rates of FACILLE.

Time of interview		All participants (N = 1552)
Injection day	n (%)	1516 (97.7)
2 weeks postinjection	n (%)	1543 (99.4)
1 month postinjection	n (%)	1544 (99.5)
3 months postinjection	n (%)	1522 (98.1)
6 months postinjection	n (%)	1409 (90.8)
9 months postinjection	n (%)	1195 (77.2)
12 months postinjection	n (%)	987 (64.1)
18 months postinjection	n (%)	571 (37.2)
24 months postinjection	n (%)	447 (29.2)
30 months postinjection	n (%)	382 (25.1)
36 months postinjection	n (%)	392 (25.9)

Table 9. Satisfactory levels of FACILLE.

Time of interview Satisfactory level		All participants (N = 1552)	With AE (N = 205)	Without AE (N = 1347)
Injection day	n (%)	1552 (100)	205 (100)	1347 (100)
Very satisfied	n (%)	352 (22.7)	57 (27.8)	295 (21.9)
Satisfied	n (%)	1124 (72.4)	145 (70.7)	979 (72.7)
Neutral	n (%)	67 (4.3)	3 (1.5)	64 (4.8)
Dissatisfied	n (%)	9 (0.6)	0	9 (0.7)
2 weeks post injection	n (%)	1552 (100)	205 (100)	1347 (100)
Very satisfied	n (%)	302 (19.5)	32 (15.6)	270 (20.0)
Satisfied	n (%)	1184 (76.3)	165 (80.5)	1019 (75.6)
Neutral	n (%)	54 (3.5)	7 (3.4)	47 (3.5)
Dissatisfied	n (%)	12 (0.8)	1 (0.5)	11 (0.8)
1 month post injection	n (%)	1552 (100)	205 (100)	1347 (100)
Very satisfied	n (%)	299 (19.3)	21 (10.2)	278 (20.6)
Satisfied	n (%)	1160 (74.7)	176 (85.9)	984 (73.1)
Neutral	n (%)	69 (4.4)	6 (2.9)	63 (4.7)
Dissatisfied	n (%)	24 (1.5)	2 (1.0)	22 (1.6)
3 month post injection	n (%)	1552 (100)	205 (100)	1347 (100)
Very satisfied	n (%)	263 (16.9)	16 (7.8)	247 (18.3)
Satisfied	n (%)	1128 (72.7)	179 (87.3)	949 (70.5)
Neutral	n (%)	122 (7.9)	8 (3.9)	114 (8.5)
Dissatisfied	n (%)	39 (2.5)	2 (1.0)	37 (2.7)

