Protocol No.: FM-COL-2026-001

A Prospective, Multicenter, Randomized, No-Treatment Controlled, Evaluator-Blinded, Superiority Clinical Trial Protocol

To Evaluate the Efficacy and Safety of a Medical Collagen Filler for Correction of Infraorbital Hollows

Item	Details
Investigational Medical Device	Medical Collagen Filler
Model / Specification	See the clinical trial protocol
Third-Class Medical Device Requiring Clinical Trial Approval	No ☑
Protocol Version No. and Date	V1.0 / August 4, 2026
Clinical Trial Institutions / Principal Investigators	See the site list
Lead Clinical Trial Institution / Coordinating Investigator	Xuanwu Hospital, Capital Medical University / Zhao Hongyi
Sponsor	Feifan (Changchun) Pharmaceutical & Biotechnology Co., Ltd.

Confidential

Confidentiality Statement

All information contained in this protocol constitutes confidential information. All personnel who have access to such information shall keep it confidential. Without the prior written consent of the Sponsor, such information shall not be used for any other research and development or for any other commercial purpose. If any information in this protocol must be used for publication of a scientific article, written consent shall be obtained in advance. Any breach of this confidentiality statement beyond the limits permitted by applicable laws and regulations shall be subject to arbitration by the arbitration institution at the Sponsor's domicile or brought before a court.

Document and Version Control

Version	Date	Reason	Revision Content
V1.0	August 4, 2026	Initial version	/

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Protocol Summary

Item	Details
Protocol Title	A Prospective, Multicenter, Randomized, No-Treatment Controlled, Evaluator-Blinded, Superiority Clinical Trial to Evaluate the Efficacy and Safety of a Medical Collagen Filler for Correction of Infraorbital Hollows
Protocol No.	FM-COL-2026-001
Sponsor	Feifan (Changchun) Pharmaceutical & Biotechnology Co., Ltd.
Objective	To evaluate the efficacy and safety of the Medical Collagen Filler for correction of infraorbital hollows
Indication	The product is intended for infraorbital injection into the deep dermis to subcutaneous tissue to improve infraorbital hollowing
Number of Sites	The study is planned to be conducted at 3 or more clinical trial institutions
Study Duration	Depending on the randomization group: participants in the experimental group will participate for up to 13.5 months (screening period up to 14 days, treatment period 1 month, follow-up up to 12 months after the last injection/randomization); participants in the control group will participate for up to 9.5 months (screening period up to 14 days, follow-up to 3 months after randomization; participants may optionally receive a compensation injection, in which case follow-up continues to 6 months after the optional compensation injection, or they may withdraw after completing the 3-month visit).
Study Design	Prospective, multicenter, randomized, no-treatment controlled, evaluator-blinded, superiority design
Randomization	Eligible participants will be assigned using block randomization via a centralized randomization system. Using SAS (version 9.4 or higher), participants will be randomized in a 2:1 ratio to the experimental group and the control group.
Blinding	Because the control group uses a no-treatment design, blinding of the injecting investigator or the participant is not possible. Therefore, to minimize bias in efficacy evaluation, endpoint blinding is adopted, i.e., the evaluating investigator is blinded.

Sample Size	The primary efficacy endpoint is the effective improvement rate of infraorbital hollowing based on the AIHS score at 3 months after the last injection for the experimental group and at 3 months after randomization for the control group (blinded investigator assessment). Based on the literature and using a superiority design, the assumed improvement rates are approximately 80% for the experimental group and 25% for the control group. With a power of 90%, a superiority margin of 30%, a significance level of alpha=0.025 (one-sided), and an experimental:control ratio of 2:1, the superiority sample size calculation yields 90 cases for the experimental group and 45 for the control group. Allowing for a 20% dropout rate, a total of 171 participants are planned: 114 in the experimental group and 57 in the control group.
Participant Selection	Inclusion criteria (must meet all): 1) Aged 18 years or older at the time of signing informed consent, of either sex; 2) Assessed by the blinded investigator as having moderate or severe bilateral infraorbital hollowing (Allergan Infraorbital Hollowing Scale [AIHS] grade 2-3) and a desire to improve it; 3) Able to complete the self-efficacy assessment without wearing frame glasses (contact lenses are acceptable); 4) Able and willing to follow the investigator's instructions, comply with treatment restrictions, and complete all study visits; 5) Voluntarily participates and signs the informed consent form. Exclusion criteria (presence of any results in exclusion): 1) Known allergy to collagen or any component of the product, or any local anesthetic (e.g., lidocaine or other amide anesthetics); 2) History of severe allergy (e.g., anaphylaxis, laryngeal edema, asthma, dyspnea, hypotension, syncope shortly after exposure to an allergen); 3) Scarring, deformity, unhealed wounds, etc. in the intended injection area or bilateral mid-face that may affect efficacy assessment or increase treatment risk, or active/recurrent inflammation or infection in either eye; 4) Previous injection of any permanent filler (e.g., PMMA, silicone, ePTFE), autologous fat, or unknown injected material in the intended area or bilateral mid-face; 5) Treatment with PLLA, PCL, CaHA, etc. in the intended area or bilateral mid-face within 24 months before screening or planned during the trial;

	6) Treatment with cross-linked hyaluronic acid, animal-derived collagen, etc. within 12 months before screening or planned during the trial; 7) Treatment with recombinant human-like collagen or botulinum toxin in the intended area or bilateral mid-face within 6 months before screening or planned during the trial; 8) Active autoimmune disease or history thereof (e.g., SLE, RA, scleroderma, dermatomyositis); 9) Non-cross-linked HA filler treatment or cosmetic procedures (IPL, RF, dermabrasion, laser, chemical peels, etc.) in the intended area or bilateral mid-face within 6 months before screening; 10) Previous lower blepharoplasty or facial lift/brow lift within 12 months before screening; 11) In the investigator's judgment, a large lower eyelid fat pad affecting treatment, or excessive pigmentation in the infraorbital area (excluding dark circles not due to hyperpigmentation); 12) History of keloids or a keloid-prone constitution; 13) Chemotherapy, immunosuppressants, immunomodulatory therapy (e.g., monoclonal antibodies), or systemic corticosteroids (except inhaled) within 3 months before screening; 14) ALT and/or AST >2x ULN, or Cr >1.5x ULN at screening, judged by the investigator as unfit to participate; 15) History of bleeding disorders (e.g., porphyria, coagulation factor deficiency, coagulopathy, platelet disorders), clinically significant coagulation abnormality at screening (e.g., APTT >1.5x ULN), or anticoagulant/antiplatelet/thrombolytic therapy within 2 weeks before screening; 16) In the investigator's judgment, severe dysfunction of vital organs (brain, heart, lung, liver, kidney), e.g., severe cardiovascular/cerebral disease, severe pulmonary disease, or uncontrolled diabetes; 17) Epilepsy, severe mental disorders, or inability to complete follow-up; 18) Breastfeeding or planning pregnancy during the study; 19) Less than 1 month since completion of another interventional clinical trial; 20) Any other condition deemed by the investigator to make participation inappropriate.
Investigational and Control Devices	Investigational device: Medical Collagen Filler Model/Specification: See the product instructions Manufacturer: Feifan (Changchun) Pharmaceutical & Biotechnology

	Co., Ltd. Control: No-treatment control
Study Procedures	All participants randomized to the experimental group will receive injection treatment with the investigational device, with up to 2 injections approximately 1 month apart. The second injection is optional: 1 month after the first injection, the investigator, based on the post-injection improvement and the participant's preference, will decide whether to perform the optional second injection. Participants will return for follow-up at 1, 3, 6, and 12 months after the last injection/randomization. All participants randomized to the control group will not receive an injection on the randomization day and will return for follow-up at 1 and 3 months after randomization. After the primary endpoint is collected at 3 months, participants may choose to receive a compensation injection; if accepted, follow-up continues at 1, 3, and 6 months after the compensation injection; if declined, the participant may exit the trial. The primary endpoint assessment time point is 3 months after the last injection/randomization. The study uses a no-treatment control and evaluates safety and efficacy through primary, secondary, and safety endpoints.
Efficacy Endpoints	Primary endpoint: Effective improvement rate of infraorbital hollowing based on AIHS at 3 months after the last injection (experimental group) / 3 months after randomization (control group), assessed by a blinded investigator. Method: The blinded investigator, trained per the scale SOP, grades bilateral infraorbital severity using the Allergan Infraorbital Hollowing Scale (AIHS, see Appendix 1). Criterion: Improvement is defined as a reduction of at least 1 grade in bilateral infraorbital severity compared with screening; otherwise, no improvement. Effective improvement rate = (number improved / total in analysis set) x 100%. Secondary endpoints (selected): (1) AIHS improvement rate at 1 month assessed by blinded investigator; (2) AIHS improvement rate at 1 and 3 months assessed by injecting investigator; (3)-(4) Periorbital Volume Deficiency Assessment Scale grade and improvement rate at 1 and 3 months (blinded/injecting investigator); (5)-(6) GAIS-based overall infraorbital aesthetic improvement rate at 1 and 3 months (injecting investigator/participant); (7) change in

	infraorbital hollowing volume by 3D image analysis at 1 and 3 months; (8) participant satisfaction with injection treatment at 1 and 3 months; (9) VAS pain score immediately after each injection. Other endpoints: For the experimental group at 6 and 12 months, and for the control group at 1, 3, and 6 months after compensation injection, the corresponding AIHS, periorbital volume, GAIS, 3D volume, and satisfaction endpoints listed above are assessed.
Safety Endpoints	1) Vital signs (temperature, pulse, seated blood pressure, respiration); 2) Laboratory tests (blood routine, blood biochemistry, urine routine); 3) Local reactions at the injection site within 30 days after each injection; 4) Incidence of adverse events and serious adverse events during the trial; 5) Incidence of device deficiencies.
Statistical Analysis	1. Statistical design: Multicenter, randomized, no-treatment controlled, evaluator-blinded, superiority trial, using SAS 9.4 or higher. All tests are two-sided except the superiority test, which uses a one-sided alpha=0.025; $p<0.05$ is considered statistically significant (unless otherwise specified). Quantitative variables are summarized by mean, SD, median, min, max, Q1, and Q3; categorical variables by count and percentage. 2. Analysis sets: FAS includes all randomized participants in the experimental group who received at least one injection and all randomized participants in the control group. PPS is a subset of FAS including participants who received the prescribed treatment, had the primary endpoint data, and had no major protocol violations. SS includes all randomized participants who received at least one injection (experimental group) or were randomized (control group) and had at least one safety evaluation. 3. Efficacy: Both FAS and PPS results are provided, with FAS as primary. For the primary endpoint, under H0: P_T - P_C <= Delta and H1: P_T - P_C > Delta, at alpha=0.025 (one-sided) and beta=0.1, the 95% CI of the difference (experimental - control) is calculated; if the lower limit of the 95% CI exceeds Delta (30%), the experimental group is considered significantly superior. 4. Safety: Planned-visit summaries of vital signs, laboratory tests, immunogenicity, ECG, etc., listing of AEs by category with descriptive statistics.

Abbreviations

Abbreviation	Full Name
AE	Adverse Event
CI	Confidence Interval
EC	Ethics Committee
CRO	Contract Research Organization
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	U.S. Food and Drug Administration
FAS	Full Analysis Set
GAIS	Global Aesthetic Improvement Scale
GCP	Good Clinical Practice for Medical Device Clinical Trials
HA	Hyaluronic Acid
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ISR	Injection Site Reaction
IWRS	Interactive Web Response System (Centralized Randomization System)
NMPA	National Medical Products Administration
PCL	Polycaprolactone
PLA	Polylactic Acid
PLLA	Poly-L-lactic Acid
PPS	Per-Protocol Set
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SG	Striae Gravidarum
SOP	Standard Operating Procedure
SS	Safety Analysis Set
WOCF	Worst Observation Carried Forward

Note: This abbreviation list does not include laboratory test items.

I. Sponsor Information

Sponsor Name: Fiman (Changchun) Pharmaceutical & Biotechnology Co., Ltd.

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II. Clinical Trial Institutions and Principal Investigators

Clinical Trial Institution	Principal Investigator
01 Xuanwu Hospital, Capital Medical University	Zhao Hongyi
02 Guangdong Second Provincial General Hospital	Wang Haibin
03 Central Hospital of Dalian University of Technology (Dalian Central Hospital)	Wang Lin
04 Cangzhou Central Hospital	Ma Chao

Note: When changes occur to the clinical trial institutions or investigators compared with the initial list, the list may be updated without a formal protocol amendment for each change; however, the final clinical trial report must provide the complete final list of all clinical trial institutions and investigators.

III. Background of the Clinical Trial

(I) Research and Development Background

Infraorbital hollowing, also known as tear trough deformity, refers to a sunken groove extending obliquely downward and outward along the infraorbital rim from the medial canthal region. It is one of the important features of facial aging and one of the most challenging problems in periocular rejuvenation treatment [1-2]. This deformity is particularly common in Asian populations, with approximately 60%-70% of middle-aged people presenting varying degrees of infraorbital hollowing [2], and its incidence rises significantly with age. The formation of

infraorbital hollowing is mainly the result of multiple factors acting together, including anatomical changes, soft tissue atrophy, skin aging, and impaired lymphatic circulation [2]. Infraorbital hollowing not only affects facial aesthetics but also gives people a negative impression of fatigue, aging, and severity, seriously impacting patients' psychological health and social life [3]. In recent years, with the growing demand for facial rejuvenation, infraorbital hollowing correction has become a hot topic in the field of non-surgical aesthetics.

However, due to the complex anatomy of the infraorbital region — thin skin, abundant blood vessels, and fragile lymphatic circulation — traditional fillers have problems such as migration, the Tyndall effect, and prolonged swelling, placing higher demands on filling materials and injection techniques [4]. As a natural biomaterial, collagen exhibits unique advantages in infraorbital hollowing correction due to its good histocompatibility, low migration, and light-scattering properties [5]. The mechanism of collagen injection for infraorbital hollowing correction is a multi-stage, multi-level complex process that achieves immediate physical filling and tissue support. After injection, collagen supplements lost volume, forming a soft, adhesive fibrous structure that supports the collapsed area and restores a smooth transition between the lower eyelid and the cheek, thereby reducing the hollowing [5,6]. At the same time, due to collagen's high adhesiveness, it can adhere loosened skin tissue caused by aging, reposition the broken fibrous scaffold network, and restore a youthful, firm state [6]. After injection, the collagen gradually dehydrates and coalesces, rearranging into collagen fibers approximating the natural state in vivo, further tightening the tissue and enhancing the supporting effect.

