Directions for Use (DFU)(US)

TissuGlu® Surgical Adhesive

CAUTION: Federal Law (USA) Restricts this device for sale by or on the order of a licensed physician or properly licensed practitioner.

DESCRIPTION

TissuGlu® is a single-use, urethane based surgical adhesive. In its pre-polymerized form, TissuGlu® Surgical Adhesive is a viscous liquid that requires no mixing during preparation. TissuGlu® is applied in pre-measured drops to the tissue surfaces to be adhered using the Multi-Tip™ Pivot Head. The tissue surfaces are then approximated for several minutes to allow the moisture in the tissue to initiate the curing process. The cured product acts as a bonding agent between the tissue layers, eliminating dead space in the wound. TissuGlu® is designed to provide a strong bond for a period of time sufficient for natural healing to occur and eventually degrades over time, breaking down into benign absorbable components.

INDICATIONS FOR USE

TissuGlu® Surgical Adhesive is indicated for the approximation of tissue layers where subcutaneous dead space exists between the tissue planes in abdominoplasty.

HOW SUPPLIED

TissuGlu® Surgical Adhesive is packaged sterile, in a pre-filled, single-use, applicator that contains 5 ml of adhesive. 5 ml of adhesive will cover approximately 740 sq cm when applied using the Multi-Tip™ Pivot Head applicator as supplied. There is one (1) unit per box. Each unit is supplied sterile in a sealed applicator tray. The sealed applicator tray is packaged in a foil pouch. The foil pouch is a moisture barrier only. The contents within the sealed tray are sterile. Do not place the sealed applicator tray in the sterile field. TissuGlu®, as supplied with the Multi-Tip™ Pivot Head, is designed for use in surgical flaps greater than five (5) cm^2 in order to properly accommodate the dimensions of the Multi-Tip™ Pivot Head.

EXPIRATION

DO NOT USE AFTER THE DATE PRINTED ON THE PACKAGING

REUSE

Do not attempt to reuse the product after opening the package or partial use of the adhesive. Do not resterilize. Resterilization will render the applicator inoperable. The applicator will likely become inoperable due to the curing of the adhesive within the applicator cartridge within 10-15 minutes of activation thus rendering the product un-reusable. Risk of contamination due to breach of sterility exists if the product is removed from the package and removed from the sterile field prior to use.

STERILITY

TissuGlu® Surgical Adhesive is originally sterilized by gamma irradiation. Do not resterilize.

PACKAGE INTEGRITY / DISPOSAL

Do not use if package is opened or damaged. The foil pouch is a moisture barrier only. Do not place the sealed applicator tray in the sterile field. Properly discard any unused material following completion of medical procedure. Used applicator(s) should be considered biohazardous and treated appropriately as medical waste. Do not recycle any part of the applicator.

STORAGE

TissuGlu® Surgical Adhesive should be stored at room temperature. Normal storage should not exceed 25ºC, and units should not be exposed to temperatures above 45ºC at any time. Keep away from fluids and excessive humidity.

CONTRAINDICATIONS

- Do not use in patients with known or suspected allergies to urethane-based or isocyanate-containing products.

WARNINGS

- Do not use TissuGlu® Surgical Adhesive in patients who have had prior exposure to TissuGlu®. Immunological response associated with repeat TissuGlu® exposure has not been studied.

- The effectiveness for the treatment of patients with BMI > 28 has not been established. Higher BMI patients have a propensity for fluid accumulation and may have an increased risk of seroma formation.

- Effectiveness was not observed in weight loss patients undergoing abdominoplasty. Weight loss patients have a propensity for fluid accumulation and may have an increased risk of seroma formation and aspiration.

PRECAUTIONS

- The safety and effectiveness of TissuGlu® has not been established in pediatric patients (22 years of age and younger).
- Do not use in conjunction with other wound adhesives or sealants, or other fluid preparations. Such use may affect the efficacy of the product.
- Do not use lavage or other wetting procedures on the adhesive after adhesive application. Such use may affect the efficacy of the product.
- Do not use in conjunction with liposuction within the field of application or other surgical techniques that may disrupt the planes of tissue to be adhered. Such use may affect the efficacy of the product.
- Do not apply greater or lesser volume than the recommended volume/spacing of adhesive to surgical site. Greater volume per area of adhesive may affect the efficacy of the product.
- If TissuGlu® is used as an adjunct to drains, care should be taken to avoid applying adhesive directly in contact with the drain(s), as the adhesive may impact the efficacy of the drain if the drain perforations are occluded.
- The external Foil pouch is a moisture barrier only. The contents of the sealed applicator tray are sterile. Do not place the sealed applicator tray in the sterile field.
- Inspect sterile package prior to use. Do not use if the sterile package is damaged or open.
- TissuGlu® Surgical Adhesive is intended for single use only. Do not resterilize or reuse.
- If applicator appears damaged do not use and dispose of safely.
- Use appropriate personal protective equipment during use of the product.
- TissuGlu® Surgical Adhesive should not be applied or exposed to the skin or eye. If contact with the skin or eye occurs, wipe the area with a dry cloth to absorb all of the spilled material and then flush the area copiously with saline or water and seek appropriate medical attention.
- Care should be used in preparation and use of TissuGlu® Surgical Adhesive to ensure adhesive does not contact unwanted tissues or surfaces.
- If adhesive is spilled onto unwanted surfaces, wipe spill immediately using alcohol or surgical towels. Other cleaning solutions such as saline or water are not recommended for cleaning/wiping as they may accelerate the curing process.
- Use caution when disposing of towels/wipes that are contaminated with adhesive to ensure no unwanted contact with other surfaces.
- After adhesive has been dispensed onto the tissue and the flap is positioned, care should be used to avoid re-elevation/manipulation of the tissue flap. Re-elevation/re-positioning of flap may affect the efficacy of the product.
- Consideration should be taken in the use of TissuGlu® as there is a possibility that cured TissuGlu® may be extruded similar to suture extrusion.
- Prior to use, adhesive shall not be exposed to liquids or excessive humidity as moisture accelerates the curing process and may affect the efficacy of the product.
- Consideration should be taken in the use of TissuGlu® with patients with known wound healing issues or in areas of poor blood supply as delayed absorption or healing may occur.

DIRECTIONS FOR USE

Read the instructions for use prior to application. The adhesive should be applied after the tissue flap has been resected and hemostasis has been obtained. The tissue flaps must be surgically prepared for final closure immediately after application of the adhesive to the field.

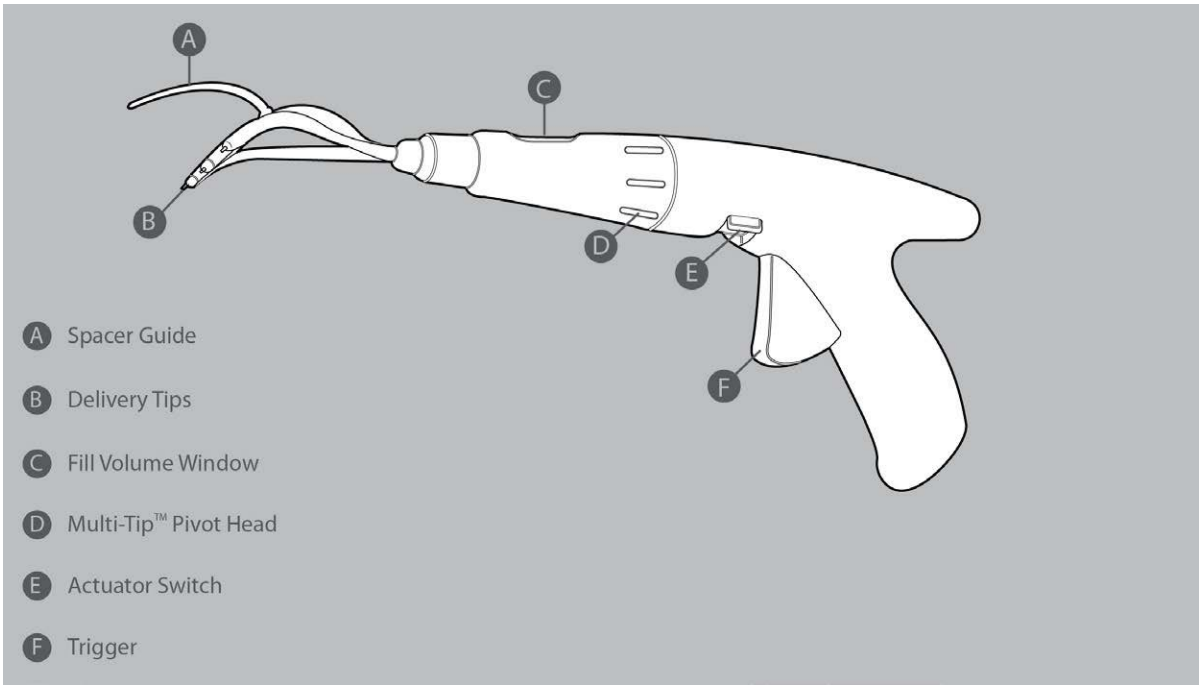
NOTE: the incision for the umbilical inset should be completed and an adequate tunnel established for that structure prior to adhesive application. This is done at the point in the operation when the surgeon determines that the abdominal flap may be safely inset and the wound closed. The surgeon should be satisfied that hemostasis is adequate, contour is adequate, and that no re-elevation of the flap is required once it is approximated (except in the case of an unexpected event that may impact the outcome of the surgery). The following steps shall be performed before preparation of the applicator:

1. The flaps should be surgically prepared for final closure.

   NOTE: secure a traction suture to umbilicus and pass suture tail through new umbilicus incision so that it may be quickly passed through the flap.

2. Prior to application of the adhesive, the field should be positioned as horizontal as possible in order to prevent running of the adhesive upon application. Failure to position the field horizontally may cause the adhesive to migrate upon application, lessening its effectiveness.

3. Drains, if utilized, should be placed prior to application of the adhesive and parallel to the suture line and away from the adhesive field, as direct contact with adhesive may affect the efficacy of the drain.



