A study of the efficacy and safety of Non-ablative Fractional Laser in the treatment of thyroidectomy scars

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I. Research Background

Aesthetic outcomes are increasingly becoming a crucial component of patient satisfaction following surgical procedures, with postoperative scars being a significant determinant. The question of "how to fade scars more quickly and make them imperceptible at social distances" is often the primary concern for patients after trauma or surgery and also a frequent challenge for physicians. Recent research has focused on scars resulting from open thyroidectomy. Thyroidectomy is commonly performed for thyroid cancer, which is one of the most prevalent head and neck tumors. According to the World Health Organization's cancer statistics report, there were 586,202 new cases of thyroid cancer worldwide in 2020, with an age-standardized incidence rate of 10.1 per 100,000 in females and 3.1 per 100,000 in males, making the incidence rate in females approximately three times that of males. According to the "2020 China Cancer Registry Annual Report," the age-standardized incidence rate of thyroid cancer in China is 10.30 per 100,000, ranking eighth among all cancers and fourth among cancers in females. Surgery is the primary treatment modality. As a surgical procedure, it causes pathological changes in normal skin tissue, ultimately leading to scar formation. Post-thyroidectomy scars can cause itching, pain, and traction at the affected site. Due to the anatomical location of the thyroid gland, scars are often exposed on the body surface. Even minor scars can affect patients' emotional states and impose psychological burdens, especially in young females, with some patients even refusing surgical treatment due to concerns about scarring.

Scars are the collective term for the changes in appearance, form, and histopathology of normal skin tissue following various types of trauma and are a normal part of the body's self-repair process. However, excessive scar proliferation is an abnormal manifestation known as pathological scarring. The histopathological characteristics of pathological scars include increased fibroblasts in the dermis, disordered collagen fiber arrangement, and the formation of nodular collagen proliferation, often accompanied by vascular proliferation. The pathogenesis of pathological scars is not yet fully understood but primarily involves fibroblasts, cytokines, and blood supply, with individual differences and wound management also being significant factors. The wound healing process includes the inflammatory phase, proliferative phase, and remodeling phase, with various inflammatory cells and mediators playing a role in the healing process and affecting the outcome. During the early stages of wound repair, local vasoconstriction and platelet aggregation occur, followed by the aggregation of inflammatory cells, endothelial cells, epidermal cells, and fibroblasts around the wound to form granulation tissue. New capillaries in the granulation tissue secrete extracellular matrix, promoting the differentiation of fibroblasts into myofibroblasts in the surrounding tissue. Myofibroblasts, which contain contractile actin filaments and produce large amounts of collagen, play a central role in the remodeling and contraction of granulation tissue after injury. Growth factors such as transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), and vascular endothelial growth factor (VEGF) are overexpressed and play a significant role in

fibroblast proliferation and collagen synthesis. TGF-β regulates fibroblast proliferation, collagen synthesis, and the differentiation of fibroblasts into myofibroblasts. Myofibroblasts contain contractile actin filaments and produce large amounts of collagen, playing a central role in the remodeling and contraction of granulation tissue after injury. In normal wound healing, TGF-β activity decreases, but in pathological scars, it may increase or remain unchanged. These factors collectively lead to the formation of pathological scars (hypertrophic scars and keloids). Pathological scar formation is a reflection of impaired wound healing, characterized by prolonged and disordered inflammation, leading to increased formation and decreased degradation of the extracellular matrix. Ogawa suggested that pathological scars are the result of chronic inflammation in the reticular dermis, defining hypertrophic scars as "weakly inflammatory scars" and keloids as "strongly inflammatory scars." Hypertrophic scars are common complications after burns and surgeries, with the incidence of hypertrophic scars after surgery ranging from 40% to 94%, and after burns from 30% to 91%. Keloids are fibroproliferative skin diseases, with genetic factors being the primary contributors to their development. The incidence is highest in individuals of African, Asian, and Hispanic descent and lowest in Caucasians.

Current clinical treatments for scars include topical medications, compression therapy, local injections, surgery, and radiation therapy, among others. While some patients achieve satisfactory results, these treatments often come with numerous side effects, such as skin atrophy, thinning, pigmentation, ulceration, and necrosis. Therefore, effective preventive and therapeutic measures for postoperative scars and reducing local side effects after scar regression are of utmost importance.

The first report on the scar improvement effects of pulsed dye laser (PDL) was published in 1993. Over the past two decades, significant progress has been made in laser scar treatment due to advancements in fractional technology. Fractional laser treatment for scars has been proven effective, and many studies have applied fractional lasers to post-thyroidectomy scars. The "focal photothermal effect" is the theoretical basis of fractional lasers. When the laser beam acts on the skin, the water in the tissue absorbs the laser energy, forming microthermal injury zones, causing a certain degree of thermal damage, and thereby initiating the body's healing and repair processes, leading to full-thickness skin reconstruction and tissue remodeling. Fractional lasers are divided into ablative fractional lasers (AFL) and non-ablative fractional lasers (NAFL) based on whether they penetrate the skin to form true pores. NAFL includes erbium glass lasers with wavelengths of 1540 nm, 1550 nm, and 1565 nm, and YAG lasers with wavelengths of 1064 nm, 1320 nm, and 1440 nm. NAFL causes less stimulation to dermal collagen, forming coagulated tissue columns in the skin, with only minor or no damage to the epidermis.

Ha et al. conducted a self-controlled study comparing PDL and NAFL treatments in 30 patients with Fitzpatrick skin types III to V who underwent thyroidectomy. Each patient's incision was divided into two equal parts, with one half treated with PDL at 2 to 3 weeks

postoperatively, with parameters set at: energy density 8.0 J/cm², pulse duration 3.0 ms, and spot size 7.0 mm. The other half was treated with NAFL at the same time point, with parameters set at: treatment density of 656 microprocessing zones/cm² and energy of 20 mJ. Treatments were spaced 4 weeks apart, for a total of three sessions, with follow-up at 6 months postoperatively. The Vancouver Scar Scale (VSS) was used to assess scar pigmentation, vascularity, pliability, and thickness. The results showed that both PDL and NAFL significantly reduced VSS scores, with no significant difference between the two treatments. Shin et al. improved upon this experiment, with 20 patients' surgical incisions divided into two halves, one treated with NAFL, with parameters set at: pulse energy 50 mJ, spot density 100 points/cm ², and average radiation dose 0.652 J/cm². The other half was treated with AFL, with parameters similar to NAFL but with a pulse width of 60 mJ/pulse. Treatments were spaced 2 months apart, and narrowband reflectance spectrophotometry was used to assess color changes, and a durometer was used to assess pliability changes before and after each treatment, with final assessments made 3 months after the last treatment. The results showed significant improvements in erythema and pigmentation after NAFL treatment and in skin hardness after AFL treatment ($P < 0.001$). AFL treatment was more effective for scars with poor pliability and severe hypertrophy, while NAFL was more effective for scars with severe pigmentation. This is determined by their mechanisms of action, as AFL often damages the epidermal barrier. Therefore, early NAFL treatment for post-thyroidectomy scars is more appropriate, effectively improving scar color, smoothness, and elasticity. The traditional view was that laser treatment should be performed several months after scar formation, but an increasing number of researchers now emphasize the effectiveness of "early" laser treatment. Kent et al. analyzed eight systematic reviews and four meta-analyses and concluded that early laser treatment within 1 month postoperatively can significantly improve scars.