The medical collagen filler developed by Fiman (Changchun) Pharmaceutical & Biotechnology Co., Ltd. was approved for marketing by the NMPA in 2016 (Registration Certificate No.: Guo Xie Zhu Zhun 20163131609). It is indicated for filling the dermal tissue of the face to correct moderate to severe nasolabial folds, with good clinical efficacy and safety. This trial adds a new indication for infraorbital filling, to improve and repair infraorbital hollowing. The objective of this study is to evaluate the efficacy and safety of the medical collagen filler developed by Fiman (Changchun) Pharmaceutical & Biotechnology Co., Ltd. in correcting the severity of infraorbital hollowing. In accordance with the requirements of the "Measures for the Administration of Medical Device Registration and Filing," the "Good Clinical Practice for Medical Device Clinical Trials" (GCP), and the "Guiding Principles for the Design of Medical Device Clinical Trials," and observing the ethical principles of the World Medical Association's "Declaration of Helsinki," the study strives to maximize benefits to research participants while avoiding harm to the greatest extent possible.

(II) Basic Product Information [7]

1. Product Composition

This product is a saline suspension of 3.5% bovine collagen and 0.3% lidocaine hydrochloride, pre-filled in a glass syringe (with injection needle) or a glass syringe (without injection needle);

the package is equipped with, or includes, 27G × 1/2” single-use sterile injection needles, and/or a syringe adapter.

2. Product Mechanism of Action

After injection with the syringe needle, the homogeneous collagen fiber solution elevates the depressed skin, smoothing the skin surface to achieve wrinkle reduction and smoothing of depressed skin. It has the effects of correcting soft tissue defects in non-gravity-loading areas, filling depressed skin areas, and repairing fine skin lines for cosmetic and plastic surgery purposes.

Bovine collagen has excellent affinity with human skin and low allergenicity. Its structural characteristics give it moderate resistance to proteolytic enzymes in the body, so it is not rapidly decomposed and eliminated. After collagen is injected into the skin, it combines appropriately with skin tissue and remains at the implantation site. The protein dehydrates, contracts, and rearranges into collagen fibers approximating the natural state in vivo, elevating the depressed skin. Several weeks later, the collagen can effectively stimulate the participant’s own fibroblasts, capillaries, and adipocytes to migrate and grow into the collagen implant, slowly absorbing the implant and synthesizing the participant’s own collagen, ultimately forming normal soft tissue, filling skin defects, and achieving the goals of wrinkle reduction and volume defect correction.

(III) Indications and Related Information

1. Indications

This product is injected infraorbitally into the deep dermis to subcutaneous tissue to improve infraorbital hollowing.

2. Contraindications

1) Individuals with a positive collagen allergy test, or with a previous history of allergic reaction to collagen;

2) Individuals with an allergic constitution or those using immunosuppressants;

3) Patients with autoimmune diseases or connective tissue diseases;

4) Individuals allergic to lidocaine;

5) Pregnant women and infant patients;

6) Patients with rheumatic diseases;

7) Patients with other serious diseases.

3. Precautions

1) Filling is prohibited when there is inflammation at the filling site (pustules, cysts, herpes, urticaria, etc.); the product may only be used after the inflammation is controlled;

2) Postoperative instructions to the patient: within one week after the procedure, avoid pressing or impacting the injection site, and avoid irritating foods or excessively high-protein diets;

3) The total filling volume for a patient within one year should be less than 30 mL;

4) The single-use volume of this product on one side should be controlled at 2 mL; the total dose for multi-site injection in a single session should not exceed 10 mL. The clinical injecting physician may adjust according to the patient's individual implantation site or actual volume loss to achieve the optimal correction effect.

4. Warnings

1) This product must not be injected into blood vessels, to avoid complications such as bleeding, redness, and ecchymosis;

2) This product must not be injected into areas beyond the approved indications (such as the breasts);

3) This is a single-use sterile product; it is strictly prohibited to use if the inner packaging is damaged;

4) Any unused portion of this product should be discarded and must not be stored for reuse;

5) Waste generated from the use of this product shall be disposed of in accordance with the medical waste management regulations of the relevant jurisdiction;

6) The safety of multi-course filling injections of this product has not been clinically validated.

IV. Trial Objective

To evaluate the efficacy and safety of the medical collagen filler in correcting infraorbital hollowing.

V. Trial Design

(I) Overall Design and Basis for Determination

1. Trial Method Selection and Rationale

In accordance with the "Guiding Principles for the Design of Medical Device Clinical Trials," the "Guiding Principles for Clinical Trials of Sodium Hyaluronate Facial Injectable Filling

Materials," and the "Guiding Principles for Registration Review of Facial Injectable Filling Materials (Draft for Comments)," this trial adopts a prospective, multicenter, randomized, no-treatment-controlled, evaluator-blinded, superiority clinical trial design to evaluate the safety and efficacy of the medical collagen filler for infraorbital filling in correcting infraorbital hollowing.

Currently, there is no injectable filler approved by the National Medical Products Administration (NMPA) for improving infraorbital hollowing, meaning there is no positive control device. Therefore, a no-treatment-controlled design is adopted (the test group receives injection of the medical collagen filler, while the control group adopts a no-treatment design).

2. Clinical Trial Content

After voluntarily signing the informed consent form, participants who meet the enrollment requirements of the protocol will enter the study. All participants entering the trial will be randomly assigned to the test group or the control group. The test group will receive two injection treatments during the trial period, with an interval of approximately one month between the two injections; the second injection is an optional supplemental injection. One month after the first injection is completed, the investigator, based on the post-injection improvement and in combination with the participant's own wishes, will decide whether to perform the second optional supplemental injection. Participants will return to the study center for follow-up at 1, 3, 6, and 12 months after randomization.

All participants randomized to the control group will not receive an injection on the day of randomization, and will return to the study center for follow-up at 1 and 3 months after randomization. After completing the primary endpoint assessment at 3 months after randomization, participants will decide whether to accept a compensation injection based on their own wishes. If a participant accepts the injection, they must return to the study center for follow-up at 1, 3, and 6 months after the optional compensation injection; if a participant does not accept the injection, they may exit the trial after completing the primary endpoint assessment and procedures at 3 months after randomization.

The observation time point for the primary endpoint is set at 3 months after the last injection / after randomization.

This study will adopt a no-treatment control and will evaluate the safety and efficacy of the investigational medical device by assessing the primary endpoint, secondary endpoints, and safety endpoints.

(II) Participant Selection

1. Inclusion Criteria

1) Age 18 years or older (based on the time of signing the informed consent form), of any gender;

2) As assessed by a blinded evaluator, both infraorbital regions of the face present with moderate or severe hollowing (i.e., an Allergan Infraorbital Hollowing Scale [AIHS] grade of 2–3), and the participant has a desire to improve the infraorbital hollowing;

3) Able to complete the efficacy self-assessment without wearing frame glasses (wearing contact lenses for the self-assessment is acceptable);

4) Able and willing to comply with the investigator's instructions, follow the treatment restrictions specified in this protocol, and complete all visits required by this trial;

5) Voluntarily participates in this clinical trial and signs the participant informed consent form.

2. Exclusion Criteria

Participants meeting any of the following exclusion criteria shall not be enrolled in the trial.

1) Known allergy to collagen or any component of this product, or to any local anesthetic (such as lidocaine or other amide-class anesthetic drugs);

2) History of severe allergic reactions (e.g., anaphylactic shock, laryngeal edema, asthma, dyspnea, hypotension, syncope shortly after contact with an allergen);

3) Presence of scars, deformities, unhealed wounds, etc. in the planned injection area and bilateral mid-face that may affect efficacy evaluation or increase treatment risk, potentially interfering with visual assessment of the infraorbital rim, or either eye having active or recurrent inflammation or infection;

4) Previous receipt of any permanent filler (such as polymethyl methacrylate [PMMA], silicone, expanded polytetrafluoroethylene [ePTFE], etc.), autologous fat, or unknown injected material in the planned injection area and bilateral mid-face;

5) Receipt within 24 months before screening, or planned during the trial period, in the planned injection area and bilateral mid-face, of treatments such as poly-L-lactic acid, polycaprolactone (PCL), calcium hydroxylapatite (CaHA), etc.;

6) Receipt within 12 months before screening, or planned during the trial period, in the planned injection area and bilateral mid-face, of treatments such as cross-linked sodium hyaluronate, animal-derived collagen, etc.;

7) Receipt within 6 months before screening, or planned during the trial period, in the planned injection area and bilateral mid-face, of recombinant human-like collagen treatment, botulinum toxin, etc.;

8) Previous history of active autoimmune disease (such as systemic lupus erythematosus, rheumatoid arthritis, scleroderma, dermatomyositis, etc.);

9) Receipt within 6 months before screening in the planned injection area and bilateral mid-face of non-cross-linked sodium hyaluronate filling treatment or cosmetic procedures (such as intense pulsed light, radiofrequency, skin dermabrasion, laser, chemical peels, etc.);

10) Previous lower blepharoplasty, or receipt within 12 months before screening of a facelift or brow lift;

11) As determined by the investigator, presence of large lower eyelid fat pads in both orbits that affect treatment, or excessive pigmentation in the infraorbital area (excluding dark circles not caused by excessive pigmentation);

12) History of keloids or a keloid-prone constitution;

13) Receipt within 3 months before screening of chemotherapy, immunosuppressants, immunomodulatory therapy (such as monoclonal antibodies, etc.), or systemic corticosteroids (except inhaled corticosteroids);

14) Liver function test results at screening showing ALT and/or AST >2 × the upper limit of normal, or renal function test results showing Cr >1.5 × the upper limit of normal, as judged by the investigator to be unsuitable for participation in this clinical trial;

15) History of bleeding disorders (e.g., porphyria, coagulation factor deficiency, coagulopathy, or platelet disorders), clinically significant abnormal coagulation function at screening (such as APTT >1.5 × the upper limit of normal), or receipt within two weeks before screening of anticoagulant, antiplatelet, or thrombolytic therapy (such as warfarin, heparin, aspirin, etc.);

16) As judged by the investigator, severe dysfunction of vital organs (such as brain, heart, lungs, liver, kidneys), such as severe cardiovascular and cerebrovascular diseases (hospitalization for myocardial infarction or cardiac surgery within 3 months, history of congestive heart failure or myocardial infarction, severe unstable arrhythmia, hypertrophic cardiomyopathy, severe aortic stenosis, aneurysm, stroke, etc.), severe pulmonary diseases (moderate to severe pneumonia, respiratory failure, etc.), and uncontrolled diabetes;

17) Epilepsy, mental disorders, or other severe psychiatric diseases that prevent completion of trial follow-up;

18) Lactating women or those planning pregnancy during the study period;

19) Less than one month has elapsed since the end of another interventional clinical trial before screening;

20) Other conditions deemed by the investigator to make participation in this clinical trial inappropriate.

3. Participant Withdrawal Criteria and Procedures

All participants who have signed the informed consent form and passed screening to enter the trial, regardless of when or why they withdraw from the study, are considered dropouts or withdrawals, including:

(1) Withdrawal Decided by the Investigator

① Occurrence of a serious adverse event (SAE), for which the investigator judges that the trial should be stopped.

② During the trial, the participant develops complications or special physiological changes that make continued participation inappropriate.

③ The participant develops other conditions that, in the investigator's judgment, prevent continuation of this clinical trial.

④ Poor participant compliance.

(2) Voluntary Withdrawal by the Participant

① For whatever reason, the participant is unwilling or unable to continue the clinical trial and requests termination from the investigator.

② The participant does not explicitly request withdrawal but refuses continued treatment and follow-up, resulting in loss to follow-up.

(3) Withdrawal Management

For all withdrawn participants, the trial conclusion form and the reason for withdrawal should be completed in the case report form. After a participant withdraws, the investigator should contact the participant as much as possible, inquire about the reason, and complete the assessable items based on the content of the exit visit.

4. Criteria and Procedures for Trial Termination

1) A major error or significant deviation is discovered in the clinical trial protocol during the trial, making it difficult to evaluate the safety and efficacy of the investigational medical device;

2) A widespread, device-related serious adverse event, or other major safety issue, occurs during the trial, judged to be directly related to the trial design, implementation, or the investigational medical device, and continuation of the trial may cause further aggravation, inability to resolve, or recurrence of the problem, necessitating timely termination of the trial;

3) Participants are currently facing or will face a risk of substantial physical harm related to the trial with an unreasonable risk-benefit ratio;

4) Insufficient experience or misconduct of relevant personnel in the clinical trial, causing participants to be currently facing or to face the risk of unreasonable harm;

5) The sponsor requests termination of the trial (e.g., due to funding or management reasons);

6) The administrative authority revokes the trial.

In the event of the above situations: (1) When the trial is terminated due to safety issues, the investigator should take appropriate therapeutic measures for active treatment based on the participant's actual condition, record the time of last use of the investigational medical device, and complete the assessable items. (2) For all terminated cases, the trial summary form and the reason for termination should be completed in the case report form. (3) The sponsor should promptly notify the investigators at each study center, the medical device clinical trial institution, and the Ethics Committee (EC); for participants who have already received treatment with the study device, the sponsor should fulfill its responsibilities to the participants during the trial period as stipulated in the signed informed consent form.

5. Enrollment Time

The time of randomization for a participant who has signed the informed consent form, met all inclusion criteria, and met none of the exclusion criteria is considered the participant's enrollment time.

6. Expected Overall Duration of the Clinical Trial and Basis for Determination

The overall duration of this clinical trial includes the ethics approval and revision of opinions after the ethics review meeting for all clinical trial institutions, the clinical trial agreement signing time, clinical trial registration, clinical trial initiation, participant enrollment time and visit times at each stage, clinical trial data collection, statistical analysis, and clinical study report writing time, etc.