PREPARATION OF THE TISSUGLU® APPLICATOR

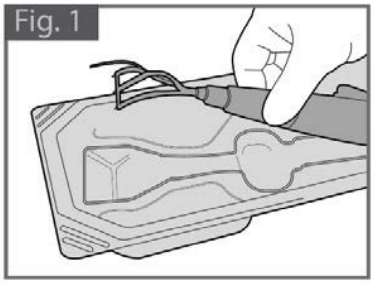
1. Remove pouched applicator from box.
2. Open the sealed foil pouch from the corners. Carefully remove the sealed applicator tray from the pouch.

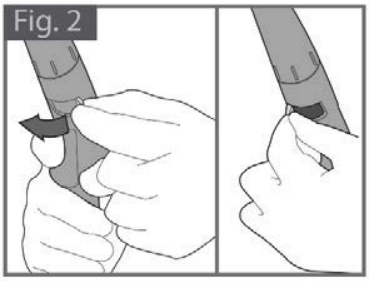
   CAUTION: The Foil pouch is a moisture barrier only. The contents of the sealed applicator tray are sterile. Do not place the sealed applicator tray in the sterile field.

3. Using appropriate surgical sterile technique, deliver applicator to the sterile field by peeling back the lid while gripping the bottom of the tray.
4. Using sterile technique, remove the plastic tray and retainer and place in the sterile field. Retainer may be used in the sterile field as a “priming reservoir”.

5. Using sterile technique, place fingers around the neck of the applicator and remove from the tray. Do not remove applicator by the Multi-Tip™ Pivot Head; care should be used not to damage Multi-Tip™ Pivot Head upon removal from tray. (Fig. 1)
6. Hold applicator with Multi-Tip™ Pivot Head up and move the Actuator Switch to the open position; the indicator will move from red to white when fully open and ready for priming. (Fig. 2)

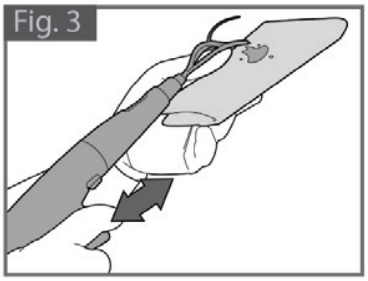
   NOTE: If Multi-Tip™ Pivot Head is damaged or disfigured do not use applicator, dispose of safely.

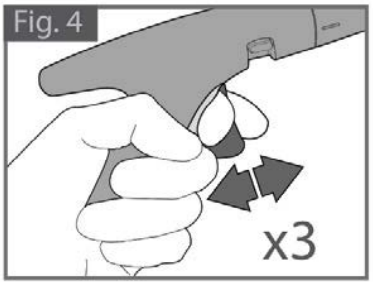




PRIMING THE APPLICATOR

1. The applicator must be primed to remove any air from the internal cartridge for optimal results.
2. Hold the applicator with the Multi-Tip™ Pivot Head up and position over the plastic retainer or surgical towel. Press the trigger multiple times until adhesive begins to be expelled. (Fig. 3)
3. Once adhesive begins to be expelled, press the trigger 3 additional times to ensure the proper volume is being dispensed. The applicator is now ready for immediate use. (Fig. 4)



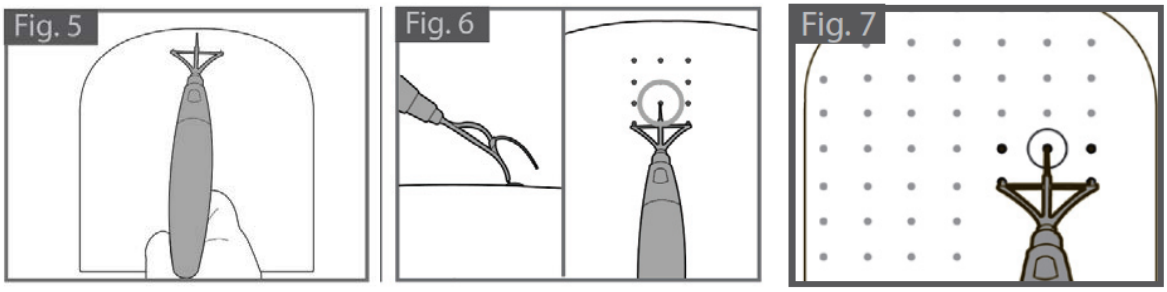


DISPENSING TISSUGLU® SURGICAL ADHESIVE

NOTE: Application of TissuGlu® Surgical Adhesive shall occur immediately prior to tissue approximation and flap closure.

1. While dispensing the adhesive, the Multi-Tip™ Pivot Head shall be placed lightly onto the surface of the tissue when the trigger is actuated, using caution not to bend or damage the Multi-Tip™ Pivot Head or penetrate the tissue. (Fig. 5)
2. To dispense a set of drops on the tissue, squeeze the trigger fully. Release the trigger and move the Multi-Tip™ Pivot Head to the next location utilizing the Spacer Guide for positioning. (Fig. 6)
3. Dispense drops of adhesive in a grid pattern throughout the exposed surgical area, beginning in a superior corner and moving downward and across. The Multi-Tip™ Pivot Head may be rotated to facilitate access to the tissue plane.

   NOTE: Avoid dispensing adhesive along the anticipated suture line area. (Fig. 7)



4. Continue dispensing until the desired application area is completely filled with the array of adhesive drops. One applicator will cover an area approximately 740 sq cm in size. If the area expected to be covered is larger than 700 sq cm it is recommended that an additional applicator be ready for use prior to dispensing. Although a second unit may be required in larger patients, product usage should not exceed one unit (5 ml) per 70 kg body weight.
5. The approximate amount of adhesive remaining in the applicator may be visualized through the Fill Volume Window. When the adhesive approaches the indicator line on the Fill Volume Window there is approximately 25% of the adhesive left in the applicator.
6. In case of idling of the applicator, re-prime (refer to the section "Priming the applicator" above) the applicator before proceeding to application. The applicator may be idled for no more than 10-15 minutes before the applicator may become unusable due to the adhesive curing within the applicator. Make sure that adhesive is flowing evenly from all three tips of the Multi-Tip™ Pivot Head after re-priming prior to resuming use.
7. Lay the flap into position and temporarily secure the incision line with towel clips or other fixation such as a staple line. NOTE: Minimal disruption of the flap should occur during the remaining steps of the procedure.
8. Close the wound per standard of care.
9. When the application is complete, the applicator(s) and any remaining adhesive shall be discarded. Use care when disposing of any components that have come in contact with the adhesive.

RECOMMENDATIONS

1. After the adhesive has been applied, it is recommended that slight pressure be placed over the entire area to assist with tissue to tissue contact between the flap and the fascia layer. It is not required to apply pressure throughout the curing process, it is only recommended for a few seconds just after opposition of the flaps to help ensure contact between the tissues.
2. Complete curing time for the adhesive averages 30-45 minutes. It is recommended that minimal movement of the patient occur during this time to allow for optimal adhesion.
3. During closing of incision line, care should be taken as not to grossly disrupt the tissue flaps. If it is suspected that the upper flap layer has become disrupted from the fascia layer, light additional pressure should be applied to the flap to ensure adhesion.

DISPOSAL

Used or partially used TissuGlu® applicators should be disposed of following proper biohazardous waste procedures. Care should be taken to ensure adhesive does not contact unwanted surfaces.

POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects (e.g., complications) associated with the use of the device, as well as with large flap procedures in general, include seroma formation, wound dehiscence, rash/redness, surgical site infection, necrosis, hypertrophic scarring, hematoma, wound complication, wound separation, and immunological reaction.

ADVERSE EVENTS THAT OCCURRED IN THE PIVOTAL CLINICAL STUDIES

In two controlled pivotal studies, one with a follow-up duration of 12 months and one with a follow-up duration of 3 months, the rates of post-operative wound-related complications were not significantly different between the test and control groups. Wound complications reported in the clinical studies included seroma formation, wound dehiscence, surgical site infection, skin necrosis, and hematoma. No unanticipated adverse device events were observed. Safety outcomes were equivalent regardless of whether or not drains were used in conjunction with the TissuGlu® Surgical Adhesive.

Combined Table of Adverse Events (Both Pivotal Trials)

	Control (N=114)		TissuGlu® (N=166)		
Adverse event	# events	# subjects	# events	# subjects	P-value*
Atelectasis	0	0 (0%)	3	2 (1.2%)	0.5155
Cellulitis	3	2 (1.8%)	1	1 (0.6%)	0.5687
Constipation	0	0 (0%)	1	1 (0.6%)	1.0000
Deep vein thrombosis	0	0 (0%)	1	1 (0.6%)	1.0000
Edema	0	0 (0%)	1	1 (0.6%)	1.0000
Hematoma	1	1 (0.9%)	7	7 (4.2%)	0.1476
Hypertrophic scar	3	3 (2.6%)	7	7 (4.2%)	0.7449
Infection	0	0 (0%)	1	1 (0.6%)	1.0000
Keloid scar	0	0 (0%)	1	1 (0.6%)	1.0000
Medication reaction	0	0 (0%)	1	1 (0.6%)	1.0000
Other (*999)	5	5 (4.4%)	8	8 (4.8%)	1.0000
Other Abdominal (*199)	4	4 (3.5%)	7	7 (4.2%)	1.0000
Other GI event (*399)	2	2 (1.8%)	5	4 (2.4%)	1.0000
Other neurologic (*299)	1	1 (0.9%)	0	0 (0%)	0.4071
Other pulmonary (*599)	1	1 (0.9%)	1	1 (0.6%)	1.0000
Other renal (*499)	2	2 (1.8%)	0	0 (0%)	0.1649
Pain	1	1 (0.9%)	0	0 (0%)	0.4071
Pneumonia	0	0 (0%)	1	1 (0.6%)	1.0000
Rash/Redness at treated area	6	6 (5.3%)	7	6 (3.6%)	0.5562
Rash/Skin irritation	2	2 (1.8%)	3	3 (1.8%)	1.0000
Seroma formation	20	17 (14.9%)	46	41 (24.7%)	0.0518
Skin Necrosis	4	4 (3.5%)	1	1 (0.6%)	0.1621
Surgical Site Infection (SSI)	1	1 (0.9%)	6	5 (3.0%)	0.4063
Urinary tract infection	0	0 (0%)	4	4 (2.4%)	0.1483
Wound complication	2	2 (1.8%)	5	5 (3.0%)	0.7045
Wound dehiscence	8	7 (6.1%)	12	12 (7.2%)	0.8121

Adverse event	Control (N=114)		TissuGlu® (N=166)		P-value*
	# events	# subjects	# events	# subjects	
Wound infection	0	0 (0%)	1	1 (0.6%)	1.0000
Wound separation	4	2 (1.8%)	3	3 (1.8%)	1.0000
Yeast Infection	1	1 (0.9%)	0	0 (0%)	0.4071
TOTAL	71	41 (36.0%)	134	83 (50.0%)	0.0273

*: P-values are from Fisher's exact test for the number of subjects experiencing an event.