To date, no laser-related parameters for the treatment of post-thyroidectomy scars have been established, such as high energy, low density, or low energy with high density. It is essential to continue accumulating clinical data and further optimize laser treatment strategies for thyroid surgery scars and other scars. This study aims to explore the efficacy and parameter settings of 1565 nm non-ablative fractional laser treatment for post-thyroidectomy scars. We will use a prospective, self-controlled study to investigate the efficacy and safety of 1565 nm non-ablative fractional laser treatment for post-thyroidectomy scars.

II. Research Objectives

1. Efficacy Study: To explore the efficacy of 1565 nm non-ablative fractional laser treatment for post-thyroidectomy scars compared to the control side.

2. Safety Study: To evaluate the safety of 1565 nm non-ablative fractional laser treatment, including any related adverse events and/or adverse reactions during and after treatment.

III. Research Content

A prospective, self-randomized, open-label, controlled study method will be employed. At baseline, the post-thyroidectomy scar on the neck of each subject will be divided into two equal parts along the midline of the body surface. One side will be randomly selected using a random number generator to receive 1565 nm non-ablative fractional laser treatment, while the other side will serve as the control side and receive sham treatment (laser probe contact with the skin without energy delivery). Results will be recorded at follow-up visits, and any adverse events and/or adverse reactions during and after treatment will be documented. The efficacy and safety of 1565 nm non-ablative fractional laser treatment for post-thyroidectomy scars will be assessed.

IV. Research Design

1. Research Design

1.1. Trial Methods

1.1.1. Trial Methods

Split Scar: The post-thyroidectomy scar will be divided into two equal parts along the midline of the body surface (the vertical line passing through the anterior aspect of the thyroid cartilage and the center of the sternum). The central 0.5 cm area of the scar will not be included in the assessment to prevent bystander effects from the NAFL treatment on the untreated control side.

Randomization: The scar on either the left or right side of the midline will be assigned numbers 0 and 1, respectively. A random number generator will be used to determine which side will be the study side, with the other side serving as the control side.

Self-Parallel Control: The post-thyroidectomy scar will be divided into left and right sides along the midline. One side will be randomly selected as the study side to receive 1565 nm non-ablative fractional laser treatment, while the other side will serve as the control side and receive sham treatment (laser probe contact with the skin without energy delivery). This design reduces individual differences and the impact of scar progression over time, ensuring good comparability between the study and control sides and allowing for a reliable conclusion regarding the causal relationship between the intervention and outcome.

Blinding: The treatment provider and subjects will not be blinded, while the assessors will be blinded. Assessors will not be involved in scar treatment. The clinical assessment team will consist of five dermatologists with extensive clinical experience, and the pathological assessment team will consist of three professional dermatopathologists.

1.1.2. Trial Cycle

The study side will receive laser treatment once every month for a total of six treatments. Follow-up visits will be conducted at 3 months, 6 months, and 1 year after the final treatment. The trial cycle will span from 0 to 17 months.

1.1.3. Trial Intervention

All subjects will begin intervention treatment either 1 week after suture removal (approximately 15 days post-thyroidectomy) or within 1 year after thyroidectomy. Before laser

treatment, compound lidocaine cream will be applied to the entire scar area for 60 minutes. The neck will then be cleaned with water and dried with sterile gauze. Both the doctor and the subject will wear protective goggles.

Study Side: The treatment device will be the 1565 nm ResurFX non-ablative fractional laser from the Lumenis M22 platform, with reference parameters set at spot size 10 to 16 mm, energy 40 to 45 mJ/cm², spot density 150 to 200/cm², and 1 to 2 passes. During treatment, the laser probe will be held vertically and in close contact with the patient's skin, with each spot overlapping by less than 10%. Each laser treatment will be performed by the same dermatologist, who will not be involved in the outcome assessment. Subjects will be advised to maintain hydration, avoid UV exposure, and use sunscreen (SPF 50+) for sun protection after treatment.

Control Side: Sham treatment (laser probe contact with the skin without energy delivery) will be administered.

1.2. Measures to Reduce and Avoid Bias

To minimize and avoid bias in trial conditions, randomization principles will be followed during baseline grouping. The daily hydration and sun protection practices of subjects, as well as any adverse reactions during and after treatment, will be recorded. Additionally, to ensure the objectivity of the evaluation of dropouts and withdrawals, the statistical analysis plan will clearly specify the statistical handling methods and evaluation criteria for these cases.

1.3. Trial Laser Device

Device Name: ResurFX™

Operating Platform: Lumenis M22 platform

Handpiece: ResurFX non-ablative fractional laser handpiece

Wavelength: 1565 nm

Energy: Up to 70 mJ per microbeam

Scan Size: Maximum diameter of 18 mm

Spot Density: Up to 500/cm²

Cooling: Continuous contact cooling

Scope of the research subject

1.4. Subject Selection Criteria

Inclusion Criteria:

1. Patients who are conscious, without intellectual disabilities or cognitive difficulties, and understand and sign the informed consent form.

2. Healthy males and females aged 18 to 70 years.

3. Fitzpatrick skin types I to V.

4. Women of childbearing age who have used contraception for three months prior to enrollment.

5. Patients who have undergone traditional thyroidectomy through the anterior neck approach within 15 days, with a midline surgical incision visible on the neck; or patients who

have undergone traditional thyroidectomy through the anterior neck approach within 1 year, with a midline, linear, hypertrophic surgical scar visible on the neck.

6. Ability to comply with all visit, treatment, and assessment plans and requirements.

Exclusion Criteria:

1. Need for modified radical neck dissection or reoperation, or any other surgical plans that may affect treatment and follow-up during the trial period.

2. Previous neck surgery.

3. Pregnancy, intention to become pregnant during the study period, less than three months postpartum, or less than six weeks after completing breastfeeding.

4. History of keloid scars or delayed wound healing.

5. Uncontrolled medical conditions.

6. History of psychiatric disorders.

7. Presence of skin tumors or skin inflammation in the treatment area.

8. Active infection in the neck area or systemic infection.

9. Oral photosensitizing drugs or retinoid use within six months prior to screening.

10. Use of anticoagulants, corticosteroids, immunosuppressants, or other medications within three months prior to screening.