7. Expected Participation Duration per Participant

Participants in the test group will participate for up to 13.5 months: a screening period of up to 14 days, a treatment period of 1 month, and follow-up for up to 12 months after the last injection.

Participants in the control group will participate for up to 9.5 months: a screening period of up to 14 days, follow-up to 3 months after randomization; if they accept the compensation injection, follow-up to 6 months after the optional compensation injection; if they do not accept the compensation injection, follow-up to 3 months after randomization.

8. Required Number of Participants

This trial plans to enroll 171 participants and is expected to be conducted at 3 or more qualified medical device clinical trial institutions, with each center recruiting participants through competitive enrollment.

(III) Evaluation Methods

1. Efficacy Evaluation

1.1 Primary Endpoint:

The effective improvement rate of infraorbital hollowing AIHS scores at 3 months after the last injection in the test group and at 3 months after randomization in the control group (assessed by a blinded evaluator).

1.2 Secondary Endpoints:

1) The effective improvement rate of infraorbital hollowing AIHS scores at 1 month after the last injection in the test group and at 1 month after randomization in the control group (assessed by a blinded evaluator);

2) The effective improvement rate of infraorbital hollowing AIHS scores at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group (assessed by the injecting investigator);

3) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group (assessed by a blinded evaluator);

4) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group (assessed by the injecting investigator);

5) The effective improvement rate of overall infraorbital aesthetic effect assessed by the injecting investigator using the Global Aesthetic Improvement Scale (GAIS) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group;

6) The effective improvement rate of overall infraorbital aesthetic effect assessed by the participant using the Global Aesthetic Improvement Scale (GAIS) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group;

7) The change in infraorbital hollowing volume assessed by 3D image analysis at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group;

8) Participant satisfaction with the injection treatment at 1 and 3 months after the last injection in the test group;

9) The Visual Analog Scale (VAS) pain score immediately after each injection in the test group and in the control group receiving the compensation injection.

1.3 Other Evaluation Endpoints:

Test group:

1) The effective improvement rate of infraorbital hollowing AIHS scores at 6 and 12 months after the last injection in the test group (assessed by a blinded evaluator);

2) The effective improvement rate of infraorbital hollowing AIHS scores at 6 and 12 months after the last injection in the test group (assessed by the injecting investigator);

3) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 6 and 12 months after the last injection in the test group (assessed by a blinded evaluator);

4) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 6 and 12 months after the last injection in the test group (assessed by the injecting investigator);

5) The effective improvement rate of overall infraorbital aesthetic effect assessed by the injecting investigator using the Global Aesthetic Improvement Scale (GAIS) at 6 and 12 months after the last injection in the test group;

6) The effective improvement rate of overall infraorbital aesthetic effect assessed by the participant using the Global Aesthetic Improvement Scale (GAIS) at 6 and 12 months after the last injection in the test group;

7) The change in infraorbital hollowing volume assessed by 3D image analysis at 6 and 12 months after the last injection in the test group;

8) Participant satisfaction with the injection treatment at 6 and 12 months after the last injection in the test group.

Control group:

1) The effective improvement rate of infraorbital hollowing AIHS scores at 1, 3, and 6 months after the compensation injection in the control group (assessed by a blinded evaluator);

2) The effective improvement rate of infraorbital hollowing AIHS scores at 1, 3, and 6 months after the compensation injection in the control group (assessed by the injecting investigator);

3) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1, 3, and 6 months after the compensation injection in the control group (assessed by a blinded evaluator);

4) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1, 3, and 6 months after the compensation injection in the control group (assessed by the injecting investigator);

5) The effective improvement rate of overall infraorbital aesthetic effect assessed by the injecting investigator using the Global Aesthetic Improvement Scale (GAIS) at 1, 3, and 6 months after the compensation injection in the control group;

6) The effective improvement rate of overall infraorbital aesthetic effect assessed by the participant using the Global Aesthetic Improvement Scale (GAIS) at 1, 3, and 6 months after the compensation injection in the control group;

7) The change in infraorbital hollowing volume assessed by 3D image analysis at 1, 3, and 6 months after the compensation injection in the control group;

8) Participant satisfaction with the injection treatment at 1, 3, and 6 months after the compensation injection in the control group.

2. Methods and Timing for Evaluating, Recording, and Analyzing Efficacy Parameters

2.1 Primary Endpoint: The effective improvement rate of infraorbital hollowing AIHS scores at 3 months after the last injection in the test group and at 3 months after randomization in the control group (assessed by a blinded evaluator)

Evaluation method: A blinded evaluator trained in the scale scoring Standard Operating Procedure (SOP) and the scale grades the participant's bilateral infraorbital hollowing severity before and after injection/randomization according to the Allergan Infraorbital Hollowing Scale (AIHS, see Appendix 1).

Evaluation criterion: Compared with the screening period, an improvement of at least one grade in the bilateral infraorbital hollowing severity grade at 3 months after the last injection / after randomization is considered improved; otherwise, it is considered not improved.

The formula for calculating the effective improvement rate is as follows:

Effective improvement rate = (Number of effectively improved cases / Total number of participants in the analysis set) × 100%.

Allergan Infraorbital Hollowing Scale (AIHS)

Score	Grade	Clinical Features
0	None	No obvious depression or volume loss medially or laterally

1	Mild	Depression medial to the midpupillary line with some volume loss; smooth lateral lid-cheek transition
2	Moderate	Definite depression extending lateral to the midpupillary line with moderate volume loss; smooth lateral lid-cheek transition with mild volume loss
3	Severe	Distinct depression extending lateral to the midpupillary line with moderate volume loss forming a definite trough along the lid-cheek junction
4	Very Severe	Distinct depression extending from the medial to the lateral canthus; severe volume loss creating a marked ledge along the lid-cheek junction

2.2 Secondary Endpoints:

1) The effective improvement rate of infraorbital hollowing AIHS scores at 1 month after the last injection in the test group and at 1 month after randomization in the control group (assessed by a blinded evaluator);

Evaluation method: Same as the primary endpoint.

Evaluation criterion: Same as the primary endpoint.

Formula for calculating the effective improvement rate: Same as the primary endpoint.

2) The effective improvement rate of infraorbital hollowing AIHS scores at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group (assessed by the injecting investigator);

Evaluation method: Grade the participant’s bilateral infraorbital hollowing severity before and after injection/randomization according to the Allergan Infraorbital Hollowing Scale (AIHS, see Appendix 1).

Evaluation criterion: Same as the primary endpoint.

Formula for calculating the effective improvement rate: Same as the primary endpoint.

3) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group (assessed by a blinded evaluator);

Evaluation method: A blinded evaluator trained in the scale scoring Standard Operating Procedure (SOP) and the scale grades the participant's bilateral infraorbital hollowing severity before and after injection/randomization according to the FIMAN Periorbital Volume Deficiency Assessment Scale (FPVDAS, see Appendix 2).

Periorbital Volume Deficiency Assessment Scale

Grade	Degree	Clinical Features
Grade 0	None	The periorbital area is naturally full with no depression whatsoever.
Grade 1	Mild	There is obvious depression in the infraorbital tear trough area, but it does not extend beyond the vertical pupil line.
Grade 2	Moderate	There is obvious depression in the infraorbital tear trough area extending beyond the vertical pupil line, with no obvious bony structure exposed in the lateral infraorbital area.
Grade 3	Severe	Severe periorbital depression, with partial palpebrojugal groove visible in the inferolateral orbital area.
Grade 4	Very Severe	Extremely severe periorbital depression, with the entire orbital rim area presenting a marked step-off.

Evaluation criterion: Compared with the screening period, an improvement of at least one grade in the bilateral infraorbital hollowing severity grade at 1 and 3 months after the last injection / after randomization is considered improved; otherwise, it is considered not improved.

Formula for calculating the effective improvement rate: Effective improvement rate = (Number of effectively improved cases / Total number of participants in the analysis set) × 100%.

4) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group (assessed by the injecting investigator);

Evaluation method: An injecting investigator trained in the scale scoring Standard Operating Procedure (SOP) and the scale grades the participant's bilateral infraorbital hollowing severity before and after injection/randomization according to the FIMAN Periorbital Volume Deficiency Assessment Scale (FPVDAS, see Appendix 2).

Evaluation criterion: Same as secondary endpoint 3.

Formula for calculating the effective improvement rate: Same as secondary endpoint 3.

5) The effective improvement rate of overall infraorbital aesthetic effect assessed by the injecting investigator using the Global Aesthetic Improvement Scale (GAIS) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group (assessed by the injecting investigator);

Definition of improvement: At 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group, the injecting investigator rates the improvement in infraorbital volume/contour using the Global Aesthetic Improvement Scale (GAIS). The proportion of participants rated as "Very Much Improved (Grade 1)," "Much Improved (Grade 2)," or "Improved (Grade 3)" is calculated.

Global Aesthetic Improvement Scale (GAIS)

Grade	Global Aesthetic Improvement
1	Very Much Improved
2	Much Improved
3	Improved
4	No Change
5	Worse

The formula for calculating the improvement rate is as follows:

Improvement rate = Number of participants rated as "Very Much Improved + Much Improved + Improved" in the infraorbital area / Total number of participants receiving the global aesthetic improvement grading × 100%.

6) The effective improvement rate of overall infraorbital aesthetic effect assessed by the participant using the Global Aesthetic Improvement Scale (GAIS) at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group;

Definition of improvement: At 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group, participants rate the improvement in infraorbital volume/contour using the Global Aesthetic Improvement Scale (GAIS). The proportion of participants rated as "Very Much Improved (Grade 1)," "Much Improved (Grade 2)," or "Improved (Grade 3)" is calculated.

Global Aesthetic Improvement Scale (GAIS)

Grade	Global Aesthetic Improvement

1	Very Much Improved
2	Much Improved
3	Improved
4	No Change
5	Worse

The formula for calculating the improvement rate is as follows:

Improvement rate = (Number of participants rated as “Very Much Improved + Much Improved + Improved”) / Total number of participants receiving the global aesthetic improvement grading × 100%.

7) The change in infraorbital hollowing volume assessed by 3D image analysis at 1 and 3 months after the last injection in the test group and at 1 and 3 months after randomization in the control group;

Evaluation criterion: By capturing 3D photographs of the participant’s infraorbital hollowing before and after injection/randomization, the change in bilateral infraorbital volume after injection is measured to compare the volume change in the bilateral infraorbital region before and after injection/randomization.

8) Participant satisfaction assessment at 1 and 3 months after the last injection in the test group

Evaluation criterion: Participants in the test group assess their satisfaction with the injection treatment at 1 and 3 months after the last injection.

“How satisfied are you with the treatment?” Satisfaction rate = Number of participants rating “Very Satisfied (5 points)” and “Satisfied (4 points)” / Total number of participants in the test group analysis set × 100%.

Satisfaction Scale

Grade	**Satisfaction**
5	Very Satisfied
4	Satisfied
3	Neutral
2	Dissatisfied

1	Very Dissatisfied

9) The Visual Analog Scale (VAS) pain score immediately after each injection in the test group and in the control group receiving the compensation injection

Assessment time: Assessed by participants in the test group at three time intervals after injection completion: 5–10 min, 15–20 min, and 25–30 min; the average of the three measurements is taken (rounded to one decimal place).

Evaluation criterion: The Visual Analog Scale (VAS) is a subjective scale for assessing pain intensity. The participant, based on subjective feeling, makes a vertical mark on a 10 cm horizontal line to indicate the approximate level of pain felt. The far left of the horizontal line is 0, representing “completely painless”; the far right is 10, representing “the worst pain imaginable.”

Please mark a vertical line (|) on the line below to indicate the level of pain you feel.

(VAS scale diagram — see original protocol Figure 1)

2.3 Other Evaluation Endpoints:

Test group:

1) The effective improvement rate of infraorbital hollowing AIHS scores at 6 and 12 months after the last injection in the test group (assessed by a blinded evaluator);

Evaluation method: Same as the primary endpoint. Evaluation criterion: Same as the primary endpoint.

2) The effective improvement rate of infraorbital hollowing AIHS scores at 6 and 12 months after the last injection in the test group (assessed by the injecting investigator);

Evaluation method: Same as secondary endpoint 2. Evaluation criterion: Same as the primary endpoint.

3) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 6 and 12 months after the last injection in the test group (assessed by a blinded evaluator);

Evaluation method: Same as secondary endpoint 3. Evaluation criterion: Same as secondary endpoint 3.

4) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 6 and 12 months after the last injection in the test group (assessed by the injecting investigator);

Evaluation method: Same as secondary endpoint 4. Evaluation criterion: Same as secondary endpoint 4.

5) The effective improvement rate of overall infraorbital aesthetic effect assessed by the injecting investigator using the Global Aesthetic Improvement Scale (GAIS) at 6 and 12 months after the last injection in the test group;

Evaluation method: Same as secondary endpoint 5. Evaluation criterion: Same as secondary endpoint 5.

6) The effective improvement rate of overall infraorbital aesthetic effect assessed by the participant using the Global Aesthetic Improvement Scale (GAIS) at 6 and 12 months after the last injection in the test group;

Evaluation method: Same as secondary endpoint 6. Evaluation criterion: Same as secondary endpoint 6.

7) The change in infraorbital hollowing volume assessed by 3D image analysis at 6 and 12 months after the last injection in the test group;

Evaluation method: Same as secondary endpoint 7. Evaluation criterion: Same as secondary endpoint 7.

8) Participant satisfaction with the injection treatment at 6 and 12 months after the last injection in the test group;

Evaluation method: Same as secondary endpoint 8. Evaluation criterion: Same as secondary endpoint 8.

Control group:

1) The effective improvement rate of infraorbital hollowing AIHS scores at 1, 3, and 6 months after the compensation injection in the control group (assessed by a blinded evaluator);

Evaluation method: Same as the primary endpoint. Evaluation criterion: Same as the primary endpoint.

2) The effective improvement rate of infraorbital hollowing AIHS scores at 1, 3, and 6 months after the compensation injection in the control group (assessed by the injecting investigator);

Evaluation method: Same as secondary endpoint 2. Evaluation criterion: Same as the primary endpoint.

3) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1, 3, and 6 months after the compensation injection in the control group (assessed by a blinded evaluator);

Evaluation method: Same as secondary endpoint 3. Evaluation criterion: Same as secondary endpoint 3.

4) The grading scores and effective improvement rate of periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) at 1, 3, and 6 months after the compensation injection in the control group (assessed by the injecting investigator);

Evaluation method: Same as secondary endpoint 4. Evaluation criterion: Same as secondary endpoint 4.

5) The effective improvement rate of overall infraorbital aesthetic effect assessed by the injecting investigator using the Global Aesthetic Improvement Scale (GAIS) at 1, 3, and 6 months after the compensation injection in the control group;

Evaluation method: Same as secondary endpoint 5. Evaluation criterion: Same as secondary endpoint 5.

6) The effective improvement rate of overall infraorbital aesthetic effect assessed by the participant using the Global Aesthetic Improvement Scale (GAIS) at 1, 3, and 6 months after the compensation injection in the control group;

Evaluation method: Same as secondary endpoint 6. Evaluation criterion: Same as secondary endpoint 6.

7) The change in infraorbital hollowing volume assessed by 3D image analysis at 1, 3, and 6 months after the compensation injection in the control group;

Evaluation method: Same as secondary endpoint 7. Evaluation criterion: Same as secondary endpoint 7.

8) Participant satisfaction with the injection treatment at 1, 3, and 6 months after the compensation injection in the control group;

Evaluation method: Same as secondary endpoint 8. Evaluation criterion: Same as secondary endpoint 8.

3. Safety Evaluation Methods

Description of Safety Parameters

1) Vital signs:

Including body temperature, blood pressure (systolic/diastolic), pulse, and respiratory rate;

Assessment time: At each visit during the clinical trial.

2) Laboratory examinations (complete blood count, urinalysis, blood biochemistry) and electrocardiogram (ECG):

Complete blood count: Red blood cell count (RBC), white blood cell count (WBC), platelet (PLT) count, hemoglobin (HGB), neutrophil percentage (NEUT%), lymphocyte percentage (LY%);

Urinalysis: Urine RBC count / occult blood (RBC/BLD), urine WBC count / urine leukocytes (WBC/LEU), urine protein (PRO);

Blood biochemistry: Alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen / urea (BUN/Urea), creatinine (Cr), blood glucose (GLU);

Assessment time for the test group: Screening, 3 months after the last injection, 12 months after the last injection;

Assessment time for the control group: Screening, 3 months after randomization, 6 months after the optional compensation injection (only for those who accept the compensation injection).

3) Local reactions at the injection site within 30 days after each injection;

Assessment time for the test group: Within 30 days after each injection.

4) Incidence of adverse events and serious adverse events during the trial;

Assessment time for the test group: From the first injection to the end of follow-up;

Assessment time for the control group: From randomization to 3 months after randomization, and to 6 months after the optional compensation injection (only for those who accept the compensation injection).

5) Incidence of device deficiencies;

Assessment time for the test group: On the day of each injection;

Assessment time for the control group: On the day of the optional compensation injection (only for those who accept the compensation injection).

（IV） Investigational and Control Medical Devices

1.Product Information of the Investigational and Control Medical Devices (Table 4)

Table 4 Product Information of the Investigational and Control Medical Devices

Item	Investigational Device	Control Device

Product Name	Medical Collagen Filler	No-Treatment Control
Model / Specification	Model: F-1.0H; Specification: 1.0 mL/vial	—
Manufacturer	Fiman (Changchun) Pharmaceutical & Biotechnology Co., Ltd.	—
Registration Certificate No.	/	—

2.Packaging, Usage, and Dosage of the Investigational Medical Device

1) Packaging specification of this product: This product is a saline suspension of 3.5% bovine collagen and 0.3% lidocaine hydrochloride, pre-filled in a glass syringe (with injection needle) or a glass syringe (without injection needle); the package is equipped with, or includes, 27G × 1/2” single-use sterile injection needles, and/or a syringe adapter.

2) Packaging form: The specific model is detailed in the instructions. The representative model used in this trial is: F-1.0H, specification: 1.0 mL/vial.

3) Storage conditions: Store at 2°C–8°C. Do not freeze.

4) Transportation conditions and method: Must not be frozen during transportation.

5) Dosage: (See the relevant operational SOP for details).

3.Device Management

1) The investigational medical device shall be uniformly labeled, marked as for clinical trial use only, and checked and recorded by designated personnel.

2) The investigational product is transported by a logistics company entrusted by the sponsor to each study center, and a complete product handover procedure shall be established between the study center and the sponsor.

3) The study site shall set up a dedicated storage location for the investigational medical device; the investigational medical device shall be stored at 2°C–8°C.

4) The study site shall assign dedicated personnel to manage the investigational product and establish a dedicated device usage record form. The administrator shall register the participant’s name, device dispensing time, etc. in the order of enrollment and sign. After the trial, the investigational medical devices shall be collected and returned to the sponsor.

（V）Trial Flow

1. Trial Flowchart

Trial Group - Trial Process Table

Trial Phase	V1	V2		V3		V4	V5	V6	V7	Unscheduled Visit / Early Termination (ET)[14]
	Screening	Injection Treatment				Follow-up				
Time Window	D-14~D0	Initial Injection Day 15 (D0)		1 Month after Initial Injection ±7 days		1 Month ±7 days after Last Injection	3 Months ±14 days after Last Injection	6 Months ±14 days after Last Injection	12 Months ±28 days after Last Injection	
		Pre-injection	Post-injection	Pre-injection	Post-injection					
Informed Consent Form Signature	X									
Demographic Data[1]	X									
Vital Signs[2]	X	X		X	X	X	X	X	X	X
Medical History / Allergy History / Aesthetic Treatment History[3]	X									
Pregnancy Test (Blood or Urine HCG)[4]	X	X			X					X
Laboratory Tests[5]	X							X		X
Immunogenicity Test[6]	X						X	X		X
Electrocardiogram (ECG)	X									X
Facial Medical Photography[7]	X	X		X	X	X	X	X	X	X
Eligibility Criteria Check[8]	X	X								
Randomizatio		X								

n[9]										
Treatment and Information Record				X		X				
3D Photography		X			X	X	X	X	X	X
Eye Examination[9]		X						X		X
AIHS Score	Blinded Investigator[9]	X			X		X	X	X	X
	Injecting Investigator[9]	X			X		X	X	X	X
GAIS Score	Injecting Investigator[9]				X		X	X	X	X
	Study Participant[9]				X		X	X	X	X
Orbital Volume Loss Score	Blinded Investigator[9]	X			X		X	X	X	X
	Injecting Investigator[9]	X			X		X	X	X	X
Participant Satisfaction Assessment[9]							X	X	X	X
VAS Pain Score[9]				X		X				
Issue Diary Card[10]				X		X				
Collect Diary					X		X			

Card[10]									
Device Deficiency[11]		X		X					
Adverse Events (AEs)[11]			X	X	X	X	X	X	X
Concomitant Medications and Treatments[12]	X	X		X	X	X	X	X	X

Note: Each month is counted as 30 days.

1. Participant demographic data (date of birth, ethnicity, sex, height, weight).

2. Vital signs: body temperature; blood pressure (systolic/diastolic); pulse rate; respiratory rate.

3. Past medical / allergy / treatment history: inquire about and record the participant's allergy history, any disease history and use of chemotherapy, immunosuppressants, immunomodulatory therapy (e.g., monoclonal antibodies), or systemic corticosteroids within 3 months prior to ICF signing, treatment history within the past 2 years from the date of ICF signing, and medication use within the past 30 days.

4. Pregnancy test:

- Applicable to women of childbearing potential only.

- Women who have undergone hysterectomy or bilateral oophorectomy, or who have medically confirmed ovarian failure, are not required to undergo urine or serum pregnancy testing.

- At the same visit, either serum or urine pregnancy testing may be selected at the discretion of the center. If a participant chooses a urine pregnancy test before injection and the result is positive, a serum pregnancy test must be repeated before injection to confirm pregnancy status.

- A negative pregnancy-test result must be obtained before each injection (except for the cases described above where testing is not required). If the initial injection is performed on the same day as screening, one test is sufficient; if on different days, a pregnancy-test result obtained within the 2-day window before the first injection is acceptable.

- The pre-injection pregnancy test at V3 applies only to participants receiving a supplemental injection.

5. Laboratory tests: include complete blood count (CBC), urinalysis, blood chemistry, coagulation function, and infectious-disease screening. Coagulation function and infectious-disease screening are performed at the screening period only.

- CBC: red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), hemoglobin (HGB), neutrophil percentage (NEUT%), lymphocyte percentage (LY%).

- Urinalysis: urinary RBC count / occult blood (RBC/BLD), urinary WBC count / leukocytes (WBC/LEU), urine protein (PRO).

- Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen / urea (BUN/Urea), creatinine (Cr), blood glucose (GLU).

- Coagulation: prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB) — screening period only.

- Infectious-disease screening: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody, Treponema pallidum antibody (TP-Ab), and human immunodeficiency virus (HIV) antibody — screening period only.

6. Immunogenicity tests: immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement C3, and complement C4.

7. Facial medical photography: digital photographs of the participant's bilateral infraorbital injection areas are taken with a digital camera.

8. Periocular examination: an ocular-safety assessment (e.g., visual acuity, ocular motility) is performed; after injection, the injecting investigator asks the participant about ocular safety.

9. VAS pain scoring: test-group participants use the VAS pain scale to rate post-injection pain at three time intervals: 5–10 min, 15–20 min, and 25–30 min after injection.

10. Diary-card distribution / collection: a diary card is issued after injection for the participant to self-record injection-site reactions within 30 days after treatment, including the presence or absence of pain, pruritus, erythema / edema, ecchymosis / bruising, redness, nodules, and other discomforts.

11. Adverse events (AEs) are recorded from the time of injection until the end of follow-up. Clinical AEs that occur after ICF signing but before injection are recorded in the electronic case-report form (eCRF) as medical history / concomitant disease and are not recorded as AEs, except when one of the following applies: any injury / harm caused by a clinical laboratory procedure; an AE resulting from treatment discontinuation related to the trial protocol; an AE caused by a drug or device other than the investigational medical device used as part of the treatment regimen.

12. Concomitant medication and treatment: record all medications and treatments other than normal saline, glucose, and anesthetics.

13. If injection is performed on the same day as screening, the same examination / photography is performed only once. If performed on a different day, vital signs, a pregnancy test (a result obtained within the 2-day window before the first injection is acceptable), and facial medical photography must also be performed on the day of injection.

14. If a participant withdraws early, pregnancy testing, laboratory tests, and 12-lead ECG need not be repeated if the same examination performed at this institution within the past 7 days is available.

Control Group - Trial Process Table

Trial Phase	V1	V2		V3	V4		V5	V6	V7	
	Screening	Randomization (D0)		Follow-up	Optional Supplementary Injection[14]		Follow-up			
Time Window	D-14 to D0	Randomization Day (D0)		1 Month ±7 days after Randomization	3 Months ±14 days after Randomization		1 Month ±7 days after Optional Injection	3 Months ±14 days after Optional Injection	6 Months ±14 days after Optional Injection	Unscheduled Visit / Early Termination[15]
		Pre-randomization	*Post-randomization*		*Pre-randomization*	*Post-randomization*				
Informed Consent Form Signature	X									
Demographic Data[1]	X									
Vital Signs[2]	X	X		X	X	X	X	X	X	X
Medical History / Allergy History / Aesthetic Treatment History[3]	X									
Pregnancy Test (Blood or Urine HCG)[4]	X	X			X				X	X
Laboratory Tests[5]	X				X				X	X
Immunogenicity Test[6]	X			X	X		X		X	X

Trial Phase		V1	V2		V3	V4		V5	V6	V7	Unscheduled Visit / Early Termination[15]
		Screening	Randomization (D0)		Follow-up	Optional Supplementary Injection[14]		Follow-up			
Time Window		D-14 to	Randomization Day (D0)		1 Month ±7	3 Months ±14 days after Randomization		1 Month	3 Month	6 Month	
Electrocardiogram (ECG)		X				X				X	X
Facial Medical Photography[7]		X	X		X	X	X	X	X	X	X
Eligibility Criteria Check[8]		X	X								
Randomization[9]			X								
Treatment and Information Record							X				
3D Photography		X			X	X	X	X	X	X	X
Eye Examination		X				X		X	X	X	X
AIHS Score	Blinded Investigator[9]	X			X	X		X	X	X	X
	Injecting Investigator[9]	X			X	X		X	X	X	X
GAIS Score	Injecting Investigator				X	X		X	X	X	X

Trial Phase		V1	V2		V3	V4		V5	V6	V7	Unscheduled Visit / Early Termination[15]
		Screening	Randomization (D0)		Follow-up	Optional Supplementary Injection[14]		Follow-up			
Time Window		D-14 to	Randomization Day (D0)		1 Month ±7	3 Months ±14 days after Randomization		1 Month	3 Month	6 Month	
	[9]										
	Study Participant[9]				X	X		X	X	X	X
Orbital Volume Loss Score	Blinded Investigator[9]	X			X	X		X	X	X	X
	Injecting Investigator[9]	X			X	X		X	X	X	X
Participant Satisfaction Assessment[9]								X	X	X	X
VAS Pain Score[9]							X				
Issue Diary Card[10]							X				
Collect Diary Card[10]								X			
Device Deficiency[11]						X					
Adverse Events				X	X	X	X	X	X	X	X

Trial Phase	V1	V2		V3	V4		V5	V6	V7	Unscheduled Visit / Early Termination[15]
	Screening	Randomization (D0)		Follow-up	Optional Supplementary Injection[14]		Follow-up			
Time Window	D-14 to	Randomization Day (D0)		1 Month ±7	3 Months ±14 days after Randomization		1 Month	3 Month	6 Month	
(AEs)[11]										
Concomitant Medications and Treatments[12]	X	X		X	X	X	X	X	X	X

Note: a. Each month is counted as 30 days.