199-other abdominal: suture granuloma, suture extruded, suture abscess, spitting suture; 299-other neurologic: visual disturbance; 399-other GI event: diverticulitis, ileus large intestine, ileus, possible pneumonia, diarrhea, stomach pain, biliary colic; 499 other renal: unable to void, kidney stone; 599 other pulmonary: asthma attack, airway congestion; 999-Other: laceration, patient diagnosed with metastatic cancer, gynecologic, musculoskeletal, infectious, hemostasis, immunological, physiological, gynecological, psychological.

Serious Adverse Events (Both Pivotal Trials): Seroma Formation

Study	Treatment Group	Days from surgery to event	Number of aspirations	Total volume aspirated (ml)	Other Adverse events	Response
Trial 1	TissuGlu®	61	NA	NA	1	No treatment
Trial 2	TissuGlu®	21	5	72	0	One drain placed
Trial 2	TissuGlu®	6	6	780 (left)	0	Two drains placed
		6	6	400 (right)	0	(See above)
Trial 2	TissuGlu®	13	7	1485	1	Two drains placed

SUMMARY OF CLINICAL STUDY INFORMATION

Four studies (two feasibility and two pivotal studies) were used to evaluate the safety and effectiveness of TissuGlu® Surgical Adhesive.

Summary of Clinical Studies

Clinical Study	Study Design	Objective	Number of Sites	Subjects (Study Duration)	Results
A. EU Feasibility Study (Drains +/- TissuGlu®in abdominoplasty)	Multicenter, open-label, prospective, randomized study comparing standard wound care (SWC) to SWC plus TissuGlu® treatment.	To determine the safety and preliminary efficacy of the TissuGlu® device	3	20 Test 20 Control (90 days)	Trend to decreased time of drain removal
B. EU Feasibility Study (TissuGlu® without Drains in abdominoplasty)	Multi-Center, Prospective, Non-Randomized, Non-Blinded study	To establish safety of TissuGlu® when used in abdominoplasty procedures without drains	2	31 Test (60 days)	Higher volume and number of aspirations in weight loss patients
C. Pivotal Study #1	Multicenter, randomized, prospective, controlled, single-blind study comparing SWC (control) to standard wound closure techniques plus TissuGlu® (test).	Superiority evaluation of the mean time to last drain removal between test and control.	5	100 Test (Drains+TissuGlu®) 50 Control (Drains only) (12 months)	No difference in time to drain removal
D. Pivotal Study #2	Multicenter, randomized, prospective, controlled unblinded study comparing SWC plus TissuGlu® without drains (test) compared to SWC with drains (control).	To TissuGlu® Non-inferiority evaluation of the number of invasive treatments between test and control.	5	66 test (TissuGlu®) 64 Control (Drains) (90 days)	See below

Summary of Pivotal Clinical Study 1:

A Prospective, Randomized, Controlled, Single-blind, Multicenter Clinical Trial Evaluating the Safety and Efficacy of the Cohera TissuGlu® Surgical Adhesive in the Management of Wound Drainage as Compared to the Standard of Care Closure Techniques Following Abdominoplasty.

Study Design: The clinical study was a pivotal, prospective clinical investigation of a randomized (2:1), controlled, single-blind, multicenter study comparing standard wound closure (SWC) techniques (control) to standard wound closure techniques plus TissuGlu® (test) during abdominoplasty. The study included 150 subjects across five centers. Follow-up visits were performed daily until drain removal, and then at post-operative days 14, 30, 60, and 90, and at 6 months and 1 year. Adverse events were adjudicated by the Clinical Events Committee (CEC).

The statistical analysis of the primary effectiveness endpoint (time to last drain removal) consisted of a between treatment group comparison of the mean time to last drain removal. The analyses of the primary endpoint, secondary endpoints, tertiary endpoints, and additional analyses were based on the Intent-to-Treat (ITT) population. Additional supportive analyses were performed on the per protocol (PP) population. The PP population includes all subjects treated as randomized.

The statistical analysis of the primary effectiveness endpoint consisted of a between-treatment group comparison of the mean time to last drain removal. A one-sided α=0.025 level of significance test of the following hypothesis of superiority of SWC plus TissuGlu® relative to SWC only was conducted using a two-sample t-test.

H0: $uT \geq uS$

Ha: $uT < uS$

where uT = the mean time to last drain removal for the SWC plus TissuGlu® treatment and uS is the mean time to last drain removal in the SWC only arm. The ITT analysis was conducted without missing value imputation.

Study Procedure: Prior to the abdominoplasty procedure, subjects were randomized to receive either Standard Wound Closure (SWC) or (SWC) plus TissuGlu® using a 2:1 (treatment: control) assignment. The test Group received TissuGlu® applied to one surface of the exposed tissue flap using the TissuGlu® delivery device followed by standard of care wound closure using sutures and placement of two size 12 Blake drains. The Control Group received standard of care closure using and placement of two size 12 Blake drains. The Blake drains were placed over the abdominal fascia, the tube delivered through stab incisions on the pubic area, and the drains were affixed with suture. Drain output was monitored and recorded from the first measurement.

Inclusion/Exclusion Criteria

Inclusion

- Be at least 18 years of age;
- Have a BMI ≤ 35;
- ≤ ASA2 -American Society of Anesthesiologists Physical Classification System (2=subject with mild systemic disease);
- Be in good general health in the opinion of the investigator with no conditions that would significantly impact wound healing as determined by medical history and review of recent concomitant medications;
- Be scheduled for at least one full thickness surgical incision of at least 20cm in length as part of an elective abdominoplasty. Surgeon must use electrocautery in the procedure;
- Be willing to follow instructions for incision care, wound exudate volume measurements, and diary completion as instructed by the investigator, and follow guidelines related to resumption of daily activities;
- Agree to return for all follow-up evaluations specified in this protocol;
- Agree not to schedule any additional elective surgical procedures that involve an incision on the abdomen, until their participation in this study is complete;
- Sign the informed consent.

Exclusion

- Pregnant or breast-feeding
- Previous abdominoplasty;
- Concurrent liposuction during procedure;
- Use of pain pumps;
- Have severe co-morbid conditions (e.g., heart disease);
- Known medical condition that results in compromised blood supply to tissues;
- Any condition known to effect wound healing, such as collagen vascular disease;
- Are currently a smoker or have smoked within 30 days of prescreening as determined by nicotine test;

- Be known to have a blood clotting disorder and/or be un-willing to discontinue anti-coagulation therapy- including aspirin;
- Diagnosis of diabetes with current medical treatment;
- Be receiving antibiotic therapy for pre-existing condition or infection;
- Have known personal or family history of keloid formation or hypertrophic scaring;
- Undergoing concurrent adjacent or congruent liposuction procedures;
- Concurrent use of fibrin sealants or other internal wound care devices;
- Be currently taking systemic steroids or immunosuppressive agents;
- Concurrent hernia repair greater than 6 cm and/or requiring the use of mesh;
- Mini-abdominoplasty (abdominoplasty without umbilical transposition);
- Have known or suspected allergy or sensitivity to any test materials or reagents; and
- Be participating in any current clinical trial or have participated in any clinical trial within 30 days of enrolment in this study.

Follow-up Schedule

Follow-up visits were performed daily until drain removal, and then at post-operative days 14, 30, 60, and 90, and at 6 months and 1 year.

Clinical endpoints

Primary Effectiveness: The primary effectiveness endpoint was identified as the mean time in days to last drain removal. The test device was determined to be effective if the results statistically demonstrated a 30% reduction in time to drain removal between for the test cases as compared to the control cases.

The criterion for determining when drain removal was appropriate was when less than 30 mL of fluid per drain in a 24 hour period was observed.

Secondary Endpoints: The secondary effectiveness variables measured on each subject were:
• Cumulative wound drainage until last drain removal
• Number of additional (unplanned) physician or clinic visits during the study
• Duration of hospital stay
• Incidence of seroma formation
• Number of additional complications
• Type of additional complications
• Number of additional procedures
• Type of additional procedures
• Dispenser performance evaluation
• VAS Pain score SF-8 Scores (Physical Component Scores (PCS), Mental Component Scores (MCS) and 8 domain sub-scale scores), measured daily until last drain removal, at day 14 and at day 30
Tertiary Endpoints:
• Number of wound complications, seroma formation, wound dehiscence, infection, skin necrosis, hematoma related to standard abdominoplasty procedures
• Other non-device related AEs/SAEs/UADEs
• Post-operative subject questionnaire

Safety: All enrolled subjects were included in the safety analyses. Adverse events were adjudicated by the Clinical Events Committee (CEC). The CEC-adjudicated data superseded the Investigator-reported adverse data for seriousness, relatedness, and adverse event type/description. For the purposes of safety analyses, adverse device effect is defined as any device-related adverse event. Any event that was classified by the CEC as either 'possibly related' or 'probably related' to the device was considered a device-related event.

Subject Accounting and Demographics

Subject Accounting

Disposition	SWC + Drains	SWC + Drains and TissuGlu®	All Subjects
Enrolled	50	100	150
Completed Daily Assessments	50	100	150
Completed 14-Day Visit	50	100	150
Completed 30-Day Visit	49	99	148
Completed 60-Day Visit	49	99	148
Completed 90-Day Visit	49	95	144
Completed 6-Month Visit	48	98	146
Completed 1-Year Visit	49	99	148
Discontinued	50	100	150
Completed Study	49	99	148
Withdrew Consent	0	0	0
Lost to Follow-up	1	1	2
Death	0	0	0
Other reason for discontinuation	0	0	0

Demographics and medical history The only notable difference in demographics between groups was the average age of patients in the control arm, which was 3.3 years older than the average age of patients in the TissuGlu® arm of the study. With the exception of 2 male subjects enrolled in the test arm, all patients in this study were female.