11. Exposure to strong UV radiation within one month prior to screening, causing neck desquamation, erythema, etc.

12. Participation in other drug or medical device clinical trials within one month prior to screening or planned participation during the study period.

13. Use of any treatments for post-thyroidectomy scars other than silicone gel sheets and topical medications within one month prior to treatment.

14. Use of silicone gel sheets or topical medications for post-thyroidectomy scars within seven days prior to treatment.

15. Allergy to compound lidocaine cream or its components, with no available alternative medication.

16. Other conditions that the investigator deems may affect compliance or make the patient unsuitable for participation in this study.

1.5. Withdrawal and Trial Termination

Withdrawal Criteria:

1. Patients who severely violate the study protocol.

2. Patients who are lost to follow-up.

3. Patients who request withdrawal.

4. Patients whom the investigator believes will face unacceptable risks if they continue to participate in the study.

5. Other circumstances requiring withdrawal.

Termination Criteria:

1. Serious adverse events occur during the trial, and the ethics committee determines that

termination is necessary.

2. Major defects are found in the trial protocol, making it difficult to evaluate the study's effectiveness.

3. The sponsor requests termination.

4. Other circumstances requiring termination.

Evaluation Criteria

1.7. Primary Evaluation Criteria

1. Scar Echo Depth, Width, and Intensity

Evaluation Tool: High-frequency skin ultrasound MD-300S II

Calculation Formula: Multiple measurements will be taken in five different regions on each side of the scar to determine the maximum and minimum values of scar echo depth and width, and the average value of the five measurement points will be calculated. Using image processing software (Adobe Photoshop), the ultrasound images will be processed. A rectangular selection tool will be used to select three areas of the same size on the scar, and the average gray value of each area will be read using the histogram function. The average gray value of the five measurement points will be calculated, with higher gray values indicating stronger echo intensity.

Evaluation Method: The echo depth, width, and intensity of the study side and control side scars will be compared at each evaluation time point.

2. Modified Vancouver Scar Scale (mVSS) Score

Rationale: The mVSS includes additional assessments of pain and itching compared to the original scale, providing a more comprehensive evaluation of scar conditions.

Evaluation Tool: mVSS scale

Evaluation Method: The mVSS scores of the study side and control side scars will be compared at each evaluation time point.

1.8. Secondary Evaluation Criteria

1. Scar Color

Evaluation Tool: Multispectral Microscopic Imaging Device Multi view®

Calculation Formula: Based on the gradient measurement formula of the Canny operator, the absolute value or maximum value is used to approximate the operation for simplification. Within the region, the average gray value is calculated. Higher average gray values indicate lighter skin color, while lower values indicate darker skin. The image is converted to an HSV image, and the red concentration in the image is calculated as follows: (area of red region in a specific area of the image / total image area) × red region area weight + (red hue in the red region / 100) × red hue weight in the red region. Higher red concentration indicates more sensitive skin or more severe inflammation, while lower values indicate milder conditions. Multiple measurements will be taken in three different regions on each side of the scar, and the average gray value and red concentration will be calculated.

Evaluation Method: The average gray value and red concentration of the study side and

control side scars will be compared at each evaluation time point.

2. Scar Area

Evaluation Tool: Multispectral Microscopic Imaging Device Multi view®

Calculation Formula: A ruler will be used to calibrate the actual size represented by each pixel. The collection of pixels with abrupt brightness changes will be identified, and edge detection algorithms will be used to calculate the area of specific objects.

Evaluation Method: The scar areas of the study side and control side will be compared at each evaluation time point.

3. Patient and Observer Scar Assessment Scale (POSAS) Score

Rationale: This scale incorporates both observer and patient perspectives, providing a comprehensive evaluation of scar attributes and patient perception of scar symptoms.

Evaluation Tool: Observer Scar Assessment Scale (OSAS) and Patient Scar Assessment Scale (PSAS)

Evaluation Method: The OSAS and PSAS scores of the study side and control side will be compared at each evaluation time point.

4. Manchester Scar Scale (MSS) Score

Rationale: This scale combines five attributes of scar appearance.

Evaluation Tool: MSS scale

Evaluation Method: The MSS scores of the study side and control side will be compared at each evaluation time point.

5. Medical Outcomes Study Health Survey Short Form-36 Item (SF-36) Score

Rationale: This scale assesses overall health status from multiple aspects, including physical and psychological functions.

Evaluation Tool: SF-36 scale

Evaluation Method: The SF-36 scores will be compared at each evaluation time point.

6. Standardized Assessment by Physicians and Patients

Rationale: To visually distinguish differences between the study side and control side scars.

Evaluation Tool: Two dermatologists will assess on-site, two dermatologists will assess through photographs, and patients will answer standardized assessment questions.

Calculation Formula: Two dermatologists will assess on-site, and two dermatologists will assess through photographs. The final result will be determined as follows: If any of the four assessments indicates "no difference," or if the assessments of the two halves of the scar do not match, the final result will be determined as "no difference."

Evaluation Method: The number of cases with "difference" and "no difference" will be compared at each evaluation time point.

7. Safety Evaluation Criteria

Adverse Event Incidence Rate: The number and severity of adverse events occurring during treatment on the study side will be recorded and statistically analyzed. This is a qualitative evaluation indicator.

Rationale: To assess the safety of 1565 nm non-ablative fractional laser treatment for post-thyroidectomy scars.

Evaluation Tool: The investigator will determine whether an event is an adverse event or adverse reaction based on medical knowledge and the criteria specified in sections 1.23 and 1.24 of this protocol.

Calculation Formula: Number of adverse event cases / number of cases in the safety dataset × 100%.

8. Histological Evaluation Criteria

Biopsy: A 3 mm punch skin biopsy will be taken from the center of the scars on both the study and control sides. The scar tissue will be longitudinally sectioned, fixed in 4% paraformaldehyde, numbered, embedded in paraffin, and sectioned continuously at a thickness of 5 μm. The sections will then be dewaxed, cleared, stained with hematoxylin and eosin (H&E), Masson's trichrome, elastic fiber stain, and anti-matrix metalloproteinase (MMP9) immunohistochemistry.

Rationale: Histological evaluation is considered the gold standard for measuring scar thickness.

