Multicenter Pivotal Study of Vacuum-Assisted Precise Tissue Release for the Treatment of Cellulite

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BACKGROUND Cellulite refers to the dimpled appearance of skin occurring where the dermis is tethered by subcutaneous fibrous septa arranged perpendicularly to the skin surface.

OBJECTIVE To demonstrate the safety and efficacy of a new system for vacuum-assisted precise tissue release for the treatment of cellulite.

MATERIALS AND METHODS Adult women with moderate to severe cellulite ($N = 55$) underwent a single treatment. Post-treatment assessments were performed after 3 and 14 days; 1, 3, and 6 months; and at 1 year. Outcome measures included blinded assessments of subject photographs, a validated Cellulite Severity Scale (CSS), and the Global Aesthetic Improvement Scale. Subject satisfaction and pain ratings were also recorded.

RESULTS The mean baseline CSS score of 3.4 decreased to 1.3 at 3 months ($p < .0001$) and 1.4 at 1 year ($p < .0001$), with 47 subjects (93%) having ≥1-point improvements. Subject satisfaction was 85% at 3 months and 94% at 1 year. Transient treatment-related adverse events were mild in severity.

CONCLUSION This study demonstrates the safety, efficacy, and subject satisfaction with vacuum-assisted precise tissue release in the treatment of cellulite. There was no reduction in treatment benefits for up to 1 year. These results supported the Food and Drug Administration clearance of the device for the long-term reduction in the appearance of cellulite.

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Cellulite refers to the dimpled appearance of skin, which is estimated to affect approximately 85% of postpubertal women of all races.[1] The appearance of cellulite has been associated with significant social stigma and can adversely affect self-esteem.[2] Although the etiology of cellulite is not completely understood,[3] changes in the underlying anatomical structures associated with cellulite have been studied.[4] A fibrous network of collagenous septa provides structural support to the dermis. In areas where cellulite forms, these subcutaneous septa generally run perpendicular to the skin and are much thicker than in other areas.[5]

Current treatments for cellulite include surgery to release fibrous bands, several devices using massage together with various forms of noninvasive energy, mesotherapy, and topical products.[6] Patients spend enormous amounts of money each year for the treatment of cellulite, although clear evidence of the efficacy for most of these products is often lacking.[6,7] Noninvasive treatments for cellulite generally target the fat cells instead of the septa. Treatments directed specifically at the fibrous septa include Subcision[8] and liposuction.[9] Subcision refers to a manual needle dissection technique developed to treat facial scars[10] and has been shown to be effective for cellulite.[11,12]

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Liposuction, which is effective for deeper fat contouring, can be performed at a shallow depth for treating cellulite but is typically ineffective even when combined with release of fibrous bands. The application of a 1,440-nm Nd:YAG laser cannula to release fibrous tissue for the treatment of cellulite is a recent focus of research with more promising results.[13] Using these approaches, the depth and specific area of release are variable and dependent on physician technique, which can lead to inconsistent outcomes. Treatment of larger areas is also difficult and time consuming.

A novel system (Cellfina System; Ulthera Inc., Mesa, AZ) has been developed, which builds on the proven approach of dermal undermining or subcision (i.e., mechanical tissue release). The system uses a unique vacuum-assisted tissue capture platform, which provides precise control of the depth and area of release. This ensures repeatable durable results, the lack of which has hindered both the acceptance and adoption of the free-hand manual approaches involving needles, cannulae, and lasers. The system components are illustrated in Figure 1.

The depth of treatment is controlled through the use of a vacuum chamber, which lifts and fixes the tissue for either an anesthesia needle or tissue release microblade, with no aspiration or removal of fat. A guidance platform attaches to the vacuum chamber and directs the external components of the device along a predetermined path, thereby controlling the distal end of the needle or microblade within the subcutaneous tissue. Treatment depth (6 or 10 mm) is adjustable with simple reversal of the chamber lid, allowing for larger areas of treatment without contiguous release and the release of deeper skin depressions at a deeper depth. Through the use of interchangeable platforms, the system enables controlled infiltration of anesthetic