1. Participant demographic data (date of birth, ethnicity, sex, height, weight).

2. Vital signs: body temperature; blood pressure (systolic/diastolic); pulse rate; respiratory rate.

3. Past medical / allergy / treatment history: inquire about and record the participant's allergy history, any disease history and use of chemotherapy, immunosuppressants, immunomodulatory therapy (e.g., monoclonal antibodies), or systemic corticosteroids within 3 months prior to ICF signing, treatment history within the past 2 years from the date of ICF signing, and medication use within the past 30 days.

4. Pregnancy test:

- Applicable to women of childbearing potential only.

- Women who have undergone hysterectomy or bilateral oophorectomy, or who have medically confirmed ovarian failure, are not required to undergo urine or serum pregnancy testing.

- At the same visit, either serum or urine pregnancy testing may be selected at the discretion of the center. If a participant chooses a urine pregnancy test before injection and the result is positive, a serum pregnancy test must be repeated before injection to confirm pregnancy status.

- A negative pregnancy-test result must be obtained before each injection (except for the cases described above where testing is not required). If the initial injection is performed on the same day as screening, one test is sufficient; if on different days, a pregnancy-test result obtained within the 2-day window before the first injection is acceptable.

- The pre-injection pregnancy test before the optional compensation injection at V4 applies only to participants receiving the compensation injection.

5. Laboratory tests: include complete blood count (CBC), urinalysis, blood chemistry, coagulation function, and infectious-disease screening. Coagulation function and infectious-disease screening are performed at the screening period only.

- CBC: red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), hemoglobin (HGB), neutrophil percentage (NEUT%), lymphocyte percentage (LY%).

- Urinalysis: urinary RBC count / occult blood (RBC/BLD), urinary WBC count / leukocytes (WBC/LEU), urine protein (PRO).

- Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen / urea (BUN/Urea), creatinine (Cr), blood glucose (GLU).

- Coagulation: prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB) — screening period only.

- Infectious-disease screening: hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B e antigen (HBeAg), hepatitis B e antibody (HBeAb), hepatitis B core antibody (HBcAb), hepatitis C virus (HCV) antibody, Treponema pallidum antibody (TP-Ab), and human immunodeficiency virus (HIV) antibody — screening period only.

6. Immunogenicity tests: immunoglobulin A (IgA), immunoglobulin G (IgG), immunoglobulin M (IgM), complement C3, and complement C4.

7. Facial medical photography: digital photographs of the participant's bilateral infraorbital injection areas are taken with a digital camera.

8. Periocular examination: an ocular-safety assessment (e.g., visual acuity, ocular motility) is performed; after injection, the injecting investigator asks the participant about ocular safety.

9. VAS pain scoring: control-group participants use the VAS pain scale to rate pain during the injection process at three time intervals: 5–10 min, 15–20 min, and 25–30 min after injection.

10. Diary-card distribution / collection: a diary card is issued after injection for the participant to self-record injection-site reactions within 30 days after treatment, including the presence or absence of pain, pruritus, erythema / edema, ecchymosis / bruising, redness, nodules, and other discomforts.

11. Adverse events (AEs) are recorded from the time of randomization until the end of follow-up. Clinical AEs that occur after ICF signing but before randomization are recorded in the electronic case-report form (eCRF) as medical history / concomitant disease and are not recorded as AEs, except when one of the following applies: any injury / harm caused by a clinical laboratory procedure; an AE resulting from treatment discontinuation related to the trial protocol; an AE caused by a drug or device other than the investigational medical device used as part of the treatment regimen.

12. Concomitant medication and treatment: record all medications and treatments other than normal saline, glucose, and anesthetics.

13. If randomization is performed on the same day as screening, the same examination / photography is performed only once. If performed on a different day, vital signs, a pregnancy test (a result obtained within the 2-day window before the first injection is acceptable), and facial medical photography must also be performed on the day of randomization.

14. Optional compensation injection: after collection of the primary evaluation endpoint at 3 months after randomization, participants decide at their own discretion whether to receive a compensation injection. If a participant accepts the injection, they must return to the study center for follow-up at 1, 3, and 6 months after

injection. If a participant declines the injection, they may withdraw from the trial after the primary evaluation endpoint has been collected and all procedures completed at 3 months after randomization.

15. If a participant withdraws early, pregnancy testing, laboratory tests, and 12-lead ECG need not be repeated if the same examination performed at this institution within the past 7 days is available.

2. Trial Implementation (Methods, Content, Procedures, etc.)

(1) Test Group:

Screening Period V1 (D-14 to D0)

1. Sign the informed consent form.
2. Collect demographic information: date of birth, ethnicity, sex, height, and weight.
3. Record vital signs.
4. Record past medical history / allergy history / treatment history.
5. Pregnancy test (serum or urine HCG).
6. Laboratory tests: complete blood count, blood chemistry, urinalysis, coagulation tests, and infectious-disease screening.
7. Immunogenicity tests.
8. Electrocardiogram (ECG).
9. Facial medical photography.
10. Verify the inclusion and exclusion criteria.
11. 3D photography.
12. Periocular examination.
13. AIHS scoring: by the blinded evaluator and the injecting investigator.
14. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
15. Record concomitant medication and treatment.

Injection-treatment Period V2 (Initial-injection Day, D0)

If injection is performed on the same day as screening, the same examinations are performed only once. If performed on a different day, vital signs, a pregnancy test (a result obtained within the 2-day window before injection is acceptable), and facial medical photography must also be performed on the day of injection.

Pre-injection:

16. Verify the inclusion and exclusion criteria.
17. Record vital signs.
18. Pregnancy test.
19. Facial medical photography.
20. Randomization.
21. Device deficiency.
22. Adverse event, concomitant medication, and treatment.

Post-injection:

23. Record vital signs.
24. Facial medical photography.
25. VAS pain scoring.
26. Injection treatment and information recording.

27. Issue the diary card and inform the participant of the instructions for completing it.
28. Device deficiency.
29. Adverse event, concomitant medication, and treatment.

Injection-treatment Period V3 (1 Month ±7 Days After Initial Injection)

Pre-injection:

30. Record vital signs.
31. Pregnancy test (applicable to participants receiving a supplemental injection only).
32. Facial medical photography.
33. 3D photography.
34. AIHS scoring: by the blinded evaluator and the injecting investigator.
35. GAIS scoring: by the injecting investigator and the participant.
36. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
37. Device deficiency.
38. Collect the diary card.
39. Record adverse events, concomitant medication, and treatment.

Post-injection:

40. Record vital signs.
41. Facial medical photography.
42. Injection treatment and information recording.
43. 3D photography.
44. VAS pain scoring.
45. Issue the diary card.
46. Device deficiency.
47. Record adverse events, concomitant medication, and treatment.

Follow-up Period V4 (1 Month ±7 Days After Last Injection)

48. Record vital signs.
49. Immunogenicity tests.
50. Facial medical photography.
51. 3D photography.
52. AIHS scoring: by the blinded evaluator and the injecting investigator.
53. GAIS scoring: by the injecting investigator and the participant.
54. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
55. Participant treatment-satisfaction assessment.
56. Collect the diary card.
57. Record adverse events, concomitant medication, and treatment.

Follow-up Period V5 (3 Months ±14 Days After Last Injection)

58. Record vital signs.
59. Laboratory tests: complete blood count, blood chemistry, and urinalysis.
60. Immunogenicity tests.
61. Facial medical photography.
62. 3D photography.
63. Periocular examination.
64. AIHS scoring: by the blinded evaluator and the injecting investigator.
65. GAIS scoring: by the injecting investigator and the participant.
66. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
67. Participant treatment-satisfaction assessment.
68. Record adverse events, concomitant medication, and treatment.

Follow-up Period V6 (6 Months ±14 Days After Last Injection)

69. Record vital signs.
70. Facial medical photography.
71. 3D photography.
72. AIHS scoring: by the blinded evaluator and the injecting investigator.
73. GAIS scoring: by the injecting investigator and the participant.
74. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
75. Participant treatment-satisfaction assessment.
76. Record adverse events, concomitant medication, and treatment.

Follow-up Period V7 (12 Months ±28 Days After Last Injection)

77. Record vital signs.
78. Pregnancy test.
79. Laboratory tests: complete blood count, urinalysis, and blood chemistry.
80. Immunogenicity tests.
81. Electrocardiogram (ECG).
82. Facial medical photography.
83. Periocular examination.
84. 3D photography.
85. AIHS scoring: by the blinded evaluator and the injecting investigator.
86. GAIS scoring: by the injecting investigator and the participant.
87. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
88. Participant treatment-satisfaction assessment.
89. Record adverse events, concomitant medication, and treatment.

(2) Control Group:

Screening Period V1 (D-14 to D0)

90. Sign the informed consent form.

91. Collect demographic information: date of birth, ethnicity, sex, height, and weight.
92. Record vital signs.
93. Record past medical history / allergy history / treatment history.
94. Pregnancy test (serum or urine HCG).
95. Laboratory tests: complete blood count, blood chemistry, urinalysis, coagulation tests, and infectious-disease screening.
96. Immunogenicity tests.
97. Electrocardiogram (ECG).
98. Facial medical photography.
99. Verify the inclusion and exclusion criteria.
100. 3D photography.
101. Periocular examination.
102. AIHS scoring: by the blinded evaluator and the injecting investigator.
103. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
104. Record concomitant medication and treatment.

Randomization Day V2 (Randomization Day, D0)

If randomization is performed on the same day as screening, the same examinations are performed only once. If performed on a different day, vital signs, a pregnancy test (a result obtained within the 2-day window before randomization is acceptable), and facial medical photography must also be performed on the day of randomization.

105. Verify the inclusion and exclusion criteria.
106. Record vital signs.
107. Facial medical photography.
108. Record concomitant medication and treatment.

Pre-randomization:

109. Pregnancy test.
110. Randomization.

Post-randomization:

111. Record adverse events.

Follow-up Period V3 (1 Month ±7 Days After Randomization)

112. Record vital signs.
113. Immunogenicity tests.
114. Facial medical photography.
115. 3D photography.
116. AIHS scoring: by the blinded evaluator and the injecting investigator.
117. GAIS scoring: by the injecting investigator and the participant.

118. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
119. Record adverse events, concomitant medication, and treatment.

Follow-up / Optional Compensation-injection Period V4 (3 Months ±14 Days After Randomization / Optional-compensation-injection Day)

Control-group participants may decide at their own discretion on the day of the 3-month follow-up visit whether to receive a compensation injection. If a participant declines the compensation injection, they may withdraw from the trial after completing the following follow-up procedures.

120. Record vital signs.
121. Pregnancy test (applicable to participants receiving the compensation injection only).
122. Laboratory tests: complete blood count, blood chemistry, and urinalysis.
123. Immunogenicity tests.
124. Electrocardiogram (ECG).
125. Facial medical photography.
126. 3D photography.
127. Periocular examination.
128. AIHS scoring: by the blinded evaluator and the injecting investigator.
129. GAIS scoring: by the injecting investigator and the participant.
130. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
131. Device deficiency.
132. Record adverse events, concomitant medication, and treatment.

If a control-group participant chooses to receive the compensation injection, the following procedures must be completed and follow-up continued through 6 months after the optional compensation injection.

Pre-compensation injection:

133. Record vital signs.
134. Pregnancy test.
135. Laboratory tests: complete blood count, blood chemistry, and urinalysis.
136. Immunogenicity tests.
137. Electrocardiogram (ECG).
138. Facial medical photography.
139. 3D photography.
140. Periocular examination.
141. AIHS scoring: by the blinded evaluator and the injecting investigator.
142. GAIS scoring: by the injecting investigator and the participant.
143. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
144. Device deficiency.
145. Record adverse events, concomitant medication, and treatment.

Post-compensation injection:

146. Record vital signs.
147. Facial medical photography.
148. Injection treatment and information recording.
149. 3D photography.
150. VAS pain scoring.
151. Issue the diary card.
152. Device deficiency.
153. Record adverse events, concomitant medication, and treatment.

Follow-up Period V5 (1 Month ±7 Days After Optional Compensation Injection; compensation-injection recipients only)

154. Record vital signs.
155. Immunogenicity tests.
156. Facial medical photography.
157. 3D photography.
158. Periocular examination.
159. AIHS scoring: by the blinded evaluator and the injecting investigator.
160. GAIS scoring: by the injecting investigator and the participant.
161. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
162. Participant satisfaction assessment.
163. Collect the diary card.
164. Record adverse events, concomitant medication, and treatment.

Follow-up Period V6 (3 Months ±14 Days After Optional Compensation Injection; compensation-injection recipients only)

165. Record vital signs.
166. Facial medical photography.
167. 3D photography.
168. AIHS scoring: by the blinded evaluator and the injecting investigator.
169. GAIS scoring: by the injecting investigator and the participant.
170. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
171. Participant satisfaction assessment.
172. Record adverse events, concomitant medication, and treatment.

Follow-up Period V7 (6 Months ±14 Days After Optional Compensation Injection; compensation-injection recipients only)

173. Record vital signs.
174. Pregnancy test (serum or urine HCG).
175. Laboratory tests: complete blood count, blood chemistry, urinalysis, coagulation tests, and infectious-disease screening.
176. Immunogenicity tests.

177. Electrocardiogram (ECG).
178. Facial medical photography.
179. 3D photography.
180. Periocular examination.
181. AIHS scoring: by the blinded evaluator and the injecting investigator.
182. GAIS scoring: by the injecting investigator and the participant.
183. Periorbital-volume-deficiency scoring: by the blinded evaluator and the injecting investigator.
184. Participant satisfaction assessment.
185. Record adverse events, concomitant medication, and treatment.

Early Withdrawal

For participants who withdraw from the study during the treatment period, the early-withdrawal visit should be completed in accordance with the trial flowchart whenever possible (pregnancy testing, laboratory tests, and ECG need not be repeated if the same examination performed at this institution within the past 7 days is available). The investigator or qualified study personnel should make every effort to contact the participant, collect the assessments required at the corresponding visit, and document the date of the last treatment with the investigational device, the date of withdrawal, the reason for withdrawal, etc.