Evaluation Tool: ImageJ software

Calculation Formula: First, in the H&E stained sections, three experienced dermatopathologists will measure the scar thickness under an optical microscope, selecting three different measurement points and recording the average value. Second, in the Masson's trichrome staining, myofibers appear red, and collagen fibers appear blue. In ImageJ software, the blue collagen fibers will be separated, and the area of collagen-positive regions and the total tissue area will be measured by adjusting the threshold. The collagen volume fraction (percentage of collagen fiber area) will be calculated as follows: (collagen fiber area / total tissue area) × 100%. The same method will be used for elastic fiber staining, where elastic fibers appear dark purple or dark brown. The area of elastic fiber-positive regions and the total tissue area will be measured by adjusting the threshold, and the percentage of elastic fiber area will be calculated as follows: (elastic fiber area / total tissue area) × 100%. Three experienced dermatopathologists will randomly select three fields of view for the above analysis, obtaining the average percentage of collagen fiber area in Masson's trichrome-stained sections and the average percentage of elastic fiber area in elastic fiber-stained sections. Tissue sections will be immunohistochemically stained with a specific MMP9 antibody, with cytoplasmic brown-yellow granules indicating positive signals. Three experienced dermatopathologists will randomly select three fields of view, count positive and negative cells, and calculate the percentage of MMP9-positive cells in each field of view as follows: (number of positive cells / total number of cells) × 100%. The average value will be obtained as the average percentage of MMP9-positive cells.

Evaluation Method: The average scar thickness in H&E stained sections, the average percentage of collagen fibers in Masson's trichrome-stained sections, the average percentage of

elastic fibers in elastic fiber-stained sections, and the average percentage of MMP9-positive cells will be compared between the study and control sides.

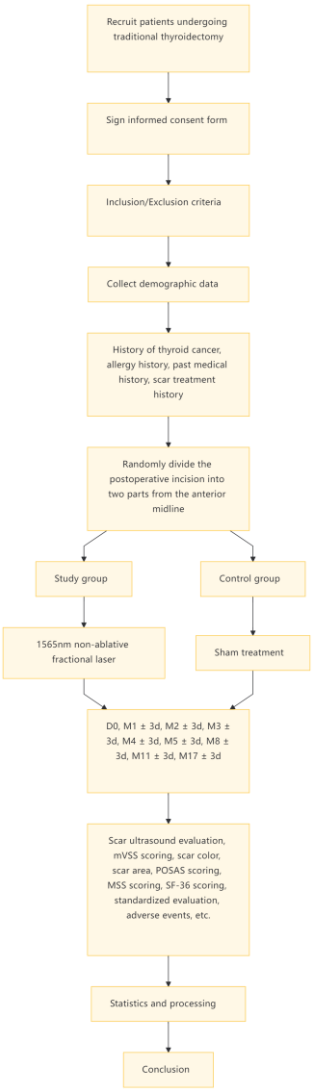
Results Judgment

Primary Evaluation Criteria: If the scar echo depth, width, and intensity, as well as the mVSS scores on the study side, show improvement compared to the control side, with significant differences or statistical significance between the two groups, it will be determined that the 1565 nm non-ablative fractional laser has a therapeutic effect on post-thyroidectomy scars.

Secondary Evaluation Criteria: If there are significant differences or statistical significance between the two groups in the assessment indicators, including scar color, scar area, POSAS score, MSS score, SF-36 score, standardized assessment, and adverse event incidence rate, it will be determined that the 1565 nm non-ablative fractional laser has a therapeutic effect on post-thyroidectomy scars.

Clinical Trial Flow

1.9. Clinical Trial Flowchart



1.10. Clinical Trial Schedule

	Screening period	Baseline period	Treatment period						Post-treatment follow-up period		
	V1	V2	V2	V3	V4	V5	V6	V7	V8	V9	V10
	W-2~D-1	D0	D0	M1±3d	M2±3d	M3±3d	M4±3d	M5±3d	M8±3d	M11±3d	M17±3d
Informed Consent	X										
Inclusion/Exclusion Criteria	X										
Demographic Data (gender, age, Fitzpatrick skin type, skin type (dry, oily, combination), ease of tanning (within 12 hours, 24 hours, 3 days, or not at all), smoking history (yes/no, duration), height, weight)	X										
Thyroid Cancer History (thyroid cancer pathology type: papillary thyroid cancer, follicular	X										

thyroid cancer, oncocytic cancer, poorly differentiated thyroid cancer, undifferentiated thyroid cancer, medullary thyroid cancer; tumor size; lymph node metastasis; surgical method: total/near-total thyroidectomy, unilateral thyroid lobectomy + isthmusectomy, unilateral thyroid lobectomy + isthmusectomy + subtotal resection of the contralateral lobe, thyroid lobectomy, neck lymph node dissection; surgery time)											

Allergy History	X										
Past Medical History (diabetes, hypertension, neuromuscular diseases, coagulation disorders, immunodeficiency diseases, chronic liver disease, anemia, heart disease, etc.)	X										
Scar Treatment History (local corticosteroid injections, compression therapy, laser treatment, drug therapy, irradiation, ultrasound therapy, cryotherapy, systemic chemotherapy, zinc application, surgical excision, etc.)	X										
Ultrasound Assessment		X		X	X	X	X	X	X	X	X

of Scars (echo depth, width, and intensity)											
mVSS Score (color, vascularity, pliability, thickness, pain, itching)		X		X	X	X	X	X	X	X	X
Scar Color		X		X	X	X	X	X	X	X	X
Scar Area		X		X	X	X	X	X	X	X	X
POSAS Score (Patient Scar Assessment Scale: pain, itching, color, hardness, thickness, irregularity; Observer Scar Assessment Scale: vascularity, pigmentation, thickness, roughness, pliability, surface area)		X		X	X	X	X	X	X	X	X
MSS Score (visual analog scale, color, luster, contour, deformity, texture)		X		X	X	X	X	X	X	X	X
SF-36 Score (health and daily		X		X	X	X	X	X	X	X	X

activities, your feelings, overall health condition)											
Standardized Assessment (2 physicians assessing on-site in a blinded manner, 2 physicians assessing through photographs in a blinded manner, patient assessment)		X		X	X	X	X	X	X	X	X
Adverse Events (pigmentation, erythema, vesicles, purpura, crusting, ulceration, infection)			X	X	X	X	X	X	X	X	X
Histological Assessment (average scar thickness in H&E stained sections, average percentage of collagen fibers in Masson's trichrome-											X

stained sections, average percentage of elastic fibers in elastic fiber-stained sections, average percentage of MMP9-positive cells)											

Monitoring Plan

The principal investigator will be responsible for monitoring the study. All adverse events related to the study intervention will be meticulously recorded in the patient's medical file and case report form and entered into the study institution's database. Additional monitoring by a monitor will also be required.

The principal investigator will regularly hold research meetings. If the risk/benefit ratio of the study changes, the ethics committee should be promptly notified. Any unexpected adverse events or serious adverse events should be reported in a timely manner to the ethics committee, the sponsor, and the regulatory authority for pharmaceuticals.

The principal investigator will conduct regular cumulative reviews of all adverse events and is responsible for submitting annual clinical trial reports. These reports should include the incidence rates of expected and unexpected adverse events, adverse event severity and attribution ratios, explanations for adverse event management, the number of subjects withdrawn from the trial and reasons for withdrawal, and the number of protocol violations and their handling.

