

Review Summary

September 15, 2026

Pharmaceuticals and Medical Devices Agency

The following is the summary of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	:	Medical products 4, Orthopedic products
Term name	:	Soft Tissue Injection Using Hyaluronan
Brand name	:	Harmonica
Applicant	:	AbbVie GK
Date of application	:	May 28, 2025
Date of approval	:	July 14, 2026
Application classification	:	☐ New medical device ☒ Improved medical device (with clinical data) ☐ Improved medical device (without clinical data)
New Approval / Partial Change	:	☒ New Approval ☐ Partial Change
Review category	:	☐ Brain and Circulatory Medicine, Respiratory Medicine, Neurology, and Psychiatry ☐ Cardiopulmonary Circulation ☐ Dentistry and Oral Medicine ☐ Gastroenterology, Genitourinary, and Reproductive Medicine ☐ Ophthalmology and Otorhinolaryngology ☒ Orthopedic and Plastic Surgery ☐ Robotics, IoT, and other devices (not classified as other categories) ☐ Program D1 ☐ Program D2
Items warranting special mention	:	☐ Designated as medical devices with high medical need ☐ Designated as specific-usage medical device ☐ Application in accordance with conditional early approval system for medical devices (Type 1)

☐Application in accordance with conditional early approval system for medical devices (Type 2: “Physical operation of items’ extrapolative and inclusive approval” (Phoenix))

☐Application in accordance with the notification on pre- and post-market rebalancing (☐1st step ☐2nd step)

☐Application in accordance with “Improvement design within approval for timely evaluation and notice” (IDATEN)

☐Designated as orphan medical device

☐Application in accordance with the 0929 notification

☐Other ()

Expert Discussion : ☐Yes ☐No

1. Submitted data

(1) Background of the development

Hyaluronic Acid Injection is a soft tissue infusion injected into adults for the purpose of restoring the volume from the middle to the lower face, adjusting it, and improving wrinkles and grooves by injection into the deep dermis, subcutaneous injection, or above the periosteum. Hyaluronate Gel containing sodium hyaluronate (NaHA), calcium hydroxyapatite (CaHAp) and lidocaine hydrochloride for pain relief during infusion is diluted with phosphate-buffered saline and prefilled in a syringe. "Juvidam Vistabolite XC" (30200BZX00389000) and others are novel because they contain CaHAp in addition to crosslinked NaHA, while the main component of the gel is crosslinked NaHA.

(2) Non-clinical data

The following nonclinical data were submitted (data items were based on applicant submission data).

- Physical and chemical properties: NaHA content, CaHAp content, lidocaine content, lidocaine analogue (2,6-dimethylaniline), lidocaine analogue (lidocaine quaternary ammonium salt), lidocaine analogue (other impurities), lidocaine analogue impurities, pH, extrusion force, endotoxin, residual BDDE, residual protein, rheology, osmotic pressure, elemental impurities, enzymatic decomposition, radical decomposition, lidocaine diffusion, lidocaine homogeneity, and kinetics
- Biological safety: Chemical properties, toxicological risk assessment, cytotoxicity, sensitization, irritation, intradermal reaction, pyrogenicity, acute systemic, subacute systemic toxicity, subchronic systemic toxicity, chronic systemic toxicity, implantation, genotoxicity, degradability profile test
- Stability: Test results using samples after 24 months at room temperature (appearance, pH,

extrusion force, NaHA content, CaHAp content, lidocaine content, lidocaine analogue (total impurity, DMA content, LQAS content, other impurities), rheological characteristics, osmotic pressure, sterility)

- Usability: Documents related to compliance with EN 62366-2015/Amd 1:2020

(3) Clinical data

The applicant submitted an international, multicenter, blinded, randomized, parallel group study to evaluate the safety and efficacy of Synvisc in restoring mid-facial soft tissue volume in foreign countries. The outline of the study is as follows (reference to the clinical results section of the package insert).

The M21-784 study is designed to evaluate the safety and efficacy of Synvisc in adults who wish to recover and reconstitute the volume of mid-facial soft tissue and to provide long-term prospective data in support of its approval. The study was conducted in compliance with the protocol, ICH guidelines, ISO 14155 guidelines, regulations and guidelines for the conduct of the study, and ethical principles based on the Declaration of Helsinki.

This was an international, multicenter, blinded, randomized, parallel group study to investigate the safety and efficacy of Synvisc in the restoration of mid-facial soft tissue volume. The objective of this study was to evaluate the clinical safety and efficacy of Synvisc in adults seeking to restore soft tissue volume in the midface.

The primary endpoint was the proportion of responders achieving at least one grade improvement from baseline on the Mid Face Volume Definitive Scale (MFVDS) based on live assessment by the physician assessing the control period (Control Period, CP) at Month 3. Secondary endpoints were as follows.

- Response status of responders achieving improvement or substantial improvement in Global Aesthetic Improvement Scale (GAIS) based on EI live assessment at the third month of CP
- Response status with GAIS improvement or substantial improvement based on subject assessment at Month 3 of CP
- Change from baseline to month 3 in overall Rasch conversion score in FACE-Q buccal, lower facial, and chin lines and facial satisfaction

Safety endpoints were treatment-emergent adverse event (TEAE), treatment-emergent serious adverse event (TESAE), injection site reaction (ISR) by the subject, and treatment-related pain assessment by the subject.