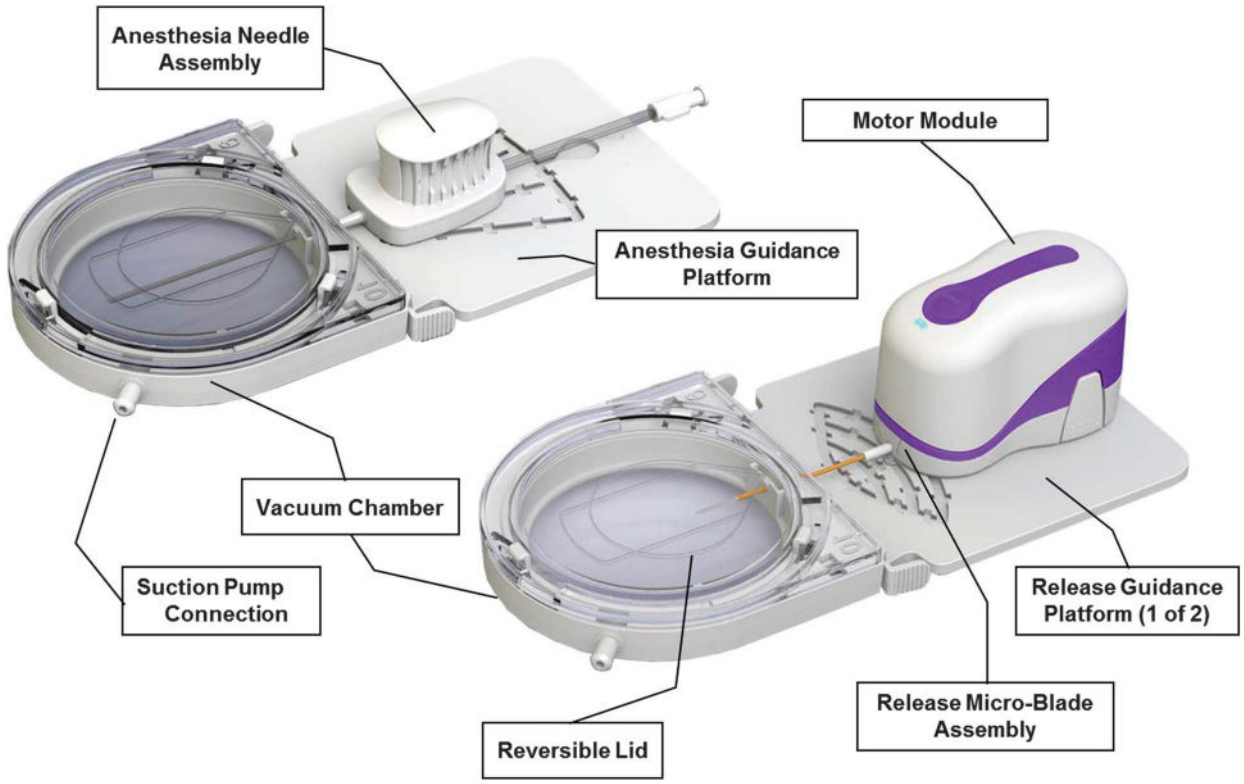

Figure 1. The system consists of several components. A sterile vacuum chamber assembly controls the depth of treatment with associated guidance platforms that define the treated area. The vacuum chamber is used with a suction pump to draw the tissue up into the chamber recess. A sterile anesthesia needle assembly is used to facilitate subcutaneous anesthetic infiltration before treatment. Tissue release is accomplished through the mechanical action of a single-use sterile release microblade, which is attached to a reusable motor module that is moved by the user through a defined path in the guidance platform. Through the use of interchangeable guidance platforms, the same vacuum chamber can be used for subcutaneous anesthesia needle guidance and several different release areas.

solution at the precise depth of the intended release with the integrated 3-inch 22-gauge multiple side-hole needle. Tissue stabilization within the vacuum chamber allows the use of this smaller needle compared with the 16- to 18-gauge needle typically necessary[14] for regional anesthesia of larger areas.

Tissue release is accomplished through the mechanical action of a reciprocated razor-thin (0.45 mm) microblade. The microblade assembly is attached to a motor module, which is moved through the defined external path in the guidance platform, creating precise release areas within the tissue at the user-selected depth. There are 2 elements to release of the cellulite depressions: (1) reciprocating movement (forward and backward) of the microblade and (2) lateral (side to side) movement of the motor module through a defined path along the radial arcs in the guidance platforms. This method allows rapid release of the intended area while still providing tactile feedback of the release similar to the free-hand manual methods. Release platforms are available for up to a 5-cm wide "tear drop" or a 3×6 cm rectangular area. The microblade position within the tear drop release area is illustrated in Figure 2. Smaller release areas can be achieved by partial completion of the radial arcs in the guidance platform(s) either laterally or distally. The system is designed to provide vacuum-assisted control of both the depth and area of tissue release to allow for a precise, reproducible, and consistently effective treatment.

Materials and Methods

The safety and efficacy of the vacuum-assisted precise tissue release system for long-term improvement in the appearance of cellulite was the subject of a multicenter, nonrandomized, open-label pivotal study with follow-up conducted out to 1 year after treatment. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by an Independent Human Research Review Committee (New England Institutional Review Board, Newton, MA). The study met all applicable requirements for ISO 14155 clinical investigation of medical devices for human subjects, first edition 2011. The study protocol was approved by the Food and Drug Administration

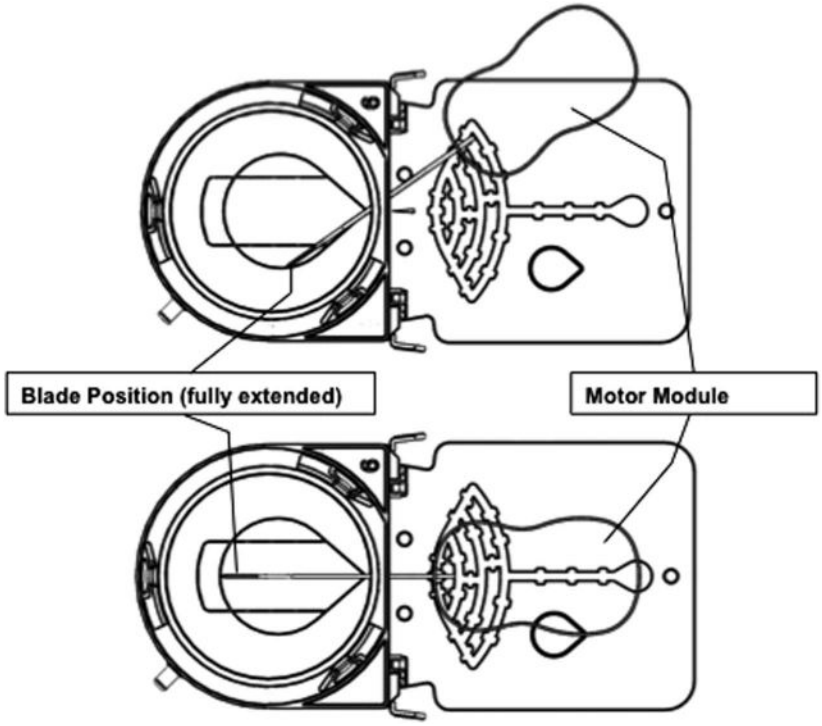

Figure 2. Schematic showing the microblade position within the 5 cm tear drop release area for 2 positions of the motor module: lateral edge of the second radial arc of the guidance platform is illustrated at the top, and the centerline distal position is illustrated at the bottom.