The principal investigator will closely monitor the study, such as real-time monitoring of adverse events. The study physician will visit the subject within the specified time after the study intervention to assess any changes in the subject's physical or clinical condition, including the emergence of new symptoms or worsening of existing conditions. The subject will be provided with self-monitoring guidelines upon discharge and will be instructed to contact the investigator immediately by phone if any relevant symptoms or signs occur.

External monitors will be involved, such as review by a safety monitor or a data safety monitoring board for adverse events. The frequency of review will be specified in advance, with the acceptance of 10% or less of serious adverse events or unexpected adverse events.

The clinical research institution will conduct annual reviews or retrospective monitoring.

Interim analyses of the main outcome indicators and other monitoring items will be performed every three months.

Data Management

Source documents refer to the original records, files, and data generated in clinical trials, such as hospital medical records, medical images, laboratory records, memos, subject diaries or assessment forms, drug distribution records, instrument auto-recorded data, microfilm, photographic negatives, magnetic media, X-ray films, subject files, pharmacy, laboratory, and medical technical department files and records related to clinical trials, including certified copies. Source documents include source data, which can exist in paper or electronic form. Source data refers to all information recorded on the original records or certified copies of clinical trials, including clinical findings, observational results, and other relevant activity records required for reconstructing and evaluating clinical trials. Source data should have attributability, readability, simultaneity, originality, accuracy, completeness, consistency, and durability. Any modifications to source data should leave a trace, not cover up the initial data, and record the reasons for modification.

In this trial, source data will exist in paper or electronic form and will then be entered into an electronic data capture (EDC) system. Researchers are responsible for ensuring the accuracy, completeness, readability, and timeliness of the collected data. All source documents should be filled out in a neat and readable manner to ensure accurate interpretation of the data and will be kept in the individual subject's medical file by the investigator.

1.11. Data Management System

The data management of this study will utilize an electronic data capture (EDC) system to ensure the authenticity, integrity, confidentiality, and traceability of clinical trial data. The database will be established by the data department according to the clinical trial protocol and will adhere to ICH GCP, CDISC, and FDA 21 CFR Part 11 standards to ensure the integrity, privacy, and traceability of clinical trial data. The database will manage system login, data entry, modification, deletion, and other data traces. Database administrators or programmers will develop data entry quality control programs, validation programs, and configure various functions within the database, such as center and permission allocation, according to the data validation plan and project requirements. The database will be tested for each role, and system log records, data entry, data revisions, or deletions will be managed. After the EDC system is officially launched, it will generate electronic case report forms (eCRFs) that comply with the clinical trial protocol.

1.12. Source Data, Case Report Form (CRF) Filling, and Submission

Data in the eCRF will originate from source data and source documents. The eCRF will be completed by the investigator or a person designated by the investigator, ensuring the completeness and accuracy of the information. If any errors that require correction are found, modifications should be made in accordance with the eCRF filling instructions. Once the eCRF is completed, it should be promptly submitted to the EDC system via the internet. After the data

in the EDC system have been verified against the source data, reviewed by the data manager, and any queries have been resolved, the investigator will need to electronically sign off on each eCRF before the database is locked. The investigator must submit a complete eCRF for each subject, including those who failed screening.

1.13. Data Entry

In accordance with the corresponding standard operating procedures (SOPs), after each visit is completed, the investigator or a person authorized by the investigator will promptly enter the information into the EDC system. The entered data should be consistent with the original data, or any discrepancies must be explained. Data should be entered into the database as soon as possible after each visit's research evaluation, in accordance with the project requirements. After the original data has been entered, any changes made to the eCRF will be automatically recorded in the system. The data manager (DM) will develop an eCRF filling guide based on the eCRF, which will be used as a reference by the research center staff for data entry and query resolution.

1.14. Data Verification

After data entry, clinical monitors (CRAs), medical monitors (MMs), and DMs will review and check the eCRF pages. If any data are missing, incorrect, or do not conform to clinical medical logic, queries will be sent through the EDC system. The investigator or designated personnel will need to explain or correct the data through the EDC system until all queries and discrepancies have been resolved. All modifications to research data must be properly tracked in the EDC system's audit trail. After all data validation steps have been completed, the principal investigator or designated personnel will electronically sign each eCRF before the database is locked. Data verification will be conducted throughout the study, including both electronic logic verification and manual verification.

(1) Electronic Logic Verification and Query Handling

Based on the logical check standards defined in the data verification specifications, electronic online verification will be conducted for the data of each subject. During the data entry process, if the entered content does not comply with the relevant rules, the system will generate a query, which needs to be handled by correcting the data. If the data are confirmed to be correct and no relevant corrections are made, an explanation should be provided and reviewed by the DM. If the explanation is reasonable, the query will be manually closed; otherwise, it will continue to be issued until a reasonable response is given.

(2) Manual Verification and Query Handling

Manual verification of the data will be conducted based on the manual verification list to identify issues that cannot be detected by electronic program verification. After the study begins, the DM will export the required information as data lists or reports to assist with the verification process. Additionally, for certain specific modules, manual verification can only be conducted after all data have been entered. Manual queries issued according to the manual verification plan will be added and sent to the center by the DM for resolution. Once the data are corrected

or confirmed, the queries will be closed. Before the database is locked, the frequency of verification can be increased as appropriate. After the last visit of the last subject in the eCRF is entered, the DM will conduct a final manual verification. The CRA will compare the data entered into the database with the original documents. In cases of inconsistency or uncertainty, the CRA will issue a query to the center for resolution or data update.

1.15. Database Locking and Unlocking

Once the database locking check is completed, the DM will send a database locking application form to the sponsor for approval. After obtaining approval, the database will be locked, and the database locking confirmation form should be signed by the principal investigator, the sponsor's project leader, and the data management project leader. After the database is locked, the DM will send the locked data to the biostatistician for statistical analysis. The DM will notify the project team members that the database has been locked. In principle, no modifications are allowed to the locked database unless a strict unlocking and relocking process is followed. The relocking of the database should follow the same procedure as the initial locking of the database.

Statistical Analysis

1.16. Procedures for Reporting Deviations from the Original Statistical Plan

The procedures and statistical methods specified in the clinical trial protocol or statistical plan should be followed. If it is necessary to change the statistical procedures and methods specified in the protocol, at least the coordinating investigator and the sponsor should be informed before the database is locked, and the reasons for the deviation and its rationality should be explained.

1.17. Selection Criteria and Rationale for Subjects Included in the Analysis

Full Analysis Set (FAS): The set of subjects determined according to the intention-to-treat (ITT) principle, which includes all subjects who participated in the randomization and used the study and control sides.