	SWC + Drains (N=50)	SWC + Drains and TissuGlu® (N=100)	P-value
Demographics			
Age (years)	44.9 ± 8.1 (50) (24.5,44.3,60.4)	41.6 ± 8.3 (100) (25.5,41.0,64.4)	0.0168
Gender			
Male	0/50 (0.0%)	2/100 (2.0%)	0.5526
Female	50/50 (100.0%)	98/100 (98.0%)	1.000
Ethnicity			
Hispanic or Latino	2/50 (4.0%)	5/100 (5.0%)	1.000
Not Hispanic or Latino	48/50 (96.0%)	95/100 (95.0%)	
Race			
American Indian or Alaska Native	1/50 (2.0%)	3/100 (3.0%)	1.000
Asian	2/50 (4.0%)	5/100 (5.0%)	1.000
Black or African American	11/50 (22.0%)	21/100 (21.0%)	1.000
Native Hawaiian or Other Pacific Islander	0/50 (0.0%)	0/100 (0.0%)	N/A
White	35/50 (70.0%)	68/100 (68.0%)	0.8536
Current Weight (kg)	69.8 ± 12.5 (50) (45.4,68.2,94.4)	71.0 ± 12.7 (100) (46	
Height (cm)	162.4 ± 6.5 (5) (152.0,162.0,181.0)	164.7 ± 7.8 (100) (152.0,165.0,211.0)	0.0687
Current BMI	26.2 ± 4.8 (50) (16.9,26.4,33.7)	25.8 ± 4.2 (100) (16.8,25.8,34.7)	0.5754
Medical History			

Any Major Medical History	26/50 (52.0%)	53/100 (53.0%)	1.0000
Any Surgical History	48/50 (96.0%)	92/100 (92.0%)	0.4970
Nicotine Use	0/50 (0.0%)	0/100 (0.0%)	N/A
Pregnancy	0/37 (0.0%)	1/80 (1.3%)	1.0000
Vital Signs/Physical Exam			
Body Temperature (^{o}F)	97.7 ± 0.7 (48) (96.2,97.6,98.9)	98.0 ± 0.9 (99) (95.4,98.0,100.0)	0.1105
Blood Pressure (mmHg)			
Systolic	120.8 ± 17.1 (50) (90.0,116.5,170.0)	121.7 ± 18.3 (100) (89.0,119.5,198.0)	0.6379
Diastolic	74.5 ± 9.1 (50) (55.0,74.0,100.0)	75.8 ± 13.2 (100) (44.0,75.0,164.0)	0.5402
Pulse (bpm)	70.0 ± 8.8 (50) (54.0,68.0,96.0)	71.1 ± 10.0 (100) 48.0,70.0,96.0)	0.3930
Any Body System Abnormalities	10/50 (20.0%)	25/100 (25.0%)	0.5450
Current Status			
Indication for Surgery			
Skin Laxity on abdomen	48/50 (96.0%)	100/100 (100.0%)	0.1096
Symptoms secondary to excess skin on abdomen	8/50 (16.0%)	24/100 (24.0%)	0.2968
Ventral hernia	1/50 (2.0%)	3/100 (3.0%)	1.0000
Weight Loss Subject	18/50 (36.0%)	36/100 (36.0%)	1.0000
Body Scars			
Abdominal	33/36 (91.7%)	59/68 (86.8%)	0.5367
Hypertrophic	0/36 (0.0%)	1/68 (1.5%)	1.0000
Keloid	0/36 (0.0%)	0/68 (0.0%)	N/A
None	14/50 (28.0%)	32/100 (32.0%)	0.7085

Summary statistics are presented as Mean ± SD (N), (Min, Median, Max) for continuous variable and Count/N (Percent) for categorical variables. P-values are from Wilcoxon test for continuous variables and Fisher's Exact test for categorical variables.

Primary Effectiveness Endpoint Results and Statistical Analysis

Subjects were considered enrolled in the study once they were randomized. All randomized subjects are included in the intent-to-treat (ITT) population and analyzed according to the treatment to which they were randomized. Additional supportive analyses were performed on the per-protocol (PP) population. The PP population included all subjects treated as randomized who do not have major inclusion/exclusion violations.

The mean days to last drain removal for TissuGlu® was 6.7 and the control was 6.6 based on the ITT population. There was no statistical difference between groups (p=0.5418) and the null hypothesis was not rejected. TissuGlu® did not have a significant effect on wound drainage in the first clinical study, which compared TissuGlu® with drains to a control group with drains and no TissuGlu®.

Primary Effectiveness Results (Intent-to-treat population)

	SWC + Drains (N=50)	SWC + Drains and TissuGlu® (N=100)	P-value
Time to last drain removal (days)	6.6 ± 6.8 (50) (1.0,4.0,29.0)	6.7 ± 6.3 (100) (1.0,5.0,31.0)	0.5418

Summary statistics are presented as Mean ± SD (N), (Min, Median, Max). P-value is from two-sample t-test.

Key Secondary Effectiveness Endpoints Results

Cumulative Wound Drainage Output

	SWC + Drains (N=50)	SWC + Drains and TissuGlu® (N=100)	P-value
Total Wound Drainage	622.1 ± 689.4 (5) (34.0,322.5,2611.0)	639.7 ± 783.5 (100) (26.0,407.5,5023.0)	0.3602
Weight Loss Subjects Only	834.5 ± 779.1 (18) (79.0,511.0,2611.0)	848.8 ± 1103.6 (36) 26.9,438.5,5023.0)	0.6268
Non-Weight loss Subjects Only	502.6 ± 614.4 (32) (34.0,238.0,2276.0)	522.1 ± 499.1 (64) (47.0,357.5,2694.0)	0.0720

Summary statistics are presented as Mean ± SD (N), (Min, Median, Max). P-values are from two-sample Wilcoxon test.

Safety: A total of 8 serious device-related adverse events occurred in 6 subjects, and a total of 39 non-serious device-related adverse events occurred in 32 subjects in the TissuGlu® treatment group. The majority of non-serious device-related adverse events were seroma formation. Serious device-related adverse events observed in the clinical study included hematoma, seroma, surgical site infection, and wound complication.

The clinical study included 12-months of follow-up to evaluate the potential for any late developing adverse events related to the slow absorption profile of the TissuGlu® adhesive.

Wound Complications

	SWC + Drains		SWC + Drains and TissuGlu®		
	Events	Subjects	Events	Subjects	P-value
Seroma Formation	11	9/50 (18.0%)	23	22/100 (22.0)	0.6711
Wound Dehiscence	8	7/50 (14.0%)	10	10/100 (10.0%	0.5855
Surgical Site Infection	1	1/50 (2.0%)	6	5/100 (5.0%)	0.6640
Skin Necrosis	4	4/50 (8.0%)	0	0/100 (0.0%)	0.0114
Hematoma	0	0/50 (0.0%)	4	4/100 (4.0%)	0.3017

Summary statistics are presented as Number of events and Number of subjects experiencing event (Percent of subjects). P- values are from Fisher's exact test for number of subjects experiencing an event.

Serious Device-Related Adverse Events

	SWC + Drains and TissuGlu® (N=100)	
	Events	Subjects
102-Hematoma	2	2 (2.0%)
108-Seoma formation	1	1 (1.0%)
110-Surgical Site Infection (SSI)	2	2 (2.0%)
111-Wound complication	1	1 (1.0%)
903-Cellulitis	1	1 (1.0%)
999-Other	1	1 (1.0%)
TOTAL	8	6 (6.0%)

Summary statistics are presented as Number of events and Number of subjects experiencing event (Percent of subjects).

999-Other: patient diagnosed with metastatic cancer

Non-Serious Device-Related Adverse Events

	SWC + Drains and TissuGlu® (N=100)	
	Events	Subjects
101-Edema	1	1 (1.0%)
102-Hematoma	2	2 (2.0%)
106-Rash/Redness at treated area	7	6 (6.0%)
108-Seroma formation	23	22 (22.0%)
110-Surgical Site Infection (SSI)	3	3 (3.0%)
111-Wound complication	2	2 (2.0%)
199-Other Abdominal	1	1 (1.0%)
TOTAL	39	32 (32.0%)

Summary statistics are presented as Number of events and Number of subjects experiencing event (Percent of subjects).

199-Other abdominal: suture granuloma

Serious Non-Device Related Adverse Events

	SWC + Drains (N=50)		SWC + Drains and TissuGlu® (N=100)		P-value
	Events	Subjects	Events	Subjects	
112-Wound Dehiscence	1	1 (2.0%)	0	0 (0%)	0.3333
199-Other Abdominal	1	1 (2.0%)	0	0 (0%)	0.3333
399-Other GI event	0	0 (0%)	2	2 (2.0%)	0.5526
602-Deep vein thrombosis	0	0 (0%)	1	1 (1.0%)	1.0000
903-Cellulitis	1	1 (2.0%)	0	0 (0%)	0.3333
999-Other	0	0 (0%)	2	2 (2.0%)	0.5526
TOTAL	3	3 (6.0%)	5	5 (5.0%)	1.0000

Summary statistics are presented as Number of events and Number of subjects experiencing event (Percent of subjects). P-values are from Fisher's Exact test for number of subjects experiencing an event.