TABLE 1. Cellulite Severity Scoring

Score	*Description*
1. Severity scoring by the independent evaluators	
A. Number of evident depressions	
0	None
1	Mild (≤4 depressions)
2	Moderate (≥5 to ≤9 depressions)
3	Severe (≥10 depressions)
B. Average depth of depressions	
0	None
1	Mild (1–2 mm)
2	Moderate (3–4 mm)
3	Severe (≥5 mm)

Severity scale (A+B−1)	*Classification*	*Severity Grade*
2. Cellulite severity grading (calculated values)		
0	None	0
1–2	Mild	1
3	Moderate	2
4–5	Severe	3

(FDA) (IDE G120116) and registered on clinicaltrials.gov under identifier NCT01671839.

Subjects

Study participants were healthy women aged 18 to 55 years with body mass index (BMI) <35 and areas of moderate to severe cellulite on the buttocks and/or thighs. Each subject was dissatisfied with the current appearance of her cellulite at baseline, expressed her willingness to comply with protocol requirements, and agreed not to undergo any other treatments for cellulite through the 1-year follow-up assessment period. Exclusion criteria included any treatment for body contouring or appearance of cellulite on the thighs or buttocks during the previous 90 days or prior liposuction in the thighs or buttocks; a >10% change in body weight during the previous 6 months; a history of resistance, hypersensitivity, or adverse reactions to local anesthetics; smoking during the previous 6 months; evidence of active infection or a fever >38°C; hypertension, diabetes, hypoglycemia, cardiopathy, or pneumopathy; history of coagulopathies, current anticoagulant therapy; severe anemia; atrophic

TABLE 2. Baseline Demographics for Subjects (N = 55)

Age	
Mean (SD)	41.8 (6.3)
Median (min–max)	43.0 (25.0–55.0)
Gender, N (%)	
Female	55 (100.0)
Race/ethnicity, N (%)	
Asian	1 (1.8)
Black	6 (10.9)
White	48 (87.3)
Hispanic or Latino	7 (12.7)
BMI, N (%)	
Mean (SD)	25.2 (3.8)
Median (min–max)	24.5 (18.3–34.6)
Fitzpatrick skin type, N (%)	
I, II	12 (21.8)
III	25 (45.5)
IV	10 (18.2)
V, VI	8 (14.5)

or keloidal scars; use of nonsteroidal anti-inflammatory agents during the previous 14 days; any disease or condition that, in the opinion of the physician, could place the subject at risk or compromise the objectives of the study; pregnancy or lactation; or participation in another clinical trial during the previous 30 days. Subjects were encouraged to maintain a stable weight, the same lifestyle for the duration of the study, and

TABLE 3. Treatment Parameters for Subjects (N = 55)

Procedure time (minutes)	
Mean (SD)	41.8 (9.5)
Median (min–max)	40.0 (25.0–63.0)
Treatment time (minutes)	
Mean (SD)	18.2 (6.3)
Median (min–max)	17.0 (5.0–37.0)
Anesthesia volume (mL)	
Mean (SD)	290.2 (85.3)
Median (min–max)	264.0 (120.0–480.0)
Lidocaine dose (mg/kg)	
Mean (SD)	4.4 (1.3)
Median (min–max)	4.4 (1.9–6.7)
Release sites	
Mean (SD)	12.6 (5.3)
Median (min–max)	11.0 (6.0–25.0)
Release depth (mm), N (%)	
6	597 (85.9)
10	98 (14.1)

TABLE 4. Independent Evaluation ICC

	Baseline Photographs Evaluation				
Parameter	*3 Months*	*12 Months*	*Overall*	*3-Month Follow-up*	*1-Year Follow-up*
Number of evident depressions	0.8697	0.8895	0.9322	0.7962	0.7940
Depth of depressions	0.8051	0.8138	0.8885	0.7881	0.8089
CSS	0.9000	0.8984	0.9451	0.8070	0.8314

refrain from the use of any creams or lotions that could affect the color of their skin.

Procedure

The areas selected for treatment by the subject and physician were marked with a surgical pen by the treating physician and cleansed with an antiseptic scrub. The vacuum chamber with anesthesia guidance platform was connected to vacuum suction at 300 mmHg, and the target tissue was acquired into the chamber recess. The anesthesia needle assembly (22 gauge) was then used for infiltration of small boluses of Klein solution[14]: buffered tumescent 0.1% lidocaine solution containing 1:1,000,000 epinephrine. The tissue acquisition and infiltration sequence were repeated until all the marked areas were infiltrated. The total allowable anesthetic volume was calculated before infiltration based on subject weight and did not exceed the lesser of 7 mg/kg of lidocaine HCl or a total of 500 mg. Blood pressure and pulse were monitored before the infiltration of anesthetic and periodically through the anesthesia delivery and release phases of the treatment.

After sufficient anesthetic dwell time (~10–15 minutes from the infiltration start time), the release guidance platform was attached to the vacuum chamber, and the system was used to provide controlled subcutaneous release of the tissue in the marked areas. The primary release depth was 6 mm, and no attempt was made to compare the efficacy of each depth. The 10-mm depth was used for cellulite depressions immediately adjacent to those treated at 6 mm to avoid connecting or overlapping sites at a single depth to prevent creation of large contiguous areas of release more susceptible to seroma formation. After the procedure, the treated areas were cleaned and bandaged. Subjects were provided compression garments and asked to wear them as often as possible for 2 weeks.