Continued

6 month post injection	n (%)	1552 (100)	205 (100)	1347 (100)
Very satisfied	n (%)	205 (13.2)	11 (5.4)	194 (14.4)
Satisfied	n (%)	1000 (64.4)	172 (83.9)	828 (61.5)
Neutral	n (%)	272 (17.5)	19 (9.3)	253 (18.8)
Dissatisfied	n (%)	75 (4.8)	3 (1.5)	72 (5.3)
9 month post injection	n (%)	1547 (100)	205 (100)	1342 (100)
Very satisfied	n (%)	143 (9.2)	0	143 (10.7)
Satisfied	n (%)	909 (58.8)	149 (72.7)	760 (56.6)
Neutral	n (%)	379 (24.5)	54 (26.3)	325 (24.2)
Dissatisfied	n (%)	116 (7.5)	2 (1.0)	114 (8.5)
12 month post injection	n (%)	1539 (100)	204 (100)	1335 (100)
Very satisfied	n (%)	171 (11.1)	2 (1.0)	169 (12.7)
Satisfied	n (%)	911 (59.2)	158 (77.5)	753 (56.4)
Neutral	n (%)	327 (21.2)	42 (20.6)	285 (21.3)
Dissatisfied	n (%)	130 (8.4)	2 (1.0)	128 (9.6)
18 month post injection	n (%)	1533 (100)	204 (100)	1329 (100)
Very satisfied	n (%)	44 (2.9)	0	44 (3.3)
Satisfied	n (%)	781 (50.9)	105 (51.5)	676 (50.9)
Neutral	n (%)	554 (36.1)	92 (45.1)	462 (34.8)
Dissatisfied	n (%)	154 (10.0)	7 (3.4)	147 (11.1)
24 month post injection	n (%)	1532 (100)	204 (100)	1328 (100)
Very satisfied	n (%)	23 (1.5)	0	23 (1.7)
Satisfied	n (%)	748 (48.8)	105 (51.5)	643 (48.4)
Neutral	n (%)	566 (36.9)	95 (46.6)	471 (35.5)
Dissatisfied	n (%)	195 (12.7)	4 (2.0)	191 (14.4)
30 month post injection	n (%)	1519 (100)	204 (100)	1315 (100)
Very satisfied	n (%)	169 (11.1)	6 (2.9)	163 (12.4)
Satisfied	n (%)	676 (44.5)	104 (51.0)	572 (43.5)
Neutral	n (%)	498 (32.8)	91 (44.6)	407 (31.0)
Dissatisfied	n (%)	176 (11.6)	3 (1.5)	173 (13.2)
36 month post injection	n (%)	1515 (100)	204 (100)	1311 (100)
Very satisfied	n (%)	96 (6.3)	3 (1.5)	93 (7.1)
Satisfied	n (%)	657 (43.4)	105 (51.5)	552 (42.1)
Neutral	n (%)	545 (36.0)	94 (46.1)	451 (34.4)
Dissatisfied	n (%)	217 (14.3)	2 (1.0)	215 (16.4)

hyaluronidase, and the other was administered loratadine. Of the two local allergic reaction cases, one was moderately correlated with FACILLE administration; specifically, the affected participant had received an injection of 1 - 2 mL of FACILLE three or more times. The other case was highly associated with FACILLE administration; the affected participant received an unknown number of injections of <1 mL of FACILLE.

After the participants were classified by the number of injections or volume of injections received, the probability of AEs was discovered to increase with the number of injections but remain similar when the injection volume increased. A possible explanation for this is that local and acute-onset AEs are mostly injection-induced.

We reviewed the cases of rare AEs and identified four cases with nodules. Two of these AEs occurred on the day of injection and persisted for 2 weeks, one occurred at 2 weeks postinjection and persisted for 2 weeks, and one occurred at 9 months postinjection and persisted for approximately 3 months. The nodules of two patients were associated with FACILLE administration; one involved pruritis and the other involved implant displacement. The participant with pruritis developed symptoms at 4 months postinjection, and these symptoms persisted for 1 month; the participant with implant displacement developed symptoms at 2 months postinjection, and these symptoms persisted for 5 months. In addition, one participant had ecchymosis, another experienced warmth at the injection site on the day of injection, and two participants developed rashes at 2 weeks and 3 months postinjection. These AEs were not correlated with FACILLE administration.

Although most of the reported AEs were acute-onset, the following chronic-onset cases were also reported:

1) Two cases of nodules: One participant developed symptoms at 19 days postinjection, and another developed symptoms at 9 months postinjection. Both participants received multiple FACILLE injections on the same day or repeated injections. The development of nodules was likely related to personal constitution and the site of injection.

2) One of the two cases involving a local allergic reaction: The participant developed symptoms at 5 months postinjection and was administered dexamethasone with hyaluronidase. Delayed-onset hypersensitivity was considered a potential cause.

3) One case of implant displacement: The participant received multiple FACILLE injections on the same day, an injection at 2 weeks postinjection, and an injection at 9 months postinjection. The participant's symptoms developed at 63 days after the second day of injection. This AE was most likely related to the administration of repeated injections.

4) One case of pruritis at the injection site: The participant received a single injection and reported an AE at 4 months postinjection that persisted for 1 month. The participant's symptoms were likely related to their personal constitution and

the site of injection.