3. Medical-Device Use Specification

This product is to be operated by the participating investigators in accordance with the product's applicable requirements and specifications.

4. Concomitant-Treatment Specification

(1) Permitted Concomitant Medication and Treatment

Other medications not listed among the prohibitions may be used if needed during the clinical trial:

186. Concomitant medications that the participant was using before entering the study and that the investigator judges will not affect the analysis of the study results.
187. All medications administered briefly for the treatment of other diseases or adverse events, after discussion with the investigator.
188. Local anesthetics used during each treatment procedure and cold-compress treatment before and after the procedure.

If concomitant medication is used, the medication name, purpose of use, dosage and administration, and duration of administration must be recorded in the medical record. If concomitant treatment is performed, the treatment name and the date / time must be recorded in the medical record.

(2) Prohibited Medication and Treatment

From 2 weeks before to 4 weeks after each injection of the investigational medical device, the use of anticoagulants such as warfarin, heparin, and aspirin is prohibited.

During the clinical trial, except for the treatment of adverse events, the use of immunosuppressants and other immunologic agents is prohibited, as is the use of systemic corticosteroids (except inhaled corticosteroids).

During the clinical trial, no permanent or semi-permanent fillers (e.g., calcium hydroxyapatite, polymethyl methacrylate, silicone, expanded polytetrafluoroethylene), collagen other than the investigational medical device, autologous fat, or temporary fillers (e.g., collagen, sodium hyaluronate (HA)) may be used in the bilateral infraorbital region, nor may any wrinkle-treatment procedures (e.g., botulinum toxin injection, radiofrequency treatment, ultrasound treatment, laser or chemical peels, dermabrasion) be performed.

（VI）Bias-Control Measures

Multicenter: Case samples drawn from multiple centers are more representative than those from a single center and protect against bias in the trial results caused by systematic error at a single center, making the resulting conclusions more credible. At the same time, to reduce inter-center procedural differences, the sponsor should organize the development of standard operating procedures (SOPs) in accordance with the clinical trial protocol, organize training for all investigators participating in the trial on the trial protocol and the use of the investigational medical device, and adopt clear assessment criteria for effectiveness and safety endpoints to ensure consistency in the execution of the clinical trial protocol and the use of the investigational medical device.

Randomization: This study uses a block-randomization method to generate the participant randomization-code table. SAS (version 9.4 or higher) software is used to generate the randomization-code table at a test-group-to-control-group ratio of 2:1. The selected block length, random seed, and other parameters are sealed together with the participant randomization-code table as confidential data. The randomization-code table is provided by the randomization statistician.

Randomization (continued): After the participant has signed the informed consent form and meets the inclusion criteria while not meeting any exclusion criteria, the investigator randomly assigns the participant to the test group or the control group via the centralized randomization system (IWRS).

Blinding: Because the control group uses a no-treatment control design, it is not possible to blind the injecting investigator or the participant to the treatment; an open-label design is therefore adopted. To minimize bias in the effectiveness assessment, endpoint blinding is used — that is, the evaluating investigator is blinded: a blinded evaluator who is designated as not participating in the study procedures, is unaware of the randomization assignments, and has received training evaluates the post-injection effectiveness endpoints.

Investigator training: Before the clinical trial begins, the monitor, together with the principal investigator at each study center, should train the investigators on the trial protocol, injection procedures, blinded assessment, facial medical photography, scale scoring, etc., so that the investigators understand and master the investigational product, the trial protocol, and the study procedures.

VI. Statistical Considerations

(1) Sample Size Estimation

The primary efficacy endpoint of this study is the response rate based on improvement in infraorbital hollowing AIHS scores (assessed by a blinded investigator) at 3 months after the last injection in the trial group and at 3 months after randomization in the control group.

This trial adopts a superiority design. Based on the registration efficacy results of the investigational device used for facial nasolabial fold wrinkle filling, and combined with the efficacy of other treatment modalities for infraorbital hollowing improvement, the expected response rate for bilateral infraorbital filling based on AIHS score improvement at 3 months after the last injection with the investigational device is estimated at 80% (a reasonable estimate based on FDA-published efficacy data for an overseas product with the same indication). According to the literature, in other blank-controlled clinical trials, the response rate of the blank control group at 3 months after randomization is approximately 25%. The superiority margin is set at 30%. With a ratio of 2:1 between the trial and control groups, a power of $1-\beta = 0.90$, and a significance level of $\alpha = 0.025$ (one-sided), the calculated required sample size is 135 subjects (90 in the trial group and 45 in the control group). Taking into account a 20% dropout rate and randomization needs, the final sample size is enlarged to 171 subjects, including 114 in the trial group and 57 in the control group.

Sample size calculation formula:

$$n_T/k = n_C = [\ (Z_(1-\alpha/2) + Z_(1-\beta))^2 \times (\ P_C(1-P_C) + P_T(1-P_T)/k\ )\ ] / (|D| - \Delta)^2$$

$$\text{where } k = n_T / n_C = 2$$

k is the ratio between the trial group and the control group; here k = 2. P_T and P_C are the expected event rates in the trial and control groups, respectively; |D| is the absolute value of the expected rate difference between the two groups, $|D| = |P_T - P_C|$; Δ is the superiority margin, taken as a positive value.

(2) Analysis Data Sets

Full Analysis Set (FAS): includes all randomized subjects in the trial group who have received at least one injection, as well as all randomized subjects in the control group.

Per Protocol Set (PPS): a subset of the FAS, including subjects who received the treatment as specified in the protocol, for whom observation data of the primary endpoint are available, and who had no major protocol deviations.

Safety Analysis Set (SS): all randomized subjects in the trial group who received at least one injection, all randomized subjects in the control group, and subjects who have undergone at least one safety evaluation.

(3) Subject Exclusion Criteria

1) Violation of a major inclusion criterion or meeting a major exclusion criterion;

2) Randomized to the trial group but did not use the investigational medical device after enrollment;

3) During the trial, the subject used other treatments or procedures that may affect the analysis of the study results without the guidance of the investigator.

(4) Statistical Methods

1. General Principles

After the trial protocol is finalized, a qualified statistician shall be responsible for developing the Statistical Analysis Plan (SAP) in consultation with the principal investigator. SAS 9.4 (or above) statistical software will be used. Except that the superiority test is conducted at a one-sided significance level of 0.025, all statistical tests are two-sided, and a P value of less than 0.05 will be considered statistically significant.

For quantitative variables, descriptive statistics will include the mean, standard deviation, median, minimum, maximum, first quartile (Q1), and third quartile (Q3). For categorical variables, the number and percentage of cases in each category will be described.

Comparisons between the two groups will be performed using appropriate methods according to the type of variable. For quantitative data, inter-group comparisons will use ANCOVA adjusting for baseline or the Wilcoxon rank-sum test, depending on the data distribution. For categorical data, the chi-square test or exact probability method (if the chi-square test is not applicable) will be used. For ordinal data, the Wilcoxon rank-sum test or the CMH test will be used.

2. Enrollment and Completion

Summarize the number of enrolled and completed subjects and laterality at each center, and list dropout cases. Describe the distribution of cases across centers by data set and laterality, compare overall dropout rates, and provide a detailed list of reasons for early withdrawal. Demographic characteristics (age, sex, etc.) of subjects will be described, with baseline analysis based on the FAS.

3. Efficacy Analysis

The efficacy analysis will provide results based on both the FAS and the PPS, with the FAS results being primary.

1) Primary Endpoint:

The response rate based on improvement in infraorbital hollowing AIHS scores (assessed by a blinded investigator) at 3 months after the last injection in the trial group and at 3 months after randomization in the control group will be calculated. A superiority test will be used for the response rate of the primary efficacy endpoint, with the following test hypotheses:

Null hypothesis H0: $P_T - P_C \leq 30\%$;

Alternative hypothesis H1: $P_T - P_C > 30\%$.

At a significance level of $\alpha = 0.025$ (one-sided) and $\beta = 0.1$, the improvement response rates of the trial and control groups will be compared, and the 95% confidence interval (CI) of the rate difference between the two groups will be calculated. If the lower limit of the 95% CI of the rate difference between the two groups is greater than 30%, the trial group can be considered superior to the control group.

For inter-group comparison, the Farrington-Manning method will be considered to calculate the difference in response rates between the two groups and its two-sided 95% CI.

2) Secondary Endpoints and Other Evaluation Indicators:

Improvement response rate based on periorbital volume deficiency (Periorbital Volume Deficiency Assessment Scale) scores assessed by the blinded evaluating investigator and the injecting investigator: categorical variable, analyzed using the Farrington-Manning method;

Improvement response rate based on infraorbital hollowing GAIS scores assessed by the blinded evaluating investigator: categorical variable, analyzed using the Farrington-Manning method;

Improvement response rate based on infraorbital hollowing GAIS scores assessed by the injecting investigator: categorical variable, analyzed using the Farrington-Manning method;

Global aesthetic effect (GAIS) score assessed by the injecting investigator: ordinal variable, inter-group comparison using the Wilcoxon rank-sum test; GAIS improvement rate analyzed as a categorical variable using the Farrington-Manning method;

Global aesthetic effect (GAIS) score assessed by the subject: ordinal variable, inter-group comparison using the Wilcoxon rank-sum test; GAIS improvement rate analyzed as a categorical variable using the Farrington-Manning method;

VAS pain score: quantitative variable, inter-group comparison using the Wilcoxon rank-sum test;

Change in infraorbital volume based on 3D image analysis: quantitative variable, analyzed using the Farrington-Manning method;

Subject satisfaction evaluation: satisfaction rate will be calculated; categorical variable, analyzed using the Farrington-Manning method.

4. Safety Evaluation Indicators

Safety evaluation is based on the Safety Analysis Set (SS).

Vital signs, laboratory tests, immunogenicity, and ECG will be quantitatively summarized by scheduled visit, describing both the observed values at each visit and the changes from baseline. Cross-tabulations will summarize the clinical significance of changes from baseline by scheduled visit and the worst post-injection result (including unscheduled examination results). Vital signs, laboratory tests, and ECG parameters will be listed, and a subject listing will be provided for those with normal/borderline baseline values that became abnormal with clinical significance after treatment.

All adverse events occurring during the trial will be recorded in detail. The number of adverse event occurrences, the number of subjects, and the incidence rates will be categorized and summarized descriptively, with an accompanying listing.

In addition to the above statistical methods, detailed and additional exploratory analyses may be required and will be confirmed in the study report and the Statistical Analysis Plan (SAP).

5. Interim Analysis and Interim Data Submission

No interim analysis is planned for this study.

(5) Handling of Missing Values and Outliers

Missing Value Handling:

For missing data, handling will be based on the data set to which the subject belongs. For missing values of the primary efficacy endpoint in the FAS, the Worst Observation Carried Forward (WOCF) method will be used for imputation. Missing values of secondary efficacy endpoints will not be imputed; the specific handling method will be described in detail in the Statistical Analysis Plan.

Irrational Data Handling:

During data management, logic checks will be performed on the data in the database. Irrational data identified will be queried to the investigator or data entry personnel in the form of a query, and the database may be locked only after all irrational data have been resolved.

Erroneous Data Handling:

During data management, quality control will be performed on the data in the database. Erroneous data identified will be queried to the investigator or data entry personnel in the form of a query, and the database may be locked only after all erroneous data have been corrected.

VII. Monitoring Plan

The sponsor or the Contract Research Organization (CRO) will appoint monitors to monitor this clinical trial.

Monitors should have a relevant academic background in clinical medicine, pharmacy, biomedical engineering, statistics, etc., and should have received necessary training, be familiar with the Good Clinical Practice for Medical Device Clinical Trials and relevant regulations, and be familiar with information on the non-clinical and clinical aspects of the investigational medical device and its 同类 products, as well as the clinical trial protocol and related documents.

The number of monitoring visits per center per month will be arranged according to the actual trial progress and the monitoring plan.

Monitors should follow the principles of the Good Clinical Practice for Medical Device Clinical Trials and urge the trial to be conducted in strict accordance with the protocol, so as to ensure that the trial data are authentic, complete, and accurate. Specific duties include:

(1) Before the trial, confirm that the trial site has appropriate conditions, including qualified personnel and training, complete and well-functioning laboratory equipment, an expected adequate number of subjects, and that the participating researchers are familiar with the trial requirements;

(2) Before, during, and after the trial, monitor whether the trial site and investigators comply with relevant regulations and the clinical trial protocol;

(3) Confirm that each subject signs the informed consent form before participating in the clinical trial, understand the subject's enrollment status and the trial progress; clearly and truthfully record any follow-up not performed by the investigator, examinations not conducted, and whether the investigator has corrected errors and omissions; for revised informed consent forms, confirm that affected subjects who have not yet completed the trial 流程重新 sign;

(4) Confirm that all case report forms are completed correctly and are consistent with the original data; any modifications to data in the case report form should ensure that the original entry remains legible, with an audit trail preserved, signed by the person making the modification and dated; the disease, total number of cases, and sex, age, and treatment outcome of each case should be confirmed and recorded;

(5) Confirm that cases of subjects withdrawing from the clinical trial or not complying with the requirements of the informed consent form are documented, and discuss such cases with the investigator;

(6) Confirm that all adverse events, complications, and other device defects are documented, and that serious adverse events and device defects that may lead to serious adverse events are reported within the required time frame and documented;

(7) Monitor the supply, use, maintenance, transport, receipt, storage, distribution, handling, and recovery of the investigational medical device;

(8) Supervise the regular maintenance and calibration of relevant equipment during the clinical trial;

(9) Ensure that all clinical trial-related documents received by the investigators are the latest versions;

(10) After each monitoring visit, a written report should be submitted to the sponsor, including the monitor's name, monitoring date, monitoring time, monitoring location, monitoring content, investigator's name, project completion status, existing problems, conclusions, and corrections made for errors and omissions.

VIII. Data Management

This trial uses electronic Case Report Forms (eCRF) to collect data. To ensure the integrity, accuracy, authenticity, and reliability of the electronic clinical trial data, data management will be conducted in accordance with the principles and requirements of the Guideline on Electronic Data Capture Technology for Clinical Trials and the Technical Guideline on Clinical Trial Data Management.