Per Protocol Set (PPS): The subgroup of subjects who completed the trial, excluding those who severely violated the protocol (i.e., subjects who violated the inclusion or exclusion criteria).

Efficacy analysis will be conducted based on the Full Analysis Set and the Per Protocol Set; all baseline demographic data analysis will be performed on the Full Analysis Set.

Safety Data Set (SS): The set of subjects who received at least one treatment with the study or control product. This set is used for safety evaluation.

1.18. Withdrawal and Loss to Follow-up Data

For subjects who withdraw from the trial, the reasons for withdrawal will be described. Subjects who withdraw from the trial will be followed up at 3 months, 6 months, and 1 year after the final treatment. At each follow-up visit, the following indicators will be recorded for both sides of the scar: echo depth, width, and intensity; mVSS score; scar color; scar area; POSAS score; MSS score; SF-36 score; standardized assessment; adverse events. For subjects

who are lost to follow-up during the trial, the reasons for loss to follow-up will be described. For handling missing data: The first category involves no action, which is commonly used in the following scenarios: when the proportion of missing outcomes does not exceed 5%; when the outcome is survival time data; when the statistical method used is a mixed-effects model or generalized estimating equations. The second category involves imputation, with common methods including last observation carried forward, baseline observation carried forward, worst-case imputation, multiple imputation, etc. The third category involves sensitivity analysis to quantify the impact of missing outcome data on the study results (e.g., using multiple imputation, regression adjustment, or inverse probability weighting).

1.19. Statistical Design, Methods, and Analysis Procedures

Descriptive Analysis: Categorical data will be described using frequency and proportion, while continuous data will be described using mean, standard deviation, maximum, and minimum values.

Efficacy Analysis: For continuous data, the difference between the study side and the control side will be calculated. If the difference is normally or approximately normally distributed, a paired t-test will be used; if the difference is severely skewed, the Wilcoxon signed-rank test will be used.

Safety Evaluation: The number and proportion of cases that were normal before treatment and abnormal after treatment will be described. Adverse events will be described using the number and incidence rate of adverse events, and the proportion will be tested using the continuity-corrected chi-square test or Fisher's exact probability test. Additionally, all adverse events that occur in cases will be detailed, including their specific manifestations, severity, and relationship with the study product.

All statistical analyses will be conducted at a two-sided significance level of 0.05. Statistical analysis will be performed using SPSS 27.0 statistical software.

Sample Size Calculation

This study is a self-controlled parallel trial.

Based on clinical practice in the literature [1-4], the estimated difference in scar thickness is 0.7, with an expected standard deviation of 1.0. For a two-tailed significance level $\alpha = 0.05$ and $\beta = 0.01$, the sample size is calculated to be 38 cases. For an estimated difference in mVSS score of 2, with an expected standard deviation of 3.5, the sample size is calculated to be 57 cases.

The above parameters were calculated using the CHISS 2010 sample size calculation software and verified using the following formula:

$$n = \frac{\left(Z_{\alpha/2} + Z_{\beta}\right)^2 * \sigma^2}{\delta^2}$$

where σ is the overall standard deviation or its estimate s of each pair of differences, and δ is the required degree of separation.

The trial is planned to enroll 120 patients, with a test power of >99%.

1.19. Quality Control

During the clinical trial, qualified clinical trial monitors will be dispatched by the sponsor to conduct regular on-site monitoring of the medical institutions undertaking this clinical trial to ensure that all contents of the clinical trial protocol are strictly adhered to.

The monitoring and auditing of this clinical trial will be conducted in accordance with the relevant SOPs of the CRO company, in combination with the processes and requirements of the study hospital.

Ethical Considerations and Informed Consent in Clinical Trials

1.20. Ethical Considerations

This clinical validation must adhere to the Declaration of Helsinki and the relevant laws and regulations of medical laser treatment clinical trials in our country. It must be approved by the ethics committee of the medical institution and filed with the provincial bureau of the sponsor before the study can commence.

Before each patient is enrolled in this clinical validation, the person in charge of the clinical trial has the responsibility to fully explain to the subject the purpose, process, and duration of this clinical validation, as well as the potential benefits and risks for the subjects. They should be informed that they have the right to withdraw from the clinical validation at any stage. Before enrollment, an informed consent form must be provided to each subject, and their signed consent must be obtained.

1.21. Approval of the Trial Protocol

Before implementing the clinical trial, the ethics committee (IRB) of the institution undertaking the trial will review the suitability of the clinical trial implementation based on the content recorded in the clinical trial protocol, case report forms, informed consent forms provided to subjects, investigator's manual, etc. The ethics committees of each participating unit will review the clinical trial protocol according to their respective standard operating procedures (SOPs).

1.22. Informed Consent Process and Informed Consent Form

Before enrolling patients, the investigator must use an informed consent form that includes the following items and explain them in detail to the patients. Sufficient time should be given to patients to consider whether to participate in the trial. If patients have any questions, the investigator should provide detailed answers. After the patients fully understand, they should voluntarily sign the informed consent form. Both the patient/legal guardian and the investigator explaining the informed consent should sign the form and note the date of signature. The signed and dated original informed consent form (in duplicate) should be kept by the investigator and the patient/legal guardian, respectively.

Additionally, if the investigator obtains information that may affect the subject's decision to participate in the trial, such information should be promptly communicated to the subjects who are currently participating in the trial. The investigator should confirm whether the subjects

wish to continue participating in the trial and document this. If the investigator obtains information that significantly affects the subject's or their legal guardian's decision to participate in the trial, the investigator should promptly communicate with the sponsor, revise the informed consent form, obtain approval from the ethics committee, and then notify the subjects or their legal guardians who are currently participating in the trial. The revised informed consent form should be used to obtain their continued informed consent through the aforementioned process. The text of the informed consent form is provided in a separate document.

Adverse Events and Serious Adverse Events

1.23. Adverse Events

1.23.1. Adverse Events

An adverse event (AE) is any unfavorable medical occurrence associated with the use of the investigational product in a clinical trial, whether or not considered related to the investigational product. An AE can be any untoward medical occurrence in a subject or clinical investigation participant, including any sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Medical conditions occurring during the screening of subjects after signing the informed consent form but before receiving the investigational product should be recorded as medical history/comorbidities.

1.23.2. Expected Adverse Events

Expected adverse events include pigmentation, erythema, vesicles, purpura, crusting, ulceration, infection, etc. If they occur, they will be treated according to clinical routine practices; if they are serious adverse events, the subject will be withdrawn from the study.

1.23.3. Content of Adverse Event Recording

An adverse event record form will be filled out, including the name of the adverse event, start and end times, severity, degree of seriousness, evaluation of the relationship with the trial, measures taken regarding the investigational medical device, outcome, and whether the subject withdrew from the trial due to the adverse event.