999-Other: laceration, gynecologic; 399-other GI event: diverticulitis, ileus large intestine, 199-other abdominal: mass in abdomen

Non-Serious Non-Device Related Adverse Events

	SWC + Drains (N=50)		SWC + Drains and TissuGlu® (N=100)		P-value
	Events	Subjects	Events	Subjects	
103-Hypertrophic Scar	1	1 (2.0%)	3	3 (3.0%)	1.0000
106-Rash/Redness at treated area	4	4 (8.0%)	0	0 (0%)	0.0114
108-Seroma formation	11	9 (18.0%)	0	0 (0%)	0.0000
109-Skin Necrosis	4	4 (8.0%)	0	0 (0%)	0.0114
110-Surgical Site Infection (SSI)	1	1 (2.0%)	1	1 (1.0%)	1.0000
111-Wound complication	2	2 (4.0%)	1	1 (1.0%)	0.2578
112-Wound Dehiscence	7	6 (12.0%)	10	10 (10.0%)	0.7810

199-Other Abdominal	2	2 (4.0%)	4	4 (4.0%)	1.0000
299-Other neurologic	1	1 (2.0%)	0	0 (0%)	0.3333
301-Constipation	0	0 (0%)	1	1 (1.0%)	1.0000
399-Other GI event	2	2 (4.0%)	2	2 (2.0%)	0.6009
402-Urinary tract infection	0	0 (0%)	4	4 (4.0%)	0.3017
403-Yeast infection	1	1 (2.0%)	0	0 (0%)	0.3333
499-Other renal	1	1 (2.0%)	0	0 (0%)	0.3333
501-Atelectasis	0	0 (0%)	2	1 (1.0%)	1.0000
599-Other pulmonary	1	1 (2.0%)	0	0 (0%)	0.3333
903-Cellulitis	2	2 (4.0%)	0	0 (0%)	0.1096
907-Infection	0	0 (0%)	1	1 (1.0%)	1.0000
908-Medication reaction	0	0 (0%)	1	1 (1.0%)	1.0000
910-Pain	1	1 (2.0%)	0	0 (0%)	0.3333
911-Rash/Skin irritation	2	2 (4.0%)	3	3 (3.0%)	1.0000
999-Other	4	4 (8.0%)	5	5 (5.0%)	0.4819
TOTAL	47	23 (46.0%)	38	29 (29.0%)	0.0463

Summary statistics are presented as Number of events and Number of subjects experiencing event (Percent of subjects). P-values are from Fisher's Exact test for number of subjects experiencing an event.

999-Other: musculoskeletal, infectious, hemostasis, immunological, physiological, gynecological: 599 other-pulmonary: airway congestion; 499 other renal: kidney stone; 399-other GI: diarrhea, stomach pain, biliary colic; 199 other-abdominal: suture extruded.

Unresolved Adverse Events

Subject ID	Treatment Group	CEC Adverse Event	Serious Adverse Event (SAE)?	Related to Study Device	Related to Study Procedure
01-206	Control	Hypertrophic scar	No	Not related	Probably related
03-101	Control	Seroma formation	No	Not related	Probably related
03-108	Control	Other: Bursitis right hip	No	Not related	Not related
03-213	Control	Other renal	No	Not related	Not related
06-206	Control	Other Abdominal: fat necrosis supra pubic	No	Not related	Probably related
01-116	TissuGlu®	Seroma formation	No	Possibly related	Probably related
01-202	TissuGlu®	Deep vein thrombosis	Yes	Not related	Probably related
01-213	TissuGlu®	Hypertrophic scar	No	Not related	Probably related
01-218	TissuGlu®	Hypertrophic scar	No	Not related	Probably related
03-215	TissuGlu®	Other: developed rheumatoid arthritis	No	Not related	Not related

Subject ID	Treatment Group	CEC Adverse Event	Serious Adverse Event (SAE)?	Related to Study Device	Related to Study Procedure
03-222	TissuGlu®	Other: Uterine Leiomyoma's	No	Not related	Not related
03-222	TissuGlu®	Urinary tract infection	No	Not related	Not related
06-101	TissuGlu®	Other: Pt diagnosed with metastatic cancer	Yes	Possibly related	Not related
06-216	TissuGlu®	Other Abdominal: Umbilicus is not midline	No	Not related	Probably related

Summary of Pivotal Study #2: No Drain Study in Abdominoplasty

Study Design:

The TissuGlu® study 2 was a pivotal, prospective clinical investigation for a randomized, controlled, multicenter non-inferiority study comparing standard wound closure (SWC) technique with drains (control) to standard wound closure (SWC) techniques plus TissuGlu® and no drains (test) during abdominoplasty. TissuGlu® was applied to the test group prior to standard closure of the abdominal flap. Closed suction drains were not placed in patients in the test group. The control cohort had closed suction drains placed per standard of care. The study evaluated the hypothesis that the elimination of dead space in the wound would prevent post-surgical fluid from developing and causing fluid-related complications. Subjects were required to attend follow-up visits at days 3, 6, 9, 12, 16, 25, 32, 39, 53, 67, and 84. Blake drains and placement locations were standardized among sites.

Sample Size: 130 subjects randomized 1:1 across 5 investigational sites.

Primary Effectiveness: The primary endpoint of the study is identified as the number of post-operative invasive treatments, where invasive treatment is defined as follows:

- Removal of an in-dwelling drain;
- Needle aspiration to remove fluid from a clinically-diagnosed palpable seroma;
- Invasive action to the drain or drain wound such as repositioning or re-attaching the drain retention sutures; and
- Re-insertion of a drain

A seroma was defined as a subcutaneous accumulation resulting in a palpable wave of fluid requiring needle aspiration.

Secondary Endpoints:

- Cumulative drain volume, aspiration volume, and total wound drainage (drain volume + aspiration volume)
- Cumulative days of invasive treatment (days with drains in+ days aspirated)
- Days to drain removal
- Seroma formation, number of aspirations, relationship between infection and needle aspiration, and seroma revisions
- VAS Pain Score
- SF-8 Score
- Activity Questionnaire

Safety: Safety assessments included collection of all device-related and non-device related adverse events. All adverse events were adjudicated by the CEC. The CEC-adjudicated data superseded the investigator-reported adverse data for seriousness, relatedness, and adverse event type/description.

Clinical Inclusion and Exclusion Criteria:

Inclusion Criteria	Exclusion Criteria
• Male or female, ≥ 18 years of age • Provide signed and dated informed consent form • Willing to comply with all study procedures, schedules and be available for the follow-up evaluations for the duration of the study • Willing to follow instructions for incision and drain care, and follow guidelines related to resumption of daily activities • Agree not to schedule any additional elective surgical procedures that involve an incision until their participation in the study is complete • In good general health in the opinion of the Investigator with no conditions that would significantly impact wound healing as determined by medical history, and review of recent concomitant medications • Requiring at least one full thickness surgical incision of at least 20cm in length as part of elective abdominoplasty • ≤ ASA2 – American Society of Anesthesiologists Physical Classification System (2=subject with mild systemic disease) • Have a Body Mass Index (BMI) ≤ 28	• Pregnancy or lactation • Previous abdominoplasty • Prior bariatric or weight loss surgery • Lost ≥ 15% of maximum lifetime bodyweight (excluding pregnancy weight gain) • Known medical condition that results in compromised blood supply to tissues • Have known or suspected allergy or sensitivity to any test materials or reagents • Have severe co-morbid conditions (e.g., heart disease) • Are currently a smoker or have smoked within 30 days of prescreening as determined by nicotine test • Any condition known to effect wound healing, such as collagen vascular disease • Be known to have a blood clotting disorder and/or be willing to discontinue anti-coagulation therapy including aspirin • Diagnosis of diabetes with current medical treatment • Receiving antibiotic therapy for pre-existing condition or infection • Have known personal or family history of keloid formation or hypertrophic scarring • Currently taking systemic steroids or immunosuppressive agents • Undergoing concurrent adjacent or congruent Liposuction agents • Use of pain pumps after the abdominoplasty procedure • Concurrent use of fibrin sealants or other internal wound care devices • Concurrent hernia repair greater than 6 cm and/or requiring the use of mesh • Mini abdominoplasty (abdominoplasty without umbilical transposition) • Be participating in any current clinical trial or have participated in any clinical trial within 30 days of enrollment in this study

Study Procedure: Prior to the abdominoplasty procedure, subjects were randomized to receive either the Standard Wound Closure with Drains (Control) or TissuGlu® without drains (Test) in a 1:1 (treatment: control) ratio. The test Group received TissuGlu® applied to one surface of the exposed tissue flap using the TissuGlu® delivery device followed by standard of care wound closure using sutures. The Control Group received standard of care closure using sutures and placement of two size 12 Blake drains. The Blake drains were placed over the abdominal fascia, the tube delivered through stab incisions on the pubic area, and the drains were affixed with suture. Drain output was monitored and recorded from the first measurement.

Subject Accounting and Demographics

Disposition	SWC + Drains	SWC + TissuGlu®	All Subjects
Enrolled	64	66	130
Completed Week 1 Vist			
Day 3	62	64	126
Day 6	63	65	128
Completed Week 2 Visit			
Day 9	63	66	129
Day 12	61	64	125
Completed Day 16 Visit	62	64	126
Completed Day 25 Visit	63	65	128
Completed Day 32 Visit	61	66	127
Completed Day 39 Visit	60	65	125
Completed Day 53 Visit	62	65	127
Completed Day 67 Visit	56	63	119
Completed Day 84 Visit	62	64	126
Discontinued	64	66	130
Completed Study	62	64	126
Withdrew Consent	1	0	1
Lost to Follow-up	0	2	2
Death	0	0	0
Other reason for discontinuation	1	0	1

Demographics and Medical History: There were no notable differences in demographics between the TissuGlu® and control patients.