(1) Access Control and Data Entry

The system administrator creates accounts for different roles—data entry personnel, data managers, investigators (principal), and clinical monitors—and grants different permissions. Each study center can only view its own center's data. Data entry personnel have permissions for data entry, modification, browsing, and query resolution; investigators have permissions for data entry, modification, browsing, and query resolution; the principal investigator has, in addition to the investigator's permissions, the permission for electronic signature; monitors have permissions for browsing, sending/closing queries, and source data verification; data management personnel have permissions for browsing, sending/closing queries, review, data freezing, and locking; medical personnel have permissions for browsing, sending/closing queries, and medical data verification confirmation.

Clinical investigators or data entry personnel designated by the investigators (clinical coordinators) shall enter the source data into the eCRF in a timely and accurate manner.

During the study, each center shall retain the original records of each subject, including not only the study medical records, laboratory data, and any other examination and evaluation results, but also visit records, the subject's basic and medical information, and the original signed informed consent forms, so as to ensure that the relevant original data required for the eCRF can be obtained and are available for inspection by on-site monitors at any time for verification.

(2) Query Generation and Resolution

After data are entered into the electronic data capture (EDC) database, the system will check the data according to the Data Validation Plan (pre-programmed edit checks), and data with discrepancies will automatically generate system queries. Clinical monitors, data managers, and medical personnel will manually review the data, and send manual queries for questionable data through the EDC database. Data entry personnel or investigators will confirm and respond to manual and system queries, and modify erroneous data when necessary, until the queries are resolved. If a response does not resolve a query, the data manager and clinical monitor may re-query that data point once; all records are retained in the EDC database.

(3) Data Modification and Review

Authorized data entry personnel or investigators may modify the data after verification; the reason for modification must be filled in on the eCRF after submission. Clinical monitors, data managers, and medical personnel are responsible for data review; the principal investigator has the authority to sign off on all final data.

(4) Medical Coding

The medical coding for this study is the responsibility of the data management unit. The coding content includes, but is not limited to, concomitant medications and adverse events.

(5) Electronic Signature on the eCRF

After the data in the database have been checked and cleaned by the monitors and data managers and are free of queries, the data manager will freeze the data, at which point the data can no longer be modified. Thereafter, the principal investigator will confirm the authenticity and completeness of the data and apply an electronic signature.

(6) Database Lock and Export

After all data have been reviewed and verified, the data manager will lock the database according to the database lock resolution. After all data have been accurately entered into the EDC, the monitors have completed source data verification for all data, the data managers have completed review of all data, and the principal investigator has applied an electronic signature to all data, the database may be locked upon approval.

If problems with the data are still found after the database is locked, an unlock may be requested if necessary; an application must be submitted and discussed and signed off on by the sponsor, investigator, project manager, data management personnel, etc., before the database unlock and modification operations can be performed.

All final data will be exported from the EDC database by the data management personnel and delivered to the statisticians for analysis.

IX. Risk–Benefit Analysis

(1) Study Benefits

The medical collagen filler developed by Fiman (Changchun) Pharmaceutical & Biotechnology Co., Ltd. has passed medical device registration testing, confirming that the product meets the product technical requirements in terms of safety requirements and device performance.

The investigational medical device is manufactured in strict accordance with the requirements of the medical device quality management system, and has been rigorously inspected according to the inspection methods before leaving the factory, ensuring the safety and efficacy of the investigational medical device.

The design of this clinical trial follows relevant national registration regulations and, based on the product's working principle, constitutes a reasonable and scientific clinical trial design. The selected clinical centers are all experienced in medical aesthetics and clinical trials, with adequate medical conditions and professional clinical experts. All treating physicians will receive corresponding training before the trial.

Possible benefits to subjects in this study:

(1) During this clinical study, subjects can receive treatment for infraorbital hollowing improvement with the investigational medical device and receive good medical care. Important information gained from this study may be beneficial to those receiving or undergoing treatment in the future, and may help increase treatment options for themselves or other patients;

(2) Compared with the current standard of care commonly used in Chinese hospitals, the study centers will perform the same number of or more frequent and closer follow-up monitoring for subjects participating in this trial.

(2) Study Risks

The product used in this study may also cause side effects (adverse reactions). The following are known adverse reactions of the medical collagen filler:

According to the results of the registration clinical trial of the sponsor's predecessor product, this product has the same pH and osmotic pressure as human tissue and is highly compatible with

human tissue; therefore, it rarely causes immune reactions or rejection. However, when exogenous biomaterial is introduced into skin under relatively high tension, the body requires an accommodation process, and transient non-inflammatory reactions are normal. These include temporary swelling, mild redness, and slight discomfort, which generally resolve within 24–48 hours. If the filling site worsens, with erythema, induration and/or urticaria, herpes recurrence, or spreading erythema or swelling, appropriate antihistamines and anti-inflammatory drugs may be taken; these reactions will disappear automatically within one week. In a very small number of users, mild periorbital edema or paroxysmal pruritus around the injection site may occur with alcohol consumption, sun exposure, exercise, or nasal congestion, due to peripheral vasodilation. The above symptoms are self-limiting and resolve upon removal of the inducing factor, without affecting the long-term aesthetic outcome.

No reports of local ischemia or vascular embolism following use of this product have been found to date; however, such cases have occurred with other injectable soft-tissue fillers. Injection of this product into a blood vessel may also carry the risk of embolism, vascular occlusion, local ischemia, or infarction. Particular care should be taken during injection. Adverse events associated with intravascular injection of soft-tissue fillers that have been reported are very rare but relatively serious, including temporary or permanent visual impairment, blindness, and compromise of facial structures. If the patient exhibits any of the following symptoms during or shortly after injection, injection should be stopped immediately, including visual changes, signs of stroke, blanching of the skin, or abnormal pain, and the patient should be evaluated and treated by a qualified physician.

Before enrolling subjects, the investigator will conduct a risk assessment in advance and prepare the relevant devices and medications needed for prevention and treatment, and will closely monitor the subject during the procedure. For any risks occurring during the study, the investigator will, based on the specific situation of the subject, promptly provide correct and reasonable medical management.

X. Quality Control of the Clinical Trial

(1) Investigator Training

Before the clinical trial begins, the trial site institution shall train the investigators according to the Investigator's Brochure and the clinical protocol.

(2) Measures to Improve Subject Compliance

Investigators should conscientiously perform the informed consent process so that subjects fully understand the trial requirements and cooperate with the trial. Subject compliance will be monitored and assessed by the center's research staff and monitors based on the original data and the eCRF.

(3) Monitoring of the Clinical Trial

Monitors dispatched by the sponsor or CRO will conduct regular on-site monitoring visits to the trial sites to ensure that all elements of the study protocol are strictly followed and to check the eCRF to ensure consistency with the original data.

(4) Clinical Trial Audit

To ensure the quality of the clinical trial, the sponsor will organize auditors independent of the medical device clinical trial, with appropriate training and experience, to audit the implementation of the clinical trial, to assess whether the trial complies with the clinical trial protocol, the Good Clinical Practice for Medical Device Clinical Trials, and relevant laws and regulations, and whether the trial data are recorded in a timely, truthful, accurate, and complete manner. The medical device clinical trial site and investigators shall cooperate with the audit organized by the sponsor.

XI. Ethical Issues and Informed Consent

(1) Ethical Considerations

The clinical trial must be conducted in accordance with the Declaration of Helsinki and the relevant clinical trial research norms and regulations of China. Before the trial begins, the trial may be implemented only after approval by the Ethics Committee of the lead trial site.

Before each subject is enrolled in this study, the investigator is responsible for providing a complete and comprehensive written introduction to the subject or their legal representative regarding the purpose, procedures, and possible risks of this study. Subjects should be informed that they have the right to withdraw from the study at any time. Before enrollment, each subject must be given a written informed consent form. The investigator is responsible for obtaining informed consent from each subject before entering the study, and the informed consent form shall be retained as a clinical trial document for reference.

(2) Informed Consent Process

Before the subject participates in the clinical trial, the investigator shall fully explain the details of the clinical trial to the subject or their family member, guardian, or legal representative, including known and foreseeable risks and possible adverse events. After sufficient and detailed explanation, the subject or their legal representative shall sign and date the informed consent form (ICF); the investigator who obtained the informed consent shall also sign and date the informed consent form.

The informed consent form should indicate the date of preparation or the date of the revised version, information that will help confirm that the correct version is being used. If the informed consent form is revised during the trial, the revised version must be reviewed and approved by the Ethics Committee before it is implemented. After the revised informed consent form is

approved and delivered to the trial site for filing, all subjects who have not yet completed the trial 流程 must sign the newly revised informed consent form.

XII. Reporting of Adverse Events and Device Defects

(1) Definition and Reporting of Adverse Events

1. Definition of Adverse Event

An adverse event (AE) refers to any untoward medical occurrence in a subject enrolled in a medical device clinical trial, whether or not it is related to the investigational medical device.

In this study, AEs are recorded starting from after randomization until the end of follow-up. Clinical AEs occurring after signing the informed consent but before randomization are recorded in the eCRF as medical history/concurrent disease and are not recorded as AEs, unless one of the following applies: harm/injury caused by any clinical laboratory procedure; an AE resulting from discontinuation related to the trial protocol; an AE caused by a drug or device other than the investigational device used as part of the treatment regimen.

2. Severity Assessment of Adverse Events

The course, severity, management, and outcome of adverse events will be observed in detail and recorded in the adverse event report form. According to the following criteria, the severity of an AE may be classified as mild, moderate, or severe.

Mild: tolerable to the subject, does not affect treatment, requires no special management, and has no impact on the subject's health.

Moderate: difficult for the subject to tolerate, requires special management, and has a direct impact on the subject's health.

Severe: life-threatening, fatal or disabling, requiring immediate emergency management.

3. Evaluation of Adverse Events

AEs are evaluated on a four-level scale: definitely related, possibly related, possibly unrelated, and definitely unrelated. The first two are counted in the incidence of adverse reactions. The evaluation criteria are for reference.

Related to the investigational medical device:

(1) a reasonable temporal relationship exists between the two; (2) the known risk of the investigational medical device or its mechanism can explain the event; (3) the harm lessens or disappears after discontinuation; (4) the harm recurs upon re-administration; (5) the event cannot

be explained by other influencing factors. Satisfying all five criteria is judged as "definitely related"; satisfying any two criteria is judged as "possibly related".

Unrelated to the investigational medical device:

(1) no reasonable temporal relationship exists between the two; (2) the event is a type that the investigational medical device could not possibly cause; (3) the event can be explained by concomitant device/medication, disease progression, or other treatment effects. Satisfying all three criteria is judged as "definitely unrelated"; satisfying any one criterion is judged as "possibly unrelated".

4. Adverse Events and Management Measures

Local injection-site reactions may occur within 30 days after injection, including temporary swelling, mild redness, and slight discomfort, which generally resolve within 24–48 hours. If the filling site worsens, with erythema, induration and/or urticaria, herpes recurrence, or spreading erythema or swelling, appropriate antihistamines and anti-inflammatory drugs may be taken; the above reactions will disappear automatically within one week. If a local reaction persists beyond 30 days after injection, the investigator will need to assess whether it should be recorded as an AE; if assessed as an AE, the investigator should follow up on the treatment-site reaction until it resolves and record the entire process in detail. The start date and severity of the AE will be recorded in the eCRF. If the severity of the AE changes, the most severe grade should be recorded in the eCRF.

All adverse events occurring during the study must be truthfully recorded in the adverse event form. The investigator should provide targeted treatment for AEs and follow them up until the symptoms disappear or stabilize.

The investigator shall report serious adverse events and other safety information occurring at their trial site to the Ethics Committee; the sponsor shall report serious adverse events related to the investigational medical device to the Ethics Committee of each center. The Ethics Committee may require modification of the clinical trial protocol, informed consent form, and other information provided to subjects, or may suspend or terminate the clinical trial.

(2) Device Defects

A device defect refers to an unreasonable risk that may endanger human health or life posed by a medical device during normal use in a clinical trial, such as labeling errors, quality problems, or malfunctions.

The investigator shall record any device defects occurring during the medical device clinical trial. When it is found that the risks of the medical device clinical trial outweigh the possible benefits and the trial needs to be suspended or terminated, the principal investigator shall report to the

sponsor, the medical device clinical trial site management, and the Ethics Committee, promptly notify the subjects, and ensure that the subjects receive appropriate treatment and follow-up.

(3) Pregnancy Events

When a female subject is found to be pregnant during the trial, the investigator must notify the sponsor immediately using a pregnancy report form within 24 hours of becoming aware.

The investigator shall diligently follow up on all pregnancy reports to obtain basic information about the pregnancy and its outcome until the end of the pregnancy (until delivery / termination of pregnancy).

Pregnancy itself is not considered an AE. If the pregnancy outcome meets the criteria for an SAE (i.e., ectopic pregnancy, spontaneous abortion [miscarriage and missed abortion], intrauterine fetal death, neonatal death, or congenital anomaly [live-born infant, fetus from a terminated pregnancy, intrauterine fetal death, or neonatal death]), the investigator shall immediately provide appropriate treatment to the pregnant woman or newborn and follow the SAE reporting procedure.

(4) Serious Adverse Events

1. Definition of Serious Adverse Event

A serious adverse event (SAE) refers to an event that results in death or a serious deterioration in health during a medical device clinical trial, including a fatal disease or injury, permanent impairment of body structure or body function, hospitalization or prolongation of hospitalization, need for medical intervention to prevent permanent impairment of body structure or function, or events leading to fetal distress, fetal death, or congenital anomaly / birth defect. Other surgeries anticipated during the trial are not recorded as SAEs.

2. SAE Reporting Procedure

When an SAE occurs during the clinical trial, regardless of whether it is related to the investigational medical device, the investigator shall immediately provide appropriate treatment to the subject, observe the subject until their condition returns to normal, to the pre-illness state, or to a state deemed reasonable by the investigator, and report it according to the reporting procedure for SAEs and device defects leading to SAEs.