The name of the adverse event will be recorded using the medical terminology from the MedDRA dictionary.

A two-point method will be used to evaluate the relationship between clinical trial adverse events and device treatment (or drug). Based on five evaluation points (whether there is a reasonable temporal relationship, whether it conforms to the known mechanism of action, characteristics, or known adverse reactions of the drug, dechallenge results, rechallenge results, whether it can be explained by other reasonable causes), the relationship between individual adverse events in clinical trials and the investigational drug will be evaluated. According to the criteria for determining the relationship between adverse events and drugs in clinical trials, if the determination fits "definitely related," "probably related," or "possibly related," it will be classified as "related" in the two-point method; if it fits "unrelated" or "probably unrelated," it

will be classified as "unrelated" in the two-point method.

1.23.4. Severity of Adverse Events

The severity classification of adverse events will refer to the classification standards in the "NIA Adverse Event and Serious Adverse Event Guidelines."

1.23.5. Follow-up of Adverse Events

When an adverse event occurs, it should be tracked until the subject returns to the state prior to the adverse event or until the investigator determines that further tracking is unnecessary.

1.24. Serious Adverse Events

1.24.1. Definition of Serious Adverse Events

A serious adverse event is an untoward medical occurrence that results in a significant worsening of health status, including fatal diseases or injuries, structural or functional damage to the body.

1.24.2. Reporting Regulations for Serious Adverse Events

If a serious adverse event occurs, it should be reported to the ethics committee responsible for and participating in the clinical trial, the applicant, and other investigators involved in the same clinical trial within 24 hours of confirmation.

Compliance with, Violations of, and Revisions to the Clinical Trial Protocol

1.25. Compliance with the Clinical Trial Protocol

Investigators must adhere to the trial protocol agreed upon with the sponsor and reviewed by the ethics committee, and must not violate or change the trial protocol. However, this does not apply when taking protocol-violating medical measures to address urgent dangers to subjects, or when changes are only related to administrative matters of the trial (e.g., changes in the sponsor's organizational structure, changes in the name of the trial institution or department, changes in the investigator's title, changes in the monitor).

1.26. Violations of the Trial Protocol

If a violation of the trial protocol occurs, the investigator must record the reasons. When taking protocol-violating medical measures to address urgent dangers to subjects, the investigator must record the reasons in writing and submit them to the sponsor, retaining a copy. When taking protocol-violating measures in response to urgent dangers to subjects, the investigator may propose reasonable changes to the trial protocol, reach an agreement with the sponsor, and obtain approval from the ethics committee.

1.27. Revisions to the Trial Protocol

When the sponsor and investigator determine that it is necessary to make changes to the trial protocol, they must reach an agreement on the protocol revision and submit it to the ethics committee for approval. However, this does not apply to revisions that do not involve substantial changes to the trial design, such as changes in organizational structure, department names, or personnel positions.

2.Direct Access to Source Data and Documents

Source data refers to the original records and their certified copies of clinical findings, observations, and other activities in clinical trials, which can be used for the reconstruction and evaluation of clinical trials. Source documents refer to printed, visual, or electronic documents containing source data.

The participating clinical trial institutions will accept direct access to source data and documents by monitors or auditors. The source data and documents of this study include: medical records of subjects in the HIS system, including identity, disease diagnosis, laboratory tests, and auxiliary diagnostic results, as well as informed consent forms, subject identification code tables, and usage records of the 1565 nm non-ablative fractional laser device.

3.Content of the Clinical Trial Report

The clinical trial report will be written in accordance with the "Regulations for the Management of Clinical Trials of Medical Devices" in our country, covering all aspects from trial design to the final submission and archiving of the report.

4.Confidentiality Principles

Except for the necessary personnel involved in the research process, the personal information of subjects must not be disclosed.

When investigators fill out case report forms and other trial data, they should use subject identification numbers and not disclose personal information of subjects.

The sponsor must not disclose the relevant information of subjects without proper justification.

5.Publication Agreement for Trial Results

The sponsor and investigator will prepare a trial summary report at the end (or termination) of the trial. They may publish the results of the clinical trial through papers or presentations at academic conferences.

If investigators wish to publish trial results, they should first consult with the sponsor and obtain consent.

Under no circumstances should the publication of trial results disclose personal information of subjects to protect their privacy.

Responsibilities of Each Party

In accordance with this protocol, each party will assume the corresponding responsibilities.

References

[1] Miletta N, Siwy K, Hivnor C, et al. Fractional Ablative Laser Therapy is an Effective Treatment for Hypertrophic Burn Scars: A Prospective Study of Objective and Subjective Outcomes. Ann Surg. 2021;274(6):e574-e580.

[2] Roohaninasab M, Khodadad F, Sadeghzadeh-Bazargan A, et al. Efficacy of fractional CO2 laser in combination with stromal vascular fraction (SVF) compared with fractional CO2 laser alone in the treatment of burn scars: a randomized controlled clinical trial. Stem Cell Res Ther. 2023;14(1):269.

[3] Blome-Eberwein S, Gogal C, Weiss MJ, Boorse D, Pagella P. Prospective Evaluation of Fractional CO2 Laser Treatment of Mature Burn Scars. J Burn Care Res. 2016;37(6):379-387.

[4] Joo SY, Cho YS, Lee SY, Seo CH. Regenerative effect of combined laser and human stem cell-conditioned medium therapy on hypertrophic burn scar. Burns. 2023;49(4):870-876.

Trial Forms

Modified Vancouver Scar Scale (mVSS) Score

Characteristic	Score	Clinical Manifestation
Color	0	Scar color is similar to adjacent normal body skin
	1	Slightly pink
	2	Mixed color
	3	Darker color
Vascularity	0	Scar color is similar to normal body skin
	1	Pink, slightly increased local blood supply
	2	Red, significantly increased local blood supply
	3	Purple or dark red, rich blood supply
Pliability	0	Normal
	1	Soft (skin can deform with minimal resistance)
	2	Pliable, can bend (can deform under pressure)
	3	Hard (no elasticity when pressed, lumpy, resistant to pressure)
	4	Tissue is cord-like
	5	Contracture deformity (permanent shortening leading to functional impairment)
Thickness	0	Same height as surrounding normal skin
	1	Higher than normal skin, but not more than 2 mm
	2	Higher than normal skin by more than 2 mm, but not more than 5 mm
	3	More than 5 mm above normal skin
Pain	0	No pain
	1	Occasionally or mildly painful
	2	Requires medication to control pain
Itching	0	None
	1	Occasionally or mildly itchy
	2	Requires medication to control itching
Total Score: 0 (best) → 18 (worst)		

Patient and Observer Scar Assessment Scale (POSAS)