Assessments

All subjects served as their own controls. Each underwent a baseline assessment, received a single treatment with the vacuum-assisted precise release system, and follow-up assessments at 3 and 14 days; 1, 3, and 6 months; and 1 year after treatment. Photographs were obtained at baseline and each follow-up visit in accordance with protocol-specific photography by professional photographers using tightly controlled lighting and fixed subject positioning. The subjects stood in a relaxed position on a rotatable platform with a fixed post for consistent hand position. The angle of the lights and distances between the

TABLE 5. Primary Efficacy End Point: CSS Reduction From Baseline After Treatment

	Baseline	*3 Months, N = 55*	*Change*	*Significance, p*
Mean (SD)	3.4 (0.8)	1.2 (0.9)	−2.1 (0.7)	.0001
Median (min–max)	3.0 (1.0–5.0)	1.0 (0.0–4.0)	−2.0 (−4.0 to 0.00)	
	Baseline	*1 Year, N = 50*	*Change*	*Significance, p*
Mean (SD)	3.4 (0.8)	1.5 (0.8)	−2.0 (0.8)	.0001
Median (min, max)	3.0 (1.0–5.0)	1.0 (0.0–3.0)	−2.0 (−4.0 to 0.0)	

TABLE 6. Physician GAIS Scores

	3 Months, N = 55, n (%)	*1 Year, N = 50, n (%)*
Very much improved	6 (10.9)	10 (20.0)
Much improved	35 (63.6)	26 (52.0)
Improved	13 (23.6)	14 (28.0)
No change	1 (1.8)	0 (0.0)
Worse	0 (0.0)	0 (0.0)

platform, lights, and camera were all standardized and confirmed for each photography session.

A simplified cellulite severity scoring methodology (Table 1) was developed and validated for this study in which the 2 key clinical morphologic features of cellulite were quantified: (A) number of evident depressions in the treatment area and (B) average depth of the depressions. The severity of each category was graded from 0 to 3 based on the definitions, and a set of associated reference photographs provided for each of the scores. The overall cellulite severity score was calculated from the evaluations by the addition of values for A (number) and B (depth) and subtracting 1. The resulting 0 to 5 Cellulite Severity Scale (CSS) provided a quantitative measure of treatment effect and was also converted to a commonly used 0 to 3 severity "grade," providing a quantitative basis for the qualitative measure.

The subject photographs and the severity scoring were used in a blinded physician evaluation of the treated areas to verify the efficacy of the controlled release system for both the 3-month and 1-year follow-up assessments. This evaluation was independently conducted (Therapeutics, Inc., San Diego, CA) with complete anonymity with respect to any details of the study sponsor, investigators, or method of treatment, and each physician evaluation was overseen by an independent monitor. Photonumeric references of the severity scores were used to train the 3 physician evaluators on the severity scoring before evaluation of study photographs. After training effectiveness was verified, blinded pre-treatment and post-treatment study images were provided side by side in a randomized orientation. The evaluators were asked to identify which images were baseline and post-treatment, rate the overall improvement according to the Global Aesthetic Improvement Scale (GAIS), and score the number and depth of cellulite depressions in each image using the photonumeric scale consisted of the definitions in Table 1 (with the accompanying set of reference slides illustrating each of the scores).

End Points

The primary efficacy end point was a mean ≥1-point reduction in the 6-point (0–5) CSS for the study population, as determined by the independent physician assessment of subject images obtained before and after treatment for the 3-month and 1-year time points. The powered secondary end point was a ≥1 grade improvement in cellulite severity grade (none, mild, moderate, severe) among >60% of treated subjects. An additional secondary efficacy measure was an improvement in subject appearance according to a GAIS. Subject satisfaction and subject pain ratings were also collected.

Adverse events (AEs) were recorded at each subject assessment. The primary safety end point for the study was the absence of device-related serious AEs. Formal data safety monitoring board (DSMB) reviews of all collected safety data were conducted after the 3-month and 1-year follow-up assessments.

TABLE 7. Subject Satisfaction

Rating, N (%)	*Baseline, N = 55*	*14 Days, N = 54*	*1 Month, N = 54*	*3 Months, N = 55*	*6 Months, N = 52*	*1 Year, N = 50*
Very satisfied	0 (0.0)	12 (22.2)	13 (24.1)	21 (38.2)	21 (40.4)	23 (46.0)
Satisfied	0 (0.0)	25 (46.3)	30 (55.6)	26 (47.3)	25 (48.1)	24 (48.0)
Neutral	0 (0.0)	16 (29.6)	9 (16.7)	7 (12.7)	4 (7.7)	3 (6.0)
Unsatisfied	27 (49.1)	1 (1.9)	2 (3.7)	1 (1.8)	2 (3.8)	0 (0.0)
Very unsatisfied	28 (50.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

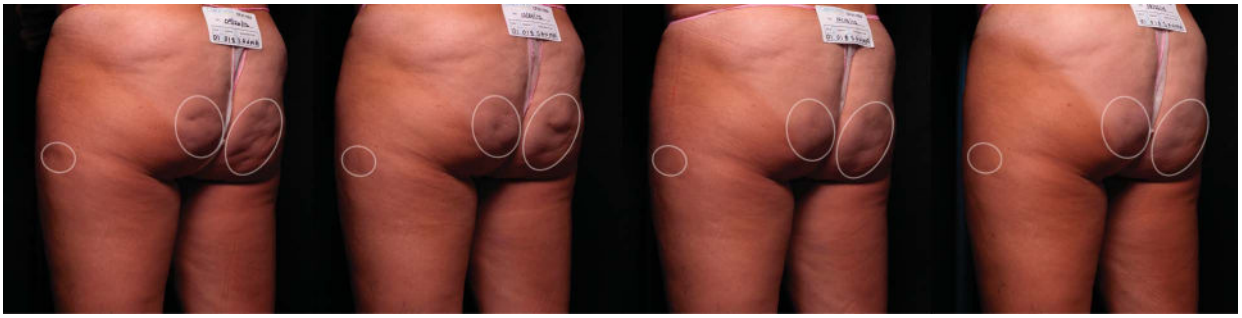

Figure 3. Images of a study subject showing (left to right) baseline cellulite severity (CSS = 4) and improvements after 1 and 3 months and 1 year (CSS = 2, GAIS = much improved).