	SWC + Drains (N=64)	SWC + TissuGlu® (N=66)	P-value
Demographics			
Age (years)	42.6 ± 10.6 (64) 23.4,40.8,67.3)	42.1 ± 8.4 (66) (26.0,40.9,66.5)	0.9610
Gender			
Male	1/64 (1.6%)	0/66 (0.0%)	0.4923
Female	63/64 (98.4%)	66/66 (100.0%)	0.4923
Ethnicity			
Hispanic or Latino	8/50 (16.0%)	7/50 (14.0%)	1.000
Not Hispanic or Latino	42/50 (84.0%)	43/50 (86.0%)	1.0000
Race			
American Indian or Alaska Native	0/64 (0.0%)	1/66 (1.5%)	1.0000
Asian	3/64 (4.7%)	3/66 (4.5%)	1.0000
Black or African American	14/64 (21.9%)	12/66 (18.2%)	0.6642
Native Hawaiian or Other Pacific Islander	1/64 (1.6%)	0/66 (0.0%)	0.4923
White	45/63 (70.3%)	50/66 (75.8%)	0.5550
Current Weight (kg)	65.4 ± 7.8 (64) (49.9,64.2,81.6)	65.0 ± 7.6 (66) (47.2,64.9,79.8)	0.9258
Height (cm)	163.2 ± 7.0 (64) (149.9,162.6,182.9)	163.9 ± 5.9 (66) (149.9,163.3,177.8)	0.3981
Current BMI	24.5 ± (2.0 (64) (18.8,24.4,27.8)	24.2 ± 2.4 (65) (18.4,23.7,28.0)	0.4453

Lifetime Body Weight Loss (%)	42 ± 4.2 (64) (0.0,4.0,14.2)	3.8 ± 5.0 (63) (0.0,2.2,25.0)	0.2727
Medical History			
Any Major Medical History	30/64 (46.9%)	34/66 (52.5%)	0.6042
Any Surgical History	52/64 (82.8%)	53/66 (80.3%)	0.8222
Nicotine Use	0/64 (0.0%)	0/66 (0.0%)	N/A
Pregnancy	46/63 (73.0%)	54/66 (81.8%)	0.2925
Vital Signs/Physical Exam			
Body Temperature (°F)	97.9 ± 0.6 (63) (96.7,97.8,98.9)	97.9 ± 0.6 (66) (96.7,97.9,99.0)	0.8555
Blood Pressure (mmHg)			
Systolic	120.8 ± 13.5 (64 (87.0,120.0,156.0)	118.7 ± 12.2 (66) (88.0,118.5,149.0)	0.3643
Diastolic	75.4 ± 8.6 (64) (57.0,76.0,102.0)	75.2 ± 9.4 (66) (56.0,76.6,97.0)	0.9366
Pulse (bpm)	71.3 ± 8.6 (64) (51.0,72.0,97.0)	71.4 ± 8.2 (66) (54.0,72.0,90.0)	0.8352
Any Body System Abnormalities	0/64 (0.0%)	0/66 (0.0%)	N/A
Current Status			
Indication for Surgery			
Skin Laxity on abdomen	64/64 (100.0%)	66/66 (100.0%)	N/A
Symptoms secondary to excess skin on abdomen	1/64 (1.6%)	3/66 (4.5%)	0.6193
Ventral hernia	0/64 (0.0%)	0/66 (0.0%)	N/A
Body Scars			
Abdominal	30/64 (46.9%)	31/66 (47.0%)	1.0000
Hypertrophic	0/64 (0.0%)	0/66 (0.0%)	N/A
Keloid	0/64 (0.0%)	0/66 (0.0%)	N/A
None	34/64 (53.1%)	35/66 (53.0%)	1.0000

Summary statistics are presented as Mean ± SD (N), (Min, Median, Max) for continuous variable and Count/N (Percent) for categorical variables. P-values are from Wilcoxon test for continuous variables and Fisher's Exact test for categorical variables.

Primary Effectiveness Endpoint Results and Statistical Analysis

The primary effectiveness criteria for the study, a comparison of invasive procedures, was met for both the per protocol and intent-to-treat populations.

The majority of patients excluded from the PP population were excluded for protocol violations that were anticipated to influence the efficacy evaluation. The majority of the exclusions were due to lack of adherence to the 3+-1 day follow up requirement for either drain or seroma management. This resulted in 110 events from the ITT analysis being excluded from the per protocol analysis.

Invasive treatments included the following: needle aspiration, removal of an in-dwelling drain, surgery, sclerotherapy, drain placement for seroma, repositioning of in-dwelling drain, reattachment of sutures, reinsertion of in-dwelling drain. However, needle aspiration and removal of in-dwelling drain were the only invasive treatments reported in the clinical study.
The primary endpoint includes a deterministic component of drain removal that can be evaluated clinically. The statistical comparison of overall invasive treatments (including drain removal) is then a comparison of required drain removals (by virtue of treatment assignment) and aspirations in SWC with drain group to needle aspirations in the TissuGlu® group.

Study Populations

Population	SWC + Drains	SWC + TissuGlu®	All Subjects
Intent-to-Treat	64	66	130
Per-Protocol	52	51	103

Primary Effectiveness Endpoints (per-protocol N=103)

Number of post-operative invasive treatments	SWC + drains (n=52)	SWC+TissuGlu® (n=51)	Non-inferiority comparison	
			Median shift [upper bound][1]	p-value[2]
Median	2.0	0.0	-2.0 [-2.0]	<0.0001
Mean (SD)	2.2 (0.9)	0.2 (0.7)		
Min, Max	2.0, 8.0	0, 4.0		
Total number of events	114	9		
Number of needle aspirations				
Median	0.0	0.0	0.0[0.0]	<0.0001
Mean (SD)	0.2 (0.9)	0.2 (0.7)		
Min, Max	0.0, 6.0	0.0, 4.0		
Total number of events	10	9		
Removal of an in-dwelling drain				
Median	2.0	0.0		N/A
Mean (SD)	2.0 (0.0)	0.0 (0.0)		
Min, Max	2.0, 2.0	0.0, 0.0		
Total number of events	104	0.0		

1. The Hodges-Lehman estimate of location shift and exact one-sided upper 97.5% confidence limit are presented.
2. P-values are from exact Wilcoxon test comparing SWC+ TissuGlu® to SWC+drains where a value of 1 was added to all SWC+drain subjects (i.e. non-inferiority test). Reported P-values are 2-sided.

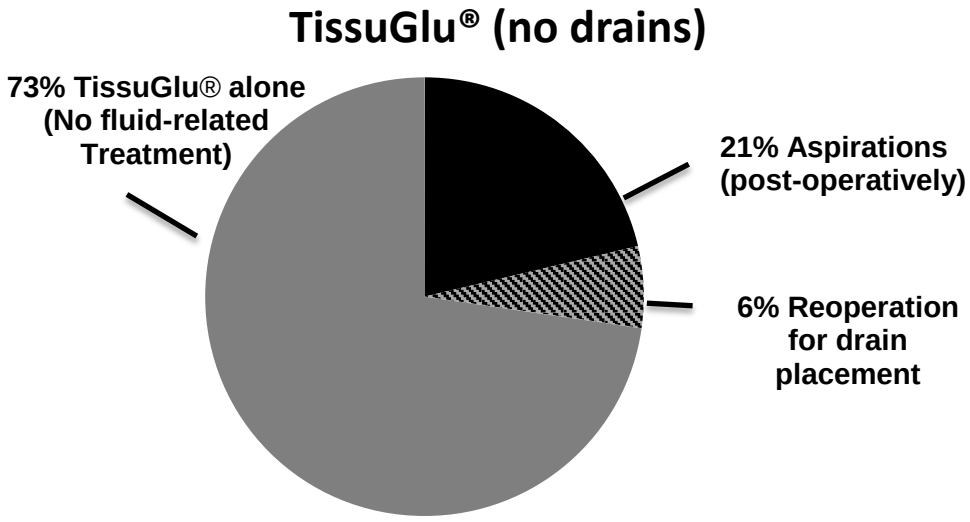
Primary Effectiveness Analysis (intent-to-treat N=130)

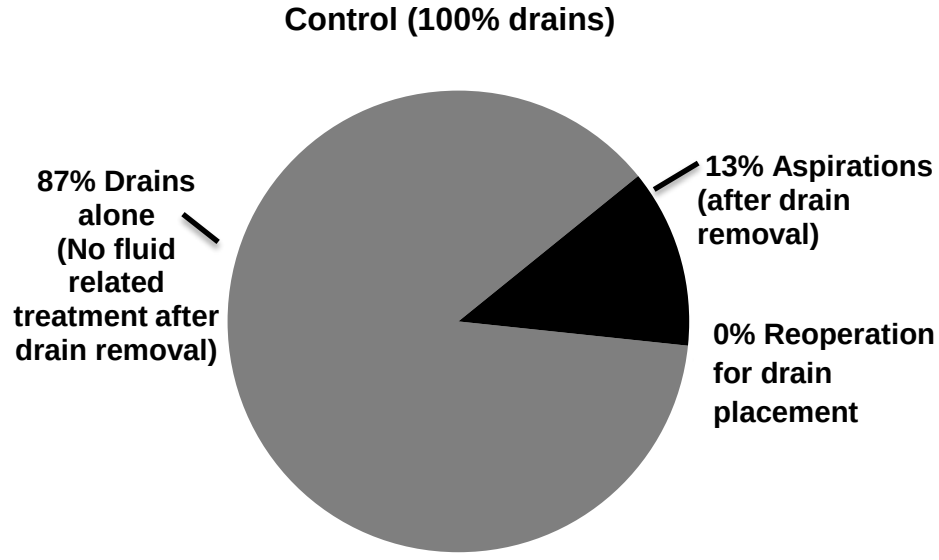
Number of post-operative invasive treatments	SWC + drains (n=64)	SWC+ TissuGlu® (n=66)	Non-inferiority comparison	
			Median shift [upper bound][1]	p-value[2]
Median	2.0	0.0	-2.0 [-2.0]	-<0.0001
Mean (SD)	2.4 (1.2)	1.8 (3.8)		
Min, Max	2.0, 8.0	0, 17.0		
Total number of events	152	119		
Needle Aspiration				
Median	0.0	0.0	0.0 [0.0]	<0.0001
Mean (SD)	0.4 (1.2)	1.7 (3.7)		
Min, Max	0.0, 6.0	0.0, 17.0		
Total number of events	24	112		
Removal of an in-dwelling drain				
Median	2.0	0.0		N/A

Mean (SD)	2.0 (0.0)	0.1 (0.4)		
Min, Max	2.0, 2.0	0, 2.0		
Total number of events	128	7†		

1 The Hodges-Lehman estimate of location shift and exact one-sided upper 97.5% confidence limit are presented.
2 P-values are from exact Wilcoxon test comparing SWC+TissuGlu® to SWC+drains where a value of 1 was added to all SWC+drain subjects (i.e. non-inferiority test). Reported P-values are 2-sided.
†: There are 7 drain removals in 4 patients in the no-drain group. Three of the patients had drains placed because they had ongoing seromas that could not be managed well by aspiration alone. Two (2) of these patients had bilateral drains and the 3rd had a single drain placement. One (1) patient had bilateral drains placed due to a surgical revision following a hematoma.