A total of 171 patients were enrolled and randomized. The control group was one that did not receive treatment at the time of CP. Subsequently, subjects in the control group could choose to complete the study at the end of CP (Month 3) or receive infusion of the study device.

Subjects who were assigned to the test group to receive the Synvisc infusion during CP received the first infusion. Subjects and treating physicians (Treating Investigator, TI) agreed to receive additional infusions as needed 30 days after the first infusion if an optimal correction was not achieved.

Subjects randomized to the control group were followed for 3 months after randomization (no treatment control period [CP]), after which they either completed the study or received the first infusion after CP and received an additional infusion (touch-up) as needed 30 days after the first infusion.

Follow-up visits were to be performed at 3 and 14 days after each infusion and at the following time points:

Test group: 1, 3, 6, 9, 12 months after last infusion (initial/additional)

Control group/control period CP infusion group: 1, 3, 6, 9, 12 months after last infusion (initial/additional)

Definitions of populations

Modified Intent-to-treat (mITT)	All randomized subjects with moderate to severe MFVDS (MFVDS grade 5, 4, or 3) at baseline
Safety	All subjects (test and untreated control) randomized to participate in the study
Injection of this product (HARmonyCa Treated, HT)	Subjects randomly assigned to receive Synvisc infusion at the start of CP or randomly assigned to control group who receive any Synvisc infusion after CP

Summary of Analysis Sets

Target	Control group	Test group	Total
mITT	55	115	170
Safety	56	115	171
HT	52	115	167

Statistical analyses of the primary, secondary, and safety endpoints were performed.

Efficacy analyses in CP were performed using the mITT population based on the assigned infusion groups.

The safety analysis was performed on the safety analysis population and the HT population based on the treatment received.

Results: Primary Efficacy Endpoints

- The primary efficacy objective was achieved and the MFVDS responder rate in the test group was statistically superior to the control group at 3 months of CP (86.8% vs. 18.5%, difference 68.4% [95% CI, 55.8%, 80.9%], $p < 0.0001$).
- The MFVDS responder rate in the Synvisc infusion group during the infusion period was generally constant until Month 12 after the first and additional infusions, with the highest response at Month 3 (77.8%, 87.4%, 84.1%, 81.9%, and 78.1%, respectively, at Months 1, 3, 6, 9, and 12, respectively).

Results: Secondary Efficacy Endpoints

Secondary efficacy objectives were achieved.

- In the mITT population, the difference in EI GAIS responder rate between the test and control groups was 80.8% (95% CI: 68.2%, 89.5%) at 3 months of CP.
- In the mITT population, the difference in the GAIS responder rate between test and control subjects was 85.3% (95% CI, 75.2%, 91.6%) at 3 months of CP.
- In the mITT population, the within-group mean improvements from baseline to 3 months CP in Rasch-transformed FACE-Q malaria, lower face, and jaw contour satisfaction and facies were statistically significant in the test group (36.9 [95% CI: 31.5, 42.3], 31.8 [95% CI: 25.9, 37.6] and 29.9 [95% CI: 25.1, 34.7], respectively; $p < 0.0001$).
- The EI GAIS responder rate was higher in the test group than in the control group at 3 months of CP (94.5% vs. 13.7% [95% CI: 68.2%, 89.5%]) in the mITT population and remained generally constant through 12 months post-dose during the infusion period (Treatment Period, TP) (88.0%, 94.6%, 92.5%, 91.4%, and 82.9%, respectively, in the HT population at 1, 3, 6, 9, 12 months).
- The subjects in the test group had a higher rate of GAIS responders at 3 months in the CP group than in the control group (87.3% vs. 2.0% [95% CI: 75.2%, 91.6%]), while in the HT group, the values remained higher during the TP period (91.4%, 87.4%, 86.9%, 81.1% and 73.3%, respectively, at 1, 3, 6, 9 and 12 months).
- The overall Rasch conversion score for mean test group satisfaction with FACE-Q cheeks increased by 36.9 points from baseline, with a mean score at 3 months CP of 75.5 (95% CI: 31.5, 42.3; $P < 0.0001$) in the mITT population and persisted in the HT population up to 12 months post-infusion (78.9, 75.5, 75.4, 69.7, and 65.2 at 1, 3, 6, 9, and 12 months, respectively).
- The overall Rasch conversion score of satisfaction with the mean FACE-Q subfacial and jaw line in the test group increased by 31.8 points from baseline in the mITT population and the mean

score at 3 months of CP was 60.7 (95% CI: 25.9, 37.6; $p < 0.0001$), while in the HT population the values remained elevated until 12 months post-infusion (63.1, 60.8, 57.9, 54.5, and 51.5, respectively, at 1, 3, 6, 9, and 12 months).