Statistical Analysis

Using data from feasibility studies, a sample size of 44 subjects was calculated to be necessary to obtain a power of at least 90% to detect a mean 1-point difference on the CSS, and 33 subjects would provide 90% power to reject the null hypothesis stated for the powered secondary end point. Assuming a 20% to 25% dropout rate, 55 subjects were therefore enrolled.

The primary analysis was based on the intent-to-treat population. Independent physician evaluation reliability was calculated by percent agreement, and intrarater reliability was also assessed by intraclass correlation coefficient calculations based on Shrout and Fleiss.[15] A paired *t*-test with a critical 1-sided alpha level of 0.025 was used for the mean CSS change, and a 1-sided 97.5% confidence limit for the CSS reduction was used in comparison with the primary 1-point reduction end point. A 1-sided alpha level of 0.05 was used for the powered secondary end point of the rate of subjects achieving at least 1 cellulite severity grade reduction from baseline. A 1-sided 95% Wilson lower confidence limit[16] for the cellulite severity grade improvement rate was reported in comparison with the target rate of 60%.

Data poolability across investigational sites was assessed with univariate regression. A multivariate regression analysis of the primary end point was completed. Cellulite Severity Scale change from baseline was adjusted for investigational site, subject age, race, skin type, baseline BMI, and percent of body weight change as covariates. The multiplicity was not adjusted for the primary and secondary efficacy end points, as the powered secondary end point hypothesis was tested only after the primary null hypothesis was rejected, and no hypothesis testing was performed for other secondary end points. Longitudinal analysis was conducted for the primary and powered secondary efficacy end points for comparison of the 3-month and 1-year results, with Bonferroni adjustment[17] used for 95% confidence limits and *p* value calculations. All statistical processing was performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

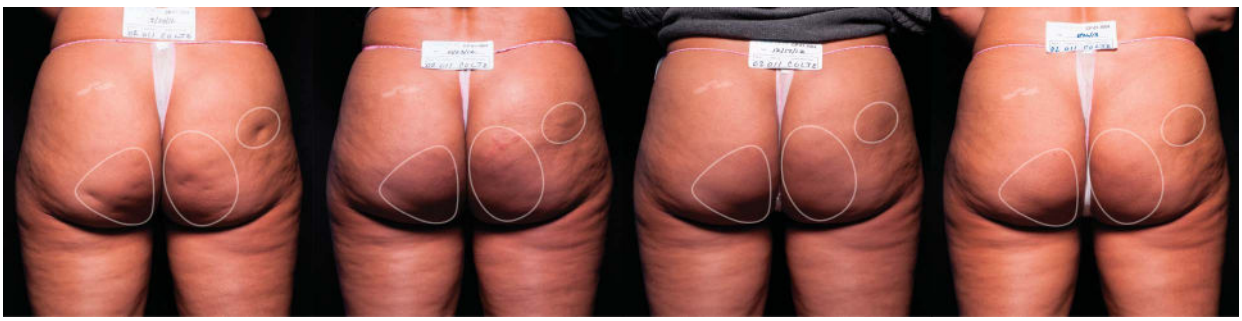

Figure 4. Images of a study subject showing (left to right) baseline cellulite severity (CSS = 4) and improvements after 1 and 3 months and 1 year (CSS = 0, GAIS = very much improved).

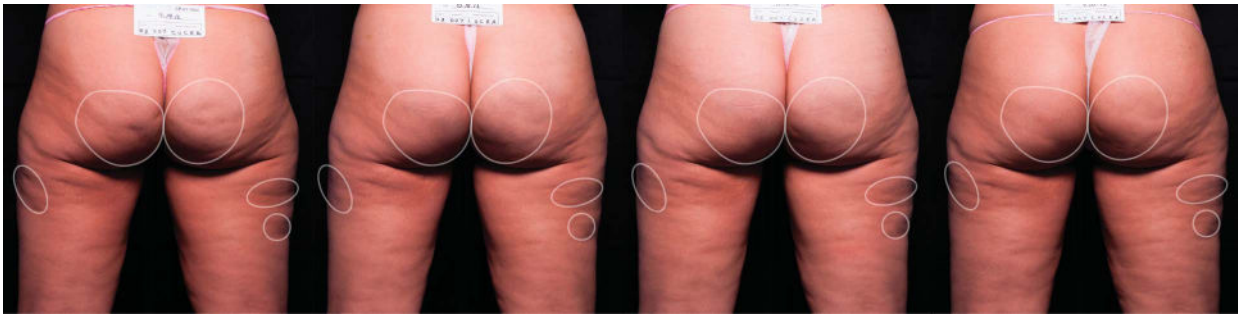

Figure 5. Images of a study subject showing (left to right) baseline cellulite severity (CSS = 3) and improvements after 1 and 3 months and 1 year (CSS = 1, GAIS = much improved).

Results

Demographics and Treatment

Fifty-five subjects were enrolled in the study and underwent treatment. A summary of the demographics and baseline characteristics of the treated subjects is provided in Table 2. The average subject age was 42 years (range, 25–55 years), and the mean BMI was 25.2 kg/m^2 (range, 18.3–34.6 kg/m^2). The study subjects represented a broad distribution of Fitzpatrick skin types. All 55 subjects returned for the 3-month follow-up visit, and 50 returned for the 1-year follow-up.