Patient Scar Assessment Scale (PSAS)	Score	Clinical Manifestation
Is the scar painful?	1	No, not at all
	↓	
	10	Yes, completely
Is the scar itchy?	1	No, not at all
	↓	
	10	Yes, completely
Is there a difference in the color of the scar compared to your normal skin?	1	No, not at all
	↓	
	10	Yes, completely
Is there a difference in the hardness of the scar	1	No, not at all

compared to your normal skin?	↓ 10	Yes, completely
Is there a difference in the thickness of the scar compared to your normal skin?	1	No, not at all
	↓ 10	Yes, completely
Is the scar more irregular compared to your normal skin?	1	No, not at all
	↓ 10	Yes, completely

Observer Scar Assessment Scale (OSAS)	Score	Clinical Manifestation
Vascular distribution	1	Normal skin
	↓ 10	Worst case scenario
Pigmentation	1	Normal skin
	↓ 10	Worst case scenario
Thickness	1	Normal skin
	↓ 10	Worst case scenario
Roughness	1	Normal skin
	↓ 10	Worst case scenario
Softness	1	Normal skin
	↓ 10	Worst case scenario
Surface area	1	Normal skin
	↓ 10	Worst case scenario

Manchester Scar Scale (MSS)

Characteristic	Score	Clinical Manifestation
Visual Analog Scale (VAS)	0	Excellent
	↓ 10	Poor
Color	1	Completely matches surrounding skin
	2	Slightly mismatched
	3	Significantly mismatched
	4	Severely mismatched
Luster	1	Dull
	2	Glossy
Contour	1	Flush with surrounding skin
	2	Slightly raised/recessed
	3	Significantly hypertrophic

	4	Keloid
Deformity	1	None
	2	Slight
	3	Moderate
	4	Severe
Texture	1	Normal
	2	Palpable texture change but not significant
	3	Firm
	4	Hard
Total Score	5 (best) → 28 (worst)	

Medical Outcomes Study Health Survey Short Form-36 Item (SF-36)

The following questions ask about your views on your own health status. If you are unsure how to answer, please try to give the best response and write any comments or notes at the end of this questionnaire.

Overall, how would you rate your health status?

1. Very good

2. Good

3. Fair

4. Poor

5. Very poor

Compared to one year ago, how would you rate your health status?

1. Much better than one year ago

2. A little better than one year ago

3. About the same as one year ago

4. A little worse than one year ago

5. Much worse than one year ago

Health and Daily Activities

3. The following questions are related to daily activities. Has your health status limited these activities? If so, to what extent?

(1) Strenuous activities, such as running, weightlifting, or participating in vigorous sports:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(2) Moderate activities, such as moving a table, sweeping, doing Tai Chi, or simple aerobics:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(3) Carrying daily items, such as grocery shopping:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(4) Climbing several flights of stairs:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(5) Climbing one flight of stairs:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(6) Bending, kneeling, or squatting:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(7) Walking more than 1600 meters:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(8) Walking 800 meters:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(9) Walking 100 meters:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

(10) Bathing or dressing yourself:

1. Greatly limited

2. Somewhat limited

3. Not limited at all

4. In the past four weeks, have your work and daily activities been affected by health reasons in the following ways?

(1) Reduced work or other activity time:

1. Yes

2. No

(2) Only able to complete part of what you wanted to do:

1. Yes

2. No

(3) The types of work or activities you wanted to do were limited:

1. Yes

2. No

(4) Increased difficulty in completing work or other activities (e.g., requiring extra effort):

1. Yes

2. No

5. In the past four weeks, have your work and daily activities been affected by emotional reasons (such as depression or anxiety) in the following ways?

(1) Reduced work or activity time:

1. Yes

2. No

(2) Only able to complete part of what you wanted to do:

1. Yes

2. No

(3) Not as careful as usual when doing things:

1. Yes

2. No

6. In the past four weeks, to what extent has your health or emotional well-being affected your normal social interactions with family, friends, neighbors, or groups?

1. Not at all

2. A little

3. Moderately

4. A lot

5. Very much

7. In the past four weeks, have you experienced bodily pain?

1. No pain at all

2. A little pain

3. Moderate pain

4. Severe pain

5. Very severe pain

8. In the past four weeks, has your bodily pain affected your work and household chores?

1. Not at all

2. A little

3. Moderately

4. A lot

5. Very much

Your Feelings

9. The following questions are about how you have been feeling over the past month. For each statement, how often have you felt this way?

(1) I felt that my life was fulfilling:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(2) I felt that I was sensitive:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(3) I felt very down and nothing could cheer me up:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(4) I felt very calm:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(5) I felt energetic:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(6) I felt depressed:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(7) I felt exhausted:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(8) I felt happy:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

(9) I felt bored:

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

10. Poor health has affected my social activities (such as visiting relatives and friends):

1. All of the time

2. Most of the time

3. A good part of the time

4. Some of the time

5. A little of the time

6. Never

Overall Health Status

11. Please look at each of the following questions and indicate which answer best applies to you:

(1) I seem to catch colds more easily than other people:

1. Definitely true

2. Mostly true

3. Can't say for sure

4. Mostly false

5. Definitely false

(2) I am as healthy as the people around me:

1. Definitely true

2. Mostly true

3. Can't say for sure

4. Mostly false

5. Definitely false

(3) I think my health is getting worse:

1. Definitely true

2. Mostly true

3. Can't say for sure

4. Mostly false

5. Definitely false

(4) I am in very good health:

1. Definitely true

2. Mostly true

3.'t Can say for sure

4. Mostly false

5. Definitely false

Standardized Assessment

Assessors and Assessment Methods		Is there a difference between the left and right scars?		If "yes," which side is superior?	
		Yes	No	Left	Right
On-site Blinded	Physician A				

Assessment by 2 Physicians	Physician B				
Blinded Assessment by 2 Physicians Based on Photographs	Physician C				
	Physician D				
Patient Assessment					

Adverse Event Record Form

Has the subject experienced any adverse events during the trial? Yes □ No □ If "yes," please fill in the following table.	
AE Name	
Start and End Dates of AE	Start Date: _____ End Date: _____
Severity of AE	□ Caused death □ Life-threatening □ Resulted in hospitalization or prolonged hospital stay □ Permanent or significant functional loss □ Caused teratogenicity or birth defects □ Other important medical events
Severity of AE	□ Mild □ Moderate □ Severe
Relevance of AE to Trial	□ Relevant □ Irrelevant
Measures Taken Regarding the Investigational Medical Device	□ Continue use □ Reduce use □ Temporarily suspend use □ Resume after temporary suspension □ Discontinue use □ Other
Outcome	□ Symptoms resolved (with/without sequelae □ Yes □ No) □ Symptoms persisted □ Symptoms relief □ Symptoms worsened □ Death □ Other
Did the subject withdraw from the trial due to AE?	□ Yes □ No