5) One of the 171 cases with local pain: The participant received a single injection at sites on the nose and chin and developed symptoms at 2 months postinjection that persisted for 1 month. The participant's symptoms were likely related to their personal constitution and the site of injection.

6) Two rash cases: One participant developed symptoms at 3 months after the second day of injection, and their symptoms persisted for 13 days. Another participant was administered other products before their FACILLE injection and developed symptoms at 18 days after their second day of injection, and their symptoms persisted for 9 days. The AEs of these participants were likely related to their personal constitution and the administration of repeated injections.

No unexpected AEs were reported in the present study. Studies have identified rare occurrences of delayed-onset hypersensitivity and granulation after HA injection [4] [5]. Such reactions have been determined to be related to the product type, personal constitution (history of atopy or allergies), and the site of injection.

In the present study, the subjective effectiveness of FACILLE remained high within 6 months postinjection. The participants who developed AEs during the follow-up period reported satisfaction levels similar to those who did not develop AEs. However, the number of participants who reported feeling *very satisfied* was lower in the group with AEs than in the group without AEs.

5. Limitation

This study was mainly performed through telephone interviews conducted by volunteers. Some participants provided an "unknown" response to various questions. Recall bias could have affected our study results; however, the likelihood that this occurred is minimal because of the large sample size.

6. Conclusion

We determined that the long-term safety of FACILLE injections was adequate, and no systemic, severe, or unexpected AEs were reported. Our study provides key information regarding the long-term safety of FACILLE use among the people of China.

Funding

The study was funded by SciVision Biotech.

Data Sharing Statement

All relevant (deidentified participant data) is made available in the manuscript and we do not have a separate repository.

Conflicts of Interest

All the authors report no conflicts of interest in this work.

References

[1] Li, J.M. (2005) Hyaluronic Acid Agent's Application in the Field of Injection Cosmetic. *Chinese Journal of Aesthetic Medicine*, **14**, 684-686.

[2] Li, J.J., Shi, X., Chen, W. and Shen, J. (2012) Research Progress of Injectable Soft Tissue Augmentation. *Chinese Journal of Aesthetic Medicine*, **21**, 2300-2304.

[3] Friedman, P.M., Mafong, E.A., Kauvar, A.N. and Geronemus, R.G. (2002) Safety Data of Injectable Nonanimal Stabilized Hyaluronic Acid Gel for Soft Tissue Augmentation. *Dermatologic Surgery*, **28**, 491-494. https://doi.org/10.1097/00042728-200206000-00010

[4] Halderman, A.A., Bryson, P.C., Benninger, M.S. and Chota, R. (2014) Safety and Length of Benefit of Restylane for Office-Based Injection Medialization—A Retrospective Review of One Institution's Experience. *Journal of Voice*: *Official Journal of the Voice Foundation*, **28**, 631-635. https://doi.org/10.1016/j.jvoice.2014.01.010

[5] Bitterman-Deutsch, O., Kogan, L. and Nasser, F. (2015) Delayed Immune Mediated Adverse Effects to Hyaluronic Acid Fillers: Report of Five Cases and Review of the Literature. *Dermatology Reports*, **7**, 5851. https://doi.org/10.4081/dr.2015.5851

Appendix

Guideline of interview

Retrospective Follow-ups	1	2	3	4	5	6	7	8	9	10	11	12
Time	Registration date	Injection date	2W	1M	3M	6M	9M	12M	18M	24M	30M	36M
Informed consent	X											
Inclusion/exclusion criteria	X											
Demographics	X											
History of previous facial injections	X											
Details of FACILLE injection		X										
Details of receiving other product at the same time as the injection day		X										
Adverse event		X	X	X	X	X	X	X	X	X	X	X
Self-evaluation of effectiveness		X	X	X	X	X	X	X	X	X	X	X
Self-assessment of satisfaction		X	X	X	X	X	X	X	X	X	X	X
Details of getting another facial injection			X	X	X	X	X	X	X	X	X	X