Each subject underwent a single treatment with the vacuum-assisted precise tissue release system. Treatment parameters are summarized in Table 3. The total mean procedure time from the start of vacuum capture of the treatment areas for anesthesia infiltration to the release of the vacuum capture for the last site was 42 minutes (range, 25–63 minutes), and the mean treatment time from the start of vacuum capture of the first site to the release to the last site was 18 minutes (range, 5–37 minutes). These times generally depended on the number of released sites per subject, which ranged from 6 to 25 (mean, 13 sites). Among the treated sites, 86% were completed at the primary depth of 6 mm and 14% at 10 mm. A mean of 290 mL of anesthetic solution was used per subject (range, 120–480 mL), representing a mean lidocaine dose of 4.4 mg/kg (range, 1.9–6.7 mg/kg). There were no AEs associated with the use of local anesthesia.

Independent Assessment

Each physician evaluator was individually trained by the evaluation monitor on the scoring of the depth and number of depressions using the definitions in Table 1 and the set of associated reference photographs for each of the scores. Once training effectiveness was verified, the physician evaluator was shown the randomized before and after photographs for each of the study subjects. Five subject slides were used to verify training, and 10 subject slides were randomly selected and replicated in the evaluation set to assess training and intrarater reliability. The physician evaluators were unaware of the replicated training or evaluation slides. Training reliability was 100% for

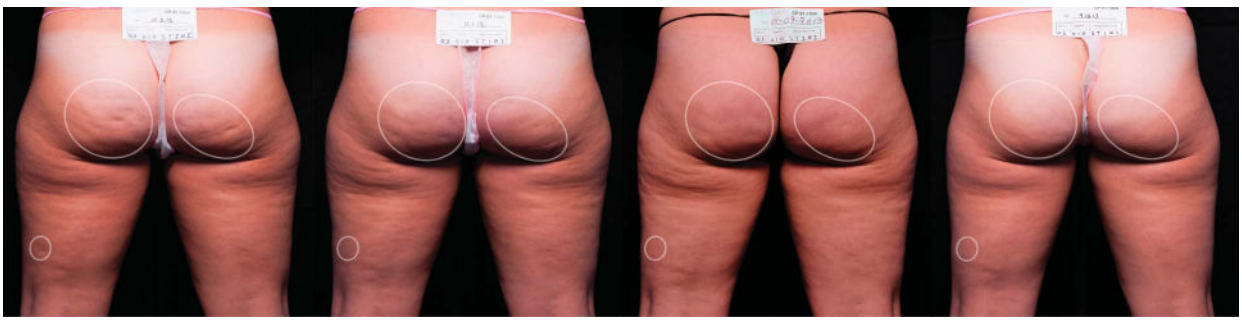

Figure 6. Images of a study subject showing (left to right) baseline cellulite severity (CSS = 4) and improvements after 1 and 3 months and 1 year (CSS = 1, GAIS = very much improved).

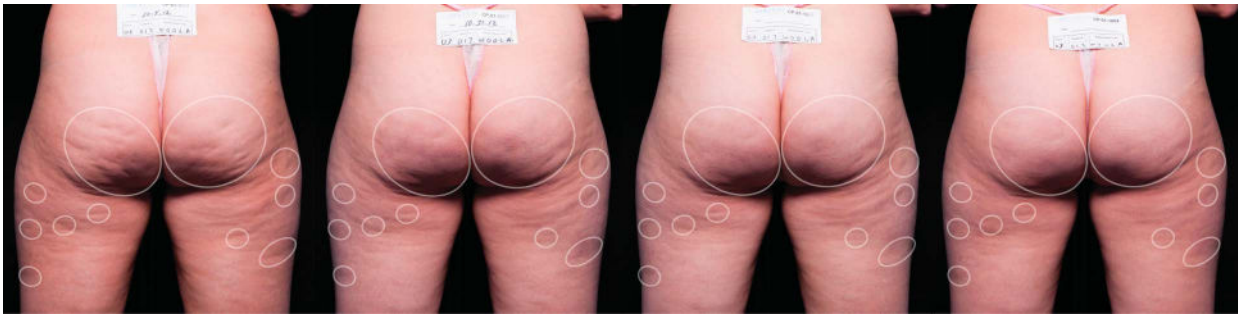

Figure 7. Images of a patient showing (left to right) baseline cellulite severity (CSS = 4) and improvements after 1 and 3 months and 1 year (CSS = 2, GAIS = very much improved).

the selection of the correct before/after and 90% for the cellulite severity scoring. Overall intrarater reliability was 97% for selection and 78% for scoring. Interrater reliability was 99% for selection, and the interclass coefficients for the scoring are summarized in Table 4. Collectively, these reliability measures validated the CSS developed for this study and the evaluation protocol methodology. This is further evidenced by identical baseline scores ($p < .0001$) for the separately conducted 3-month and 1-year evaluations.

Efficacy

The primary and powered secondary end points were met by large margins (Table 5). The mean (SD) CSS score before treatment was 3.4 (0.8), decreasing 2.1 (0.7) points at the 3-month follow-up ($N = 55$; $p < .0001$) and 2.0 (0.8) points at the 1-year follow-up ($N = 50$; $p < .0001$), meeting the primary efficacy end point for both evaluations. The number of subjects that improved ≥1 point in cellulite severity grade (none, mild, moderate, and severe) at 3 months was 51 of the 55 subjects (92.7%) and 47 of the 50 subjects (94.0%) at 1 year, exceeding the powered secondary end point performance goal of 60%.

A worst case imputation analysis (missing values counted as failures) demonstrated no effect of the 5 subjects that missed the 1-year follow-up on either end point. Univariate regression analysis was completed to determine any effect of baseline cellulite severity, investigational site, subject age, race, skin type, baseline BMI, and percent of body weight change from baseline. Only the baseline cellulite severity had a significant influence on effect size ($p = .0011$). The subjects that scored a baseline value of 1 or 2 (mild cellulite, $N = 4$) from the independent evaluation had the smallest effect size. No significant interactions between tested covariates were found. Longitudinal analysis demonstrated no significant difference in treatment effect seen at 3 months and 1 year, demonstrating the durability of response.