Additional analysis
In the TissuGlu® treatment group, 73% of patients had no fluid-related invasive treatments. 27% of patients had invasive treatments with 21% receiving aspirations alone, and 6% receiving both aspirations and drains for persistent seroma. These data highlight the clinical benefit received by a majority of patients in the TissuGlu® treatment group.





Key Secondary Effectiveness Endpoints Results

Secondary effectiveness analyses were performed on the ITT population. Analyses of the secondary efficacy endpoints are descriptive without formal hypothesis testing.

Secondary Endpoints

	SWC + drains (N=64)	SWC + TissuGlu® no drains (N=66)
Total wound drainage per patient (ml)		
Mean (SD)	411.4 (366.6)	96.6 (270.1)
Median	306.5	0.0
(Min, Max)	(65.0, 2034.0)	(0.0, 1572.0)
Cumulative drain volume per patient (ml)		
Mean (SD)	396.5 (339.9)	--
Median	306.5	--
(Min, Max)	(65.0, 2034.0)	--
Aspiration volume per patient (ml)		
Mean (SD)	14.9 (67.1)	96.6(270.1)
Median	0.0	0.0
(Min, Max)	(0.0, 445.0)	(0.0, 1572.0)
Days to drain removal		
Mean (SD)	6.9 (3.3)	--
Median	6.5	--
(Min, Max)	(2, 18)	--
Number of needle aspirations		
Mean (SD)	0.4 (1.2)	1.7 (3.7)
Median	0.0	0.0
Min, Max	0.0, 6.0	0.0, 17.0
Number of seroma revisions		
Mean (SD)	0.0 (0.0)	0.0 (0.1)
Median	0.0	0.0
(Min, Max)	(0.0, 0.0)	(0.0, 1.0)
Cumulative days of invasive treatment		
Mean (SD)	7.3(3.3)	1.6 (3.4)

Median	7.0	0.0
(Min, Max)	(2.0, 18.0)	(0.0, 16.0)

Patient reported outcomes (Activity Questionnaire)

At each scheduled follow-up visit, patients completed a questionnaire that evaluated Quality of Life (QoL) measures. The analyses of these outcomes are descriptive with no formal hypothesis testing. The percentage of subjects who took a shower was nearly 20% greater in the SWC+TissuGlu® group than in the SWC+drains group on Day 3 and Day 6, and over 10% greater on Day 9.

Patient reported Outcomes SWC+Drains

	Day 3 (N=62)	Day 6 (N=63)	Day 9 (N=63)	Day 12 (N=61)	Day 16 (N=62)	Day 25 (N=63)	Day 32 (N=61)	Day 39 (N=60)	Day 53 (N=62)	Day 67 (N=56)	Day 84 (N=62)
Hours out of bed											
0-1 hours	24.2%	6.3%	0.0%	3.3%	1.6%	0.0%	0.0%	0.0%	0.0%	0.0%	1.6%
1-3 hours	41.9%	17.5%	11.1%	3.3%	4.8%	3.2%	0.0%	0.0%	0.0%	0.0%	0.0%
3-5 hours	16.1%	34.9%	23.8%	14.8%	12.9%	4.8%	1.6%	1.7%	3.2%	1.8%	1.6%
5-8 hours	12.9%	12.7%	28.6%	26.2%	19.4%	12.7%	18.0%	23.3%	3.2%	5.4%	1.6%
8+ hours	4.8%	28.6%	36.5%	53.5%	61.3%	79.4%	80.3%	75.0%	93.5%	92.9%	95.1%
Hours out of home											
0-1 hours	85.5%	50.8%	22.2%	13.1%	11.3%	9.5%	0.0%	1.7%	1.6%	1.8%	4.9%
1-3 hours	0.7%	31.7%	28.6%	21.3%	22.6%	9.5%	4.9%	5.0%	6.5%	1.8%	1.6%
3-5 hours	0.0%	7.9%	28.6%	18.0%	27.4%	19.0%	18.0%	16.7%	12.9%	7.1%	6.6%
5-8 hours	3.2%	7.9%	11.1%	27.9%	12.9%	20.6%	19.7%	21.7%	12.9%	14.3%	18.0%
8+ hours	1.6%	1.6%	9.5%	19.7%	25.8%	41.3%	57.4%	55.0%	66.1%	75.0%	68.9%
Returned to normal work schedule	0.0%	7.9%	20.6%	39.3%	45.2%	62.9%	73.8%	78.3%	93.5%	96.4%	98.4%
Activities performed											
Took a shower	28.1%	65.6%	81.3%	90.6%	96.9%	95.3%	93.8%	92.2%	95.3%	87.3%	96.8%
Walked up stairs	43.8%	67.2%	73.4%	78.1%	79.7%	85.9%	79.7%	82.8%	89.1%	82.5%	91.9%
Drove a car	1.6%	25.0%	51.6%	70.3%	84.4%	89.1%	92.2%	90.6%	89.1%	84.1%	95.2%
Heavy lifting	0.0%	1.6%	4.7%	10.9%	20.3%	29.7%	46.9%	48.4%	73.4%	71.4%	82.3%
Exercised	0.0%	0.0%	1.6%	10.9%	21.9%	25.0%	35.9%	54.7%	68.8%	77.8%	80.6%

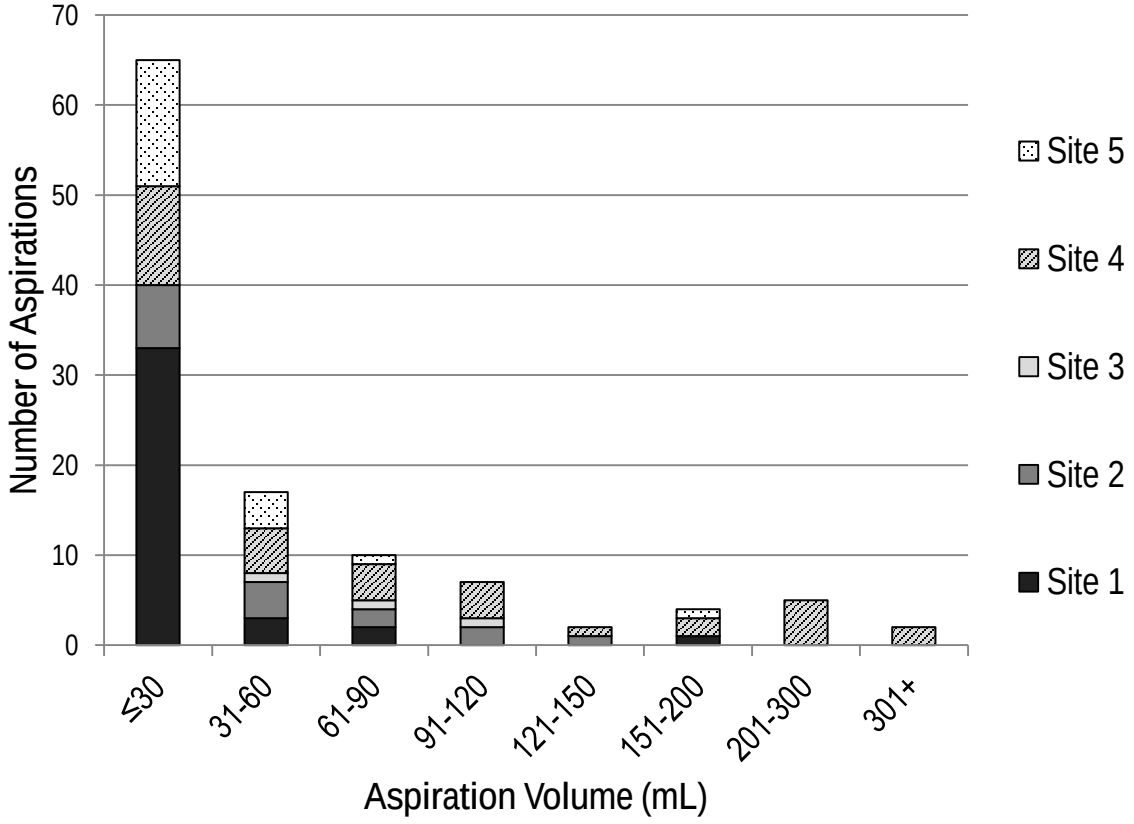
Patient reported Outcomes SWC+TissuGlu®

	Day 3 (N=64)	Day 6 (N=65)	Day 9 (N=66)	Day 12 (N=64)	Day 16 (N=64)	Day 25 (N=65)	Day 32 (N=66)	Day 39 (N=65)	Day 53 (N=63)	Day 67 (N=63)	Day 84 (N=64)
Hours out of bed											
0-1 hours	25.4%	4.6%	0.0%	0.0%	0.0%	0.0%	0.0%	1.5%	0.0%	1.6%	0.0%
1-3 hours	41.3%	20.0%	6.1%	9.4%	3.2%	0.0%	1.5%	0.0%	0.0%	0.0%	0.0%
3-5 hours	19.0%	32.3%	25.8%	10.9%	9.5%	3.1%	3.0%	3.1%	0.0%	1.6%	1.6%
5-8 hours	6.3%	20.0%	28.8%	21.9%	17.5%	15.4%	10.6%	9.2%	7.7%	3.2%	6.3%
8+ hours	7.9%	23.1%	39.4%	57.8%	69.8%	81.5%	84.8%	86.2%	92.3%	93.5%	92.1%
Hours out of home											
0-1 hours	82.5%	43.1%	24.2%	15.6%	12.7%	9.2%	4.5%	3.1%	4.6%	4.8%	1.6%
1-3 hours	12.7%	30.8%	27.3%	18.8%	11.1%	6.2%	4.5%	3.1%	4.6%	6.5%	1.6%
3-5 hours	1.6%	10.8%	28.8%	15.6%	23.8%	18.5%	15.2%	24.6%	12.3%	1.6%	9.5%
5-8 hours	0.0%	10.8%	9.1%	31.3%	23.8%	20.0%	19.7%	16.9%	15.4%	22.6%	17.5%
8+ hours	3.2%	4.6%	10.6%	18.8%	28.6%	46.2%	56.1%	52.3%	63.1%	64.5%	69.8%
Returned to normal work schedule	0.0%	7.7%	21.2%	46.9%	58.7%	67.7%	78.8%	83.1%	92.3%	93.5%	95.2%
Activities performed											
Took a shower	47.0%	83.3%	92.4%	95.5%	93.9%	97.0%	98.5%	98.5%	97.0%	90.9%	92.4%
Walked up stairs	48.5%	75.8%	77.3%	83.3%	83.3%	89.4%	95.5%	95.5%	93.9%	89.4%	93.9%
Drove a car	0.0%	24.2%	51.5%	75.8%	87.9%	89.4%	95.5%	92.4%	95.5%	89.4%	93.9%
Heavy lifting	0.0%	6.1%	3.0%	15.2%	18.2%	34.8%	53.0%	51.5%	69.7%	77.3%	80.3%
Exercised	0.0%	1.5%	7.6%	13.6%	18.2%	27.3%	42.4%	53.0%	63.6%	63.6%	81.8%

Safety: There were a total of 5 serious device-related adverse events in the SWC+ TissuGlu® group with hematoma and seromas being reported in the study. There were a total of 23 non-serious device-related events with seromas being the most frequently reported adverse event in the TissuGlu® treatment group. There was one serious adverse event (hematoma) in the control group.