Reporting procedure for SAEs and device defects leading to SAEs:

When an SAE occurs during a medical device clinical trial, the investigator shall immediately provide appropriate treatment to the subject; at the same time, the investigator shall complete the SAE report form within 24 hours of becoming aware of the SAE and report it by email to the sponsor, the medical device clinical trial site management, and the Ethics Committee; the investigator shall follow up on the SAE according to the clinical trial protocol and submit an

SAE follow-up report by email, with the follow-up/summary report submitted within 24 hours of receiving new information. For fatal events, the trial site and investigator shall provide all required information to the Ethics Committee and the sponsor.

The sponsor shall, within 7 days of becoming aware of a death or life-threatening SAE related to the investigational medical device, or within 15 days of becoming aware of a non-fatal or non-life-threatening SAE related to the investigational medical device or other serious safety risk information, report to the other medical device clinical trial sites, Ethics Committees, and principal investigators participating in the clinical trial; report to the drug regulatory department of the province, autonomous region, or municipality directly under the central government where the sponsor is located; and report to the drug regulatory department and health administration department of the province, autonomous region, or municipality directly under the central government where each medical device clinical trial site is located, and shall implement risk control measures.

When a widespread SAE related to the investigational medical device occurs, or when other significant safety issues arise, the sponsor shall suspend or terminate the medical device clinical trial and report to the management of all medical device clinical trial sites, the Ethics Committees, and the principal investigators; report to the drug regulatory department of the province, autonomous region, or municipality directly under the central government where the sponsor is located; and report to the drug regulatory departments and health administration departments of the provinces, autonomous regions, or municipalities directly under the central government where all medical device clinical trial sites are located.

SAE Reporting Contact Information

Organization	**Email**
Sponsor: Fiman (Changchun) Pharmaceutical & Biotechnology Co., Ltd.	yangdandan@fiman.com

XIII. Protocol Deviations and Protocol Amendments

A medical device clinical trial must comply with the Good Clinical Practice for Medical Device Clinical Trials (GCP-MD) and the trial protocol approved by the Ethics Committee. Any intentional or unintentional failure to follow the requirements of the medical device clinical trial protocol is referred to as a protocol deviation.

By the responsible party, protocol deviations may be classified into: deviations due to non-compliance by the investigator / trial institution; deviations caused by participant non-compliance; and deviations due to non-compliance on the sponsor's part. By severity, they may be classified into minor protocol deviations and major protocol deviations.

Minor protocol deviations are generally reported to the Ethics Committee periodically, and the sponsor and/or investigator shall provide an explanation of the cause, impact, and corrective measures taken.

After each protocol deviation occurs, corrective or improvement measures shall be implemented to prevent recurrence of similar deviations.

After this protocol is approved by the Ethics Committee, any modification shall be documented in a "Protocol Amendment Description," signed by the Principal Investigator, and shall be implemented only after being re-approved by the Ethics Committee. After amendment, the protocol shall be acknowledged and signed by the sponsor.

XIV. Direct Access to Source Data and Documents

The trial institution and the investigator shall permit trial-related monitoring, audits, Ethics Committee reviews, and inspections by regulatory authorities, who shall have direct access to source data and source documents.

XV. Contents of the Clinical Trial Report

In accordance with the requirements set out in the Good Clinical Practice for Medical Device Clinical Trials (No. 28 of 2022), jointly issued by the National Medical Products Administration (NMPA) and the National Health Commission, and the NMPA Announcement on Matters Related to the Implementation of the GCP-MD (No. 21 of 2022), the clinical trial report shall cover the following:

(1) Summary of the report;

(2) Background of the clinical trial;

(3) Objectives of the clinical trial;

(4) Conduct of the clinical trial;

(5) Statistical analysis methods;

(6) Clinical trial results;

(7) Analysis and discussion of the clinical trial results, particularly the scope of application, indications, contraindications, and precautions;

(8) Conclusions of the clinical trial;

(9) Existing problems and suggestions for improvement;

(10) All trial institutions in a multi-center clinical trial;

(11) List of trial personnel;

(12) Ethical considerations;

(13) Other information to be disclosed (description of protocol amendments during the trial, and protocol deviations);

(14) Signature of the Principal Investigator (for single-center trials) / Coordinating Investigator (for multi-center trials), dated, with the trial institution's review seal and signature.

XVI. Confidentiality

This trial protocol is confidential and is provided to medical experts related to this trial, investigators participating in this trial and other trial-related staff, as well as to the medical institutions undertaking this trial, the Ethics Committee, and the contract research organization (CRO) and other relevant commissioned parties. Except for informing the trial participants, no content of this trial protocol shall be disclosed or leaked to any third party without the sponsor's prior written consent. Furthermore, the publication of part or all of the results of this clinical trial

to external entities such as academic societies or journals shall require the sponsor's written consent.

XVII. Responsibilities of Each Party

The sponsor, the investigator, and the trial institution shall all faithfully fulfill their respective responsibilities in accordance with the GCP-MD and the provisions of this protocol.

(1) Sponsor's Responsibilities

(1) The sponsor shall be responsible for the authenticity and compliance of the medical device clinical trial.

(2) The sponsor shall organize the preparation and revision of the Investigator's Brochure, the trial protocol, the informed consent form, the case report form, standard operating procedures, and other relevant documents, and shall provide them to the medical device trial institution and the Principal Investigator.

(3) The sponsor shall, based on the characteristics of the investigational medical device, select a registered medical device trial institution, specialty, and Principal Investigator.

(5) When information arises that may affect participant safety, may affect the conduct of the medical device clinical trial, or may alter the opinion of the Ethics Committee, the sponsor shall promptly organize amendments to the trial protocol, the informed consent form and other information provided to the participants, and other relevant documents, and shall submit them for review by the Ethics Committee.

(6) The sponsor shall pay the costs associated with the medical device clinical trial for the participants. When a participant suffers damage or death related to the medical device clinical trial, the sponsor shall bear the corresponding treatment costs, compensation, or indemnity, excluding damage caused by the investigator's or the trial institution's own fault, as well as damage resulting from the natural progression of the participant's underlying disease.

(7) The sponsor shall bear the responsibility for monitoring the medical device clinical trial, establish monitoring standard operating procedures, and select qualified monitors to perform monitoring duties. When the trial is suspended, terminated, or completed, the sponsor shall submit a written report to all Principal Investigators, the trial institution's management department, and the Ethics Committee within 10 working days.

(8) Other responsibilities specified in the GCP-MD.

(2) Responsibilities of the Trial Institution

(1) The medical device clinical trial institution shall meet the registration requirements, establish a clinical trial management organizational structure and management system. The medical device clinical trial institution shall have a corresponding clinical trial management department responsible for managing the clinical trial.

(2) The management department of the medical device clinical trial institution shall be responsible for entering, managing, and updating the registration information of the medical device clinical trial institution in the registration management information system, including information on the trial specialty and Principal Investigator; shall be responsible for submitting the annual summary report of medical device clinical trials conducted in the previous year through the registration system online; and shall be responsible for organizing the assessment of the qualifications of the Principal Investigator and completing the registration before the Ethics Committee's review of the medical device clinical trial.

(3) The medical device clinical trial institution shall establish a quality management system covering the entire process of the clinical trial, including training and assessment, trial conduct, medical device management, biospecimen management, adverse event and device deficiency handling, and safety information reporting, recording, and quality control systems, so as to ensure that the Principal Investigator fulfills the relevant trial responsibilities, that participants receive proper medical care, and that the data generated by the trial are authentic.

(4) Before accepting a medical device clinical trial, the medical device clinical trial institution shall assess the relevant resources based on the characteristics of the investigational medical device to ensure that it possesses matching qualifications, personnel, facilities, and conditions.

(5) The medical device clinical trial institution and the investigator shall cooperate with the monitoring and audits organized by the sponsor, as well as inspections conducted by the drug regulatory and health management authorities.

(6) The medical device clinical trial institution shall properly preserve clinical trial records and essential documents in accordance with relevant laws and regulations and the contract with the sponsor.

(3) Responsibilities of the Investigator

The Principal Investigator shall ensure that the medical device clinical trial complies with the latest version of the trial protocol agreed upon by the Ethics Committee, and shall conduct the medical device clinical trial within the agreed timeframe in accordance with the GCP-MD and relevant laws and regulations. The Principal Investigator may, as required by the medical device clinical trial, authorize investigators who have received relevant clinical trial training to organize participant recruitment and informed consent, screening and follow-up; management and use of the investigational medical device; management and use of biospecimens (if applicable); handling of adverse events and device deficiencies; and recording of clinical trial data and completion of case report forms. Investigators participating in the medical device clinical trial shall:

(1) Possess the corresponding professional qualifications, training experience, and relevant experience for conducting medical device clinical trials;

(2) Attend the training organized by the sponsor relevant to the medical device clinical trial, and participate in the medical device clinical trial within the scope authorized by the Principal Investigator;

(3) Be familiar with the principles, intended scope of use or intended purpose, product performance, operating methods, installation requirements, and technical specifications of the investigational medical device, and understand the relevant preclinical research data of the investigational medical device;

(4) Fully understand and comply with the trial protocol, this code, relevant laws and regulations, and the responsibilities related to the medical device clinical trial;

(5) Master the prevention and emergency management of risks that may arise during the clinical trial.

(6) The investigator has management responsibility for the investigational medical device provided by the sponsor, shall ensure that it is used only for participants enrolled in the medical device clinical trial, shall store and safeguard it as required during the trial, and shall handle it in accordance with relevant laws and regulations and the contract with the sponsor upon completion or termination of the trial.

(7) The investigator shall ensure that the collection, processing, storage, transport, and destruction of biospecimens in the medical device clinical trial comply with the trial protocol and relevant laws and regulations.

(8) When an adverse event occurs during the medical device clinical trial, the investigator shall provide the participant with adequate and timely treatment and management; when a participant develops a concurrent disease requiring treatment and management, the investigator shall promptly inform the participant. The investigator shall record adverse events occurring during the trial and any device deficiencies identified.

(9) The investigator shall promptly report safety information arising from the medical device clinical trial: (1) When a serious adverse event (SAE) occurs during the trial, the investigator shall immediately provide appropriate treatment to the participant; at the same time, the investigator shall report to the sponsor, the trial institution's management department, and the Ethics Committee within 24 hours of becoming aware of the SAE; and shall follow up the SAE and submit a follow-up report in accordance with the trial protocol. (2) When it is found that the risks of the medical device clinical trial exceed the possible benefits and the trial needs to be suspended or terminated, the Principal Investigator shall report to the sponsor, the trial institution's management department, and the Ethics Committee, promptly notify the participants, and ensure that the participants receive appropriate treatment and follow-up.

(10) The Principal Investigator shall promptly handle safety information received: (1) Upon receiving information on device-related SAEs and other safety information provided by the sponsor, the Principal Investigator shall promptly acknowledge and review it, consider whether the participant's treatment requires corresponding adjustment, and communicate with the participant as early as possible when necessary. (2) Upon receiving notification from the sponsor or the Ethics Committee that the medical device clinical trial needs to be suspended or terminated, the Principal Investigator shall promptly notify the participants and ensure that they receive appropriate treatment and follow-up.

(11) The Principal Investigator shall report the progress of the medical device clinical trial to the Ethics Committee on schedule, and promptly report events affecting participants' rights and safety or deviations from the trial protocol.

(12) Other responsibilities specified in the GCP-MD.

XVIII. Finance and Insurance

For this clinical trial, the sponsor will enter into a written agreement with the clinical trial institution, which will specify in detail the financial arrangements and payment method for this clinical trial. For details, please refer to the agreement signed by the parties.

The sponsor undertakes that, when a participant suffers damage or death related to the clinical trial during the trial, the sponsor shall bear the corresponding treatment costs, compensation, or indemnity, excluding damage caused by the investigator's or the medical institution's own fault, as well as damage resulting from the natural progression of the participant's underlying disease.

The sponsor has purchased medical device clinical trial liability insurance related to this trial.

XIX. Publication of Trial Results

All data and trial results of this trial shall be jointly owned by the investigators and the sponsor. Without the sponsor's consent, the investigators shall not independently communicate or publish articles related to the trial. If an article related to the trial is to be published in the form of a paper, with the sponsor's consent, the Principal Investigator of the center shall be responsible for designating the final list of authors (Principal Investigator or co-investigators). In all publications, the sponsor's name shall be cited, and at least one member of the project team in the primary author list shall be from the sponsor.

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XXI. Appendices

Appendix 1: Allergan Infraorbital Hollowing Scale (AIHS) [14]

Score	Grade	Clinical Features

0	None	No obvious depression or volume loss on the medial or lateral side.
1	Mild	Depression medial to the pupil midline with some volume loss; smooth lateral lid-cheek transition.
2	Moderate	Definite depression extending lateral to the pupil midline with moderate volume loss; smooth lateral lid-cheek transition with mild volume loss.
3	Severe	Definite depression extending lateral to the pupil midline with moderate volume loss, forming a distinct concavity along the lid-cheek junction.
4	Very severe	Definite depression extending from the medial canthus to the lateral canthus; severe volume loss, forming a marked trough along the lid-cheek junction.



Figure 2 Schematic diagram of the severity grading of infraorbital hollowing

Appendix 2: Periorbital Volume Deficiency Assessment Scale



Investigator Statement and Signature Page

Investigator Statement:

I hereby agree to:

1. Conduct this clinical trial strictly in accordance with the Declaration of Helsinki, the current regulations of China, and the requirements of the trial protocol.

2. Accurately record all required data in the case report form (eCRF) and cooperate in completing the clinical trial report.

3. Use the investigational medical device and the control medical device solely for this clinical trial, completely and accurately record the receipt and use of the investigational and control medical devices during the trial, and retain such records.

4. Permit monitors, auditors, and regulatory authorities authorized or dispatched by the sponsor to conduct monitoring, audits, and inspections of this clinical trial.

5. Strictly fulfill the terms of the clinical trial contract/agreement signed by all parties.

I have read the entire clinical trial protocol, including the above statement, and I agree to all of the above.

Principal Investigator signature: Date: (YYYY) (MM) (DD)
Medical Device Clinical Trial Institution seal: Date: (YYYY) (MM) (DD)
Sponsor seal: Date: (YYYY) (MM) (DD)