The additional secondary measures confirmed the efficacy and tolerability of the vacuum-assisted precise release system. The overall frequency of correctly selected pre-treatment and post-treatment images at 3 months was 98% and 99% at 1 year, which exceeded the target performance goal of 80%. The results of the physician GAIS assessments are summarized in Table 6. At 3 months, 54 of the 55 subjects (98.2%) were determined to have noticeable improvement, of which 74.5% were considered to be markedly improved or better. At 1 year, all 50 subjects (100%) were determined to have noticeable improvement, and 72% were characterized as having marked improvement or better.

Self-reported subject satisfaction with the appearance of cellulite according to a 5-point Likert-type scale after treatment is shown in Table 7. Subject satisfaction was 0% at baseline, increasing to 85% at 3 months, 88% at 6 months, and 94% at 1 year, demonstrating no subject-perceived decrease in efficacy over time. Several subject photographic panels are provided in Figures 3–7, which demonstrate the control and consistency of the study photography and the durability of the treatment results for up to 1 year.

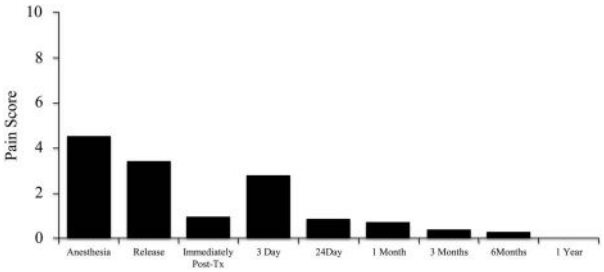

Figure 8. Subject reports of mean pain severity at various time points throughout the study.

Subject responses to pain severity at various time points throughout the study are depicted in Figure 8. The highest level of procedural pain occurred during anesthetic infiltration and was moderate (mean score, 4.5), which means that pain scores were low at each subsequent follow-up evaluation with 71% of subjects reporting pain scores ≤3 at Day 3 and >95% of subjects rating pain ≤3 thereafter. There was no report of pain at the 1-year follow-up. The majority of subjects reporting pain described it as "aching," which occurred only with touch or pressure. Rapid recovery after the treatment was evidenced by 49% of subjects taking no postprocedure analgesic medication. Post-treatment pain was managed with acetaminophen or ibuprofen in only 51% of subjects for an average of 1.5 days.

Safety

Expected treatment effects were recorded, with none meeting the definition of an AE (Table 8). The most common effects were bruising, fluid accumulation, areas of palpable softness or firmness, tingling, and soreness. All were mild in severity, of short duration, and all resolved spontaneously. There were only 3 AEs considered to be possibly device-related, treatment-related, or study-related, which were scratching because of pruritus at a treatment location resulting in a sore, itching related to the compression garments, and a slip during a study-related photography session. The DSMB concluded that device-related AEs were all minor in severity.

There were a total of 23 unrelated AEs reported by 18 subjects, including colds, upper respiratory infection, bronchitis, nausea/vomiting, diarrhea, constipation, upset stomach ($N = 11$), seasonal allergy ($N = 1$), hypercholesterolemia ($N = 2$), toothache/tooth abscess ($N = 2$), falls/accidents ($N = 3$), numbness/tingling after elective colonoscopy ($N = 1$), dizziness ($N = 1$), headache ($N = 2$), and rash ($N = 1$). The relatedness to the investigational device or protocol and the severity were assessed by the DSMB. All were mild or moderate in severity, except 1 accidental injury resulting a torn anterior cruciate ligament and fractured tibia requiring surgical repair.

Discussion

Currently, there are several available options for the treatment of cellulite including noninvasive lasers,[18,19] acoustic wave therapy,[20,21] massage

TABLE 8. Expected Treatment Effects

Observation	*14 Days, N = 54*	*1 Month, N = 54*	*3 Months, N = 55*	*6 Months, N = 52*	*1 Year, N = 50*
Anxiety	1	2	0	0	0
Ecchymosis/bruising	37	5	0	0	0
Hematoma	4	2	0	0	0
Hemosiderosis	19	8	1	0	0
Hyperpigmentation	1	2	0	0	0
Hypopigmentation	0	0	0	0	0
Numbness, tingling	2	5	2	0	0
Palpable areas of firmness	3	8	8	6	2
Palpable areas of softness	14	21	6	0	0
Petechiae or purpura	1	2	0	0	0
Redness, erythema, or rash	1	1	0	0	0
Red spots	0	2	0	0	0
Soreness	19	15	0	1	0

therapy,[22,23] and radiofrequency devices.[24,25] Although published studies of these therapies report varying degrees of efficacy, a recent review suggests that the use of these treatments may provide only minor short-term improvements in the appearance of cellulite.[6] In addition, a common disadvantage is the need for multiple treatment sessions ranging from 3 to 6 treatments over 4 weeks,[18,20] once or twice weekly for 7 weeks,[21–23] or once every 1 to 2 weeks for 8 to 12 weeks.[24,25] Single-treatment options include minimally invasive laser[13] and needle-based subcision release procedures[11,12]; however, the depth and specific area of release are variable with these technologies and dependent on physician technique, which can lead to inconsistent outcomes.