In the clinical study, a seroma was defined as a clinically identifiable collection of serous fluid. The clinical protocol specified a seroma to be diagnosed by manually palpating the suspected area and determining if there was a palpable wave of fluid present. Once diagnosed, a seroma was percutaneously diminished via needle aspiration every three days until resolved. Seromas that required an additional surgical procedure in the O.R. to clean the wound and insertion of drains were categorized as serious adverse events. Seromas that only required needle aspiration or insertion of drains outside of the O.R. were categorized as non-serious adverse events.

Aspiration Volumes Early in the trial, overly aggressive treatment of the TissuGlu® no drain group led to aspirating seromas frequently and at low volumes.



Serious Device-related Adverse Events The serious hematoma in the TissuGlu® group was classified as "possibly device related". This patient had the left lateral gutter opened, and the hematoma was evacuated and all oozing points were cauterized with electrocautery. Two drains were placed and the wounds were closed without complication and the hematoma resolved. There were four serious seromas reported in the TissuGlu® group (with two in the same patient). In each case, the subject was noted to have a seroma with persistent drainage of ~100 cc of serous fluid. The seroma was evacuated and Doxycycline was injected; however, the drainage persisted. The subjects were taken to the operating room for wound exploration, drain placement and obliteration of seroma cavity. Fluid pockets were identified, drained, and drains were placed. There were no further complications and the seroma resolved.

	SWC +TissuGlu® (N=66)	
	Events	Subjects
102-Hematoma	1	1 (1.5%)
109-Seroma formation	4	3 (4.5%)
TOTAL	5	4 (6.1%)

Summary statistics are presented as Number of events and Number of Subjects experiencing event (Percent of subjects).

Non-Serious Device-related Adverse Events

	SWC +TissuGlu® (N=66)	
	Events	Subjects
102-Hematoma	2	2 (3.0%)
109-Seroma formation	18	16 (24.2%)
113-Wound dehiscence	2	2 (3.0%)
114-Wound infection	1	1 (1.5%)
TOTAL	23	21 (31.8%)

Summary statistics are presented as Number of events and Number of Subjects experiencing event (Percent of subjects).

Serious Non Device-related Adverse Events

	SWC + Drains (N=64)		SWC + TissuGlu® (N=66)		P-value
	Events	Subjects	Events	Subjects	
102-Hematoma	1	1 (1.6%)	0	0 (0%)	0.4923
399-Other GI event	0	0 (0%)	1	1 (1.5%)	1.0000
TOTAL	1	1 (1.6%)	1	1 (1.5%)	1.0000

Summary statistics are presented as number of events and Number of subjects experiencing event (Percent of subjects). P-values are from Fisher's Exact test for number of subjects experiencing an event.

399-other GI: ileus, possible pneumonia

Non-Serious Non-Device-related Adverse Events

	SWC + Drains (N=64)		SWC + TissuGlu® (N=66)		P-value
	Events	Subjects	Events	Subjects	
103-Hypertrophic scar	2	2 (3.1%)	4	4 (6.1%)	0.6803
105-Keloid Scar	0	0 (0%)	1	1 (1.5%)	1.0000
107-Rash/Redness at treated area	2	2 (3.1%)	0	0 (0%)	0.2404
109-Seroma formation	9	8 (12.5%)	0	0 (0%)	0.0027
110-Skin Necrosis	0	0 (0%)	1	1 (1.5%)	1.0000
112-Wound complication	0	0 (0%)	1	1 (1.5%)	1.0000
115-Wound separation	4	2 (3.1%)	3	3 (4.5%)	1.0000
199-Other Abdominal	1	1 (1.6%)	2	2 (3.0%)	1.0000
499-Other renal	1	1 (1.6%)	0	0 (0%)	0.4923
501-Atelectasis	0	0 (0%)	1	1 (1.5%)	1.0000
502-Pneumonia	0	0 (0%)	1	1 (1.5%)	1.0000
599-Other pulmonary	0	0 (0%)	1	1 (1.5%)	1.0000
999-Other	1	1 (1.6%)	0	0 (0%)	0.4923
TOTAL	20	16 (25.0%)	15	11 (16.7%)	0.2833

Summary statistics are presented as number of events and Number of subjects experiencing event (Percent of subjects). P-values are from Fisher's Exact test for number of subjects experiencing an event.

999-Other: psychological; 199 other abdominal: suture abscess, spitting suture; 499 other renal: unable to void; 599 other pulmonary: asthma attack

STUDY CONCLUSIONS:

A. Effectiveness Conclusions

Effectiveness in terms of reduced drain output was not observed when drains were used with TissuGlu®. TissuGlu® Surgical Adhesive met the primary effectiveness endpoint in the second pivotal clinical trial, and was effective in patients with BMIs less than 28 for the approximation of tissue layers where subcutaneous dead space exists between the tissue planes in abdominoplasty. The results of the second Pivotal Trial demonstrate that TissuGlu® is non-inferior to post-surgical drains (the current Standard of Care) for the management of fluid-related complications after abdominoplasty. The use of TissuGlu® to adhere tissue flaps and reduce dead space leads to fewer post-operative invasive treatments for the patient, with no increased risk of other post-operative complications. Patients receiving TissuGlu® had reduced drainage output and fewer overall days of invasive treatment.

B. Safety Conclusions

The use of TissuGlu® Surgical Adhesive in abdominoplasty is safe. In two controlled pivotal studies, one with a follow-up duration of 12 months and one with a follow-up duration of 3 months, the rates of post-operative wound-related complications were not significantly different between the test and control groups. Wound complications reported in the clinical studies included seroma formation, wound dehiscence, surgical site infection, skin necrosis, and hematoma. No unanticipated adverse device events were observed. Safety outcomes were equivalent regardless of whether or not drains were used in conjunction with the TissuGlu® Surgical Adhesive.

C. Benefit -Risk Conclusions

The probable benefits outweigh the risks for select patients. Pivotal Study #2 showed that 73% of TissuGlu® treated patients (non-weight loss and BMIs ≤ 28) required neither postoperative drains nor seroma aspirations following abdominoplasty. 27% of TissuGlu® treated patients required additional post-operative wound management with 6% requiring reoperation for drain placement and seroma fluid aspiration. This result is in contrast to the control arm in which all patients received postoperative drains and some patients required seroma aspiration. A subset of abdominoplasty patients treated with TissuGlu® without drains were able to shower, walk up stairs, and return to work earlier. No benefit for device use in weight loss patients who have undergone abdominoplasty was observed. Adverse events in the TissuGlu® treated group were minimal in both of the pilot studies and in the pivotal studies. There is a risk of allergic reaction to the device although this was not observed in the clinical studies. Due to lack of direct comparisons between patients receiving TissuGlu® without drains and patients receiving standard wound closure without drains, it is not possible to quantify device effectiveness as compared to abdominoplasty closure without drains. Patients in the clinical trial were willing to accept the risks, which are minimal and similar to current standard of care, in exchange for the benefits of improved quality of life during recovery, elimination of drain use, and no additional drain site scars.

SUPPLEMENTARY CLINICAL INFORMATION

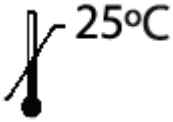
A. Post Market Experience

TissuGlu® received CE Marking for use in large flap surgical procedures such as abdominoplasty in 2011. During the time TissuGlu® has been on the market in Germany, over 1500 procedures have been performed in a variety of large flap procedures such abdominoplasty, mastectomy, inguinal lymph node dissection, latissimus dorsi flap reconstruction, decubitus flaps, and body contouring. Studies are underway in Europe to evaluate additional indications. However, pivotal clinical trial data is only available for the abdominoplasty indication.

B. Additional clinical information

The clinical trial reported by Andrades et al. included a control group of abdominoplasty patients that did not receive drains or fixation. This was a prospective, randomized, double-blind, controlled trial designed to evaluate the seroma-reducing capabilities of

progressive tension sutures. Patients were evaluated weekly by ultrasound and clinical examination. If these evaluations were positive for seroma, the volume, compartments, and localization of the liquid were recorded. Patients in the control group not receiving drains or fixation required more punctures for drainage, had a higher number of positive punctures, and had larger amounts of fluid drained by puncture than the other groups. The control arm was stopped after the intermediate analysis with 10 patients completed. These data support the conclusion that some method of seroma management is required to prevent seroma formation in abdominoplasty patients. *Andrades , et al., Plast Reconstr Surg. 2007 120(4):935-951.*

	Caution, consult accompanying documents		Do not re-use
	Do not exceed 45°C Store at room temperature		Use by date
	Manufactured by		Batch code
	Catalog number		Sterilized using irradiation
	Do not use if package is damaged		CAUTION: Federal law restricts the device to sale by or on the order of a physician

TissuGlu®

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TissuGlu® is covered by one or more of the following U.S. Patents 7,264,823; 8,182,647. Other Patents Pending.