- The test group's overall Rasch conversion score for FACE-Q facial satisfaction increased by 29.9 points from baseline to a mean CP score of 63.9 (95% CI: 25.1, 34.7; $p < 0.0001$) and the HT population remained high until 12 months post-infusion (65.4, 63.9, 62.1, 60.2, and 55.0 at 1, 3, 6, 9, and 12 months, respectively).

Results: Subgroup Analysis of Primary Efficacy Endpoints

The MFVDS responder rates in the test group were generally similar among the Baseline MFVDS severity, age, Fitzpatrick skin type classification, and infusion route subgroups.

Results: Other Efficacy Endpoints

- The Allergan Cheek Smoothness Scale (ACSS) responder rate (percentage of subjects achieving at least 1 grade improvement from baseline on both sides of the face based on EI live assessments) differed favorably between the test and control groups. In the mITT population, the ACSS responder rates for CP were higher in the test group than in the control group at 1 month (41.1% vs. 14.3%, respectively) and 3 months (37.3% vs. 11.8%, respectively).
- The change from baseline in skin position and orientation with 3-dimensional standardized images was higher in the test group than in the control group in the mITT population at Month 1 and Month 3. Improvements from baseline were observed laterally in the zygomatic molar and subzygomatic regions, and anteromedially in the zygomatic molar, subzygomatic, and anteromedial regions.

Results: Safety endpoints

- Infusion site reactions were reported in 80.0% of subjects after the first infusion and 67.2% of subjects after the additional infusion in the HT population. The most frequently reported ISRs after the first infusion were tenderness, redness, and postinfusion pain.
- Most ISRs were mild or moderate in severity after the first or second infusion for the HT population. The median duration of all ISRs was 5.0 days after the first infusion and 4.0 days after the second infusion.
- No serious adverse events considered related to the drug (TESAE), serious adverse events considered related to the drug (TEAE), TEAE that led to discontinuation of the drug infusion, or death were observed by the data cut-off date.

Adverse events (TEAE) during infusion of this product

- Most TEAEs reported in the HT population were mild or moderate at the time of the data cut-off.
- The most commonly reported TEAEs in the HT population during the infusion period were novel coronavirus infection (6.0%), intra-infusion hemorrhage (5.4%), and influenza (5.4%), with all other TEAEs occurring in less than 5% of the HT population.
- At the time of data cut-off, a TEAE related to Synvisc was reported in 18.0% of subjects in the HT population during the infusion period. The most common adverse events related to this product were intrajection site hemorrhage (5.4%) and injection site pain (2.4%). Most of the TEAEs related to this product were mild and occurred within 7 days after the start of infusion and recovered within 14 days of onset.
- No TESAE, TESAE or death that was considered related to the drug, or TEAE or death that led to discontinuation of the drug infusion were observed by the data cut-off date.

Summary of TEAEs in the control period (CP) (Safety Analysis Set)

	Control group		Test group	
	Test subjects (N=56) n (%)	Event n	Test subjects (N=115) n (%)	Event n
All adverse events that occurred after infusion(TEAE)	9 (16.1)	12	42 (36.5)	67
Causal relationship with this product	0 (0.0)	0	18 (15.7)	23
Injection site	0 (0.0)	0	12 (10.4)	16
Other than the injection site	0 (0.0)	0	7 (6.1)	7
All SAEs (TESAEs)	1 (1.8)	1	4 (3.5)	5
Causal relationship with this product	0 (0.0)	0	0 (0.0)	0
Injection site	0 (0.0)	0	0 (0.0)	0
Other than the injection site	0 (0.0)	0	0 (0.0)	0
The injection of this product was discontinued (TEAE).	0 (0.0)	0	0 (0.0)	0
Death	0 (0.0)	0	0 (0.0)	0

Percentages are based on the number of subjects in a particular population.

Summary of TEAEs during the infusion period (TP) (HT population)

	Injection of this product Test group		Control period (CP) Group that received this product infusion after a short time		Total	
	Test subjects (N=115) n (%)	Event n	Test subjects (N=52) n (%)	Event n	Test subjects (N=167) n (%)	Event n
All adverse events that occurred after infusion (TEAE)	59 (51.3)	118	24 (46.2)	64	83 (49.7)	182
Causal relationship with this product	19 (16.5)	25	11 (21.2)	22	30 (18.0)	47
Injection site	13 (11.3)	18	10 (19.2)	17	23 (13.8)	35
Other than the injection site	7 (6.1)	7	3 (5.8)	5	10 (6.0)	12
All serious adverse events (TESA) that occurred after the infusion of this product	11 (9.6)	17	2 (3.8)	2	13 (7.8)	19
Causal relationship with this product	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Injection site	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Other than the injection site	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
The injection of this product was discontinued. (TEAE)	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0
Death	0 (0.0)	0	0 (0.0)	0	0 (0.0)	0

Percentages are based on the number of subjects in a particular population.

2. Review results

<Intended Use>

As a result of the review of the submitted data, PMDA concluded that the product could be approved for the following intended use shown below.

<Conditions for Approval >

This product is used in adults to restore the volume from the middle to the lower face, to adjust the volume, and to improve wrinkles and grooves by deep dermal, subcutaneous, and epiperiosteal injections.