The vacuum-assisted precise tissue release system described here was highly effective for improving the appearance of cellulite. This was defined as achieving a mean ≥1 point reduction in the 0 to 5 point CSS (primary end point; 2.1 and 2.0 points at 3 months and 1 year, respectively), and improvement of1 grade or more in severity grade (none, mild, moderate, and severe) in >60% (powered secondary end point; 93% and 94% at 3 months and 1 year, respectively) of treated subjects as determined by independent physician assessment of subject photographs taken before and after treatment. The number of subjects with improvements (including improved, much improved, and very much improved) according to GAIS scores at 3 months and 1 year were 98.2% and 100%, respectively. Self-reported subject satisfaction with the appearance of cellulite at 3 months and 1 year were 85.5% and 94%, respectively. Together, these results indicate that the vacuum-assisted precise tissue release system is highly effective for treating the appearance of cellulite, and the aesthetic improvement is durable, persisting for at least 1 year.

Treatment with the vacuum-assisted precise tissue release system was also safe. The level of reported pain was moderate (a mean score of 4.5 on a 0–10 scale) during anesthetic infiltration, which is consistent with similar cosmetic procedures. Treatment-related AEs were mild and resolved with no sequelae. As there were no unexpected device-related AEs and no device-related serious AEs, the primary safety end point for the study was also achieved.

Conclusion

The results of this multicenter study showed a single treatment with a novel controlled tissue release system improved the appearance of cellulite on the thighs and buttocks through 12 months of follow-up with minimal AEs. This study supported the FDA clearance of the device as an effective and safe treatment for the long-term improvement in the appearance of cellulite on the buttocks and thighs with no diminishment of benefit for up to 1 year.

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References

1. Sainio EL, Rantanen T, Kanerva L. Ingredients and safety of cellulite creams. Eur J Dermatol 2000;10:596–603.
2. Hexsel D, Hexsel CL, Weber MD. Social impact of cellulite and its impact on quality of life. In: Goldman MP, Hexsel D, editors. Cellulite pathophysiology and treatment. 2nd ed. London: Informa; 2010.
3. Terranova F, Berardesca E, Maibach H. Cellulite: nature and aetiopathogenesis. Int J Cosmet Sci 2006;28:157–67.
4. Omi T, Sato S, Kawana S. Ultrastructural assessment of cellulite morphology: clues to a therapeutic strategy? Laser Ther 2013;22: 131–6.
5. Hexsel D, Abreu M, Rodrigues Y, et al. Side-by-side comparison of areas with and without cellulite depressions using magnetic resonance imaging. Derm Surg 2009;35:1–7.
6. Wanner M, Avram M. An evidence-based assessment of treatments for cellulite. J Drugs Dermatol 2008;7:341–5.
7. Emanuele E. Cellulite: advances in treatment: facts and controversies. Clin Dermatol 2013;31:725–30.
8. Orentreich DS, Orentreich N. Subcutaneous incisionless (subcision) surgery for the correction of depressed scars and wrinkles. Dermatol Surg 1995;21:543–9.
9. Toledo L. Syringe liposculpture: a two-year experience. Aesth Plast Surg 1991;15:321–6.
10. Alam M, Omura N, Kaminer MS. Subcision for acne scarring: technique and outcomes in 40 patients. Dermatol Surg 2005;31:310–7.
11. Hexsel DM, Mazzuco R. Subcision: a treatment for cellulite. Int J Dermatol 2000;39:539–44.

12. Hexsel D, Dal'Forno T, Soirefmann M, et al. Reduction of cellulite with subcision. In: Alam M, Pongprutthipan M, editors. Body rejuvenation. New York: Springer; 2010.

13. DiBernardo B, Sasaki G, Katz BE, et al. A multicenter study for a single, three-step laser treatment for cellulite using a 1440-nm Nd:YAG laser, a novel side-firing fiber, and a temperature-sensing cannula. Aesthet Surg J 2013;33:576–84.

14. Klein JA. Tumescent technique for regional anesthesia permits lidocaine doses of 35 mg/kg for liposuction: peak plasma lidocaine levels are diminished and delayed 12 hours. J Dermatol Surg Oncol 1990;16: 248–63.

15. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. Psychol Bull 1979;86:420–8.

16. Agresti A, Coull BA. Approximate is better than "exact" for interval estimation of binomial proportions. J Am Stat Assoc 1998;52: 119–26.

17. Dunn J. Multiple comparisons among means. J Am Stat Assoc 1961;56: 52–64.

18. Truitt A, Elkeeb L, Ortiz A, et al. Evaluation of a long pulsed 1064-nm Nd:YAG laser for improvement in appearance of cellulite. J Cosmet Laser Ther 2012;14:139–44.

19. Jackson RF, Roche GC, Shanks SC. A double-blind, placebo-controlled randomized trial evaluating the ability of low-level laser therapy to improve the appearance of cellulite. Lasers Surg Med 2013;45:141–7.

20. Adatto M, Adatto-Neilson R, Servant JJ, et al. Controlled, randomized study evaluating the effects of treating cellulite with AWT/EPAT. J Cosmet Laser Ther 2010;12:176–82.

21. Russe-Wilflingseder K, Russe E, Vester JC, et al. Placebo controlled, prospectively randomized, double-blinded study for the investigation of the effectiveness and safety of the acoustic wave therapy (AWT) for cellulite treatment. J Cosmet Laser Ther 2013;15:155–62.

22. Kutlubay Z, Songur A, Engin B, et al. An alternative treatment modality for cellulite: LPG endermologie. J Cosmet Laser Ther 2013;15:266–70.

23. Güleç AT. Treatment of cellulite with LPG endermologie. Int J Dermatol 2009;48:265–70.

24. Alexiades-Armenakas M, Dover JS, Arndt KA. Unipolar radiofrequency treatment to improve the appearance of cellulite. J Cosmet Laser Ther 2008;10:148–53.

25. Manuskiatti W, Wachirakaphan C, Lektrakul N, et al. Circumference reduction and cellulite treatment with a TriPollar radiofrequency device: a pilot study. J Eur Acad Dermatol Venereol 2009;23:820–7.

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