

SUMMARY OF SAFETY AND EFFECTIVENESS (SSED)

I. GENERAL INFORMATION

Device Generic Name: Tissue Adhesive

Device Trade Name: TissuGlu[®] Surgical Adhesive

Device Procode: PJK

Applicant's Name and Address: Cohera Medical, Inc.
209 Sandusky Street
Pittsburgh, PA 15212

Date of Panel Recommendation: August 1, 2014

Premarket Approval Application (PMA) Number: P130023

Date of FDA Notice of Approval: February 3, 2014

II. 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.

III. CONTRAINDICATIONS

- Do not use TissuGlu[®] Surgical Adhesive in patients with known or suspected allergies to urethane-based or isocyanate-containing products.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TissuGlu[®] Surgical Adhesive labeling.

V. DEVICE DESCRIPTION

TissuGlu[®] is a surgical adhesive based on a polyurethane pre-polymer. In its pre-polymerized form, TissuGlu[®] is a viscous liquid. The liquid is applied drop-wise to the tissue surfaces to be adhered, and then the tissue surfaces are approximated for several minutes to allow the moisture in the tissue to initiate the curing process. The curing process proceeds over a period of approximately 30-45 minutes, while other steps in the surgical closure procedure are completed. The cured product acts as a bonding agent between the tissue layers, to eliminate dead space in the wound.

The TissuGlu[®] applicator is a hand-held, disposable device that stores 5 mL of adhesive for delivery in drops onto planar surfaces of tissue. When actuated, the TissuGlu[®] applicator delivers 3 linear drops of adhesive, at an average drop volume of 0.025-0.040 mL, spaced 2.5 cm apart. The applicator includes a safety lock that punctures the internal cartridge filled with adhesive when the device is ready to be used. It features a rotating head for access into tight spaces, as well as a spacer guide on the tip to allow for consistent application in a grid-like pattern.



VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternatives to using TissuGlu[®] include:

- Closure of the abdominoplasty incision with the use of closed suction drains
- Closure of the abdominoplasty incision using progressive tension or quilting suture techniques with or without the use of drains

As with the use of TissuGlu[®], there is the option following these alternatives for postoperative aspiration of clinically discernable seroma. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

Cohera received CE Marketing approval to market TissuGlu[®] Surgical Adhesive in the EU in August of 2011, and TissuGlu[®] Surgical Adhesive has been marketed in Germany. The

device has not been withdrawn from marketing for any reason related to its safety or effectiveness.

VIII. 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.

For the specific adverse events that occurred in the clinical studies, see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Biocompatibility Testing

TissuGlu[®] Surgical Adhesive was evaluated with *in vitro* and *in vivo* biocompatibility studies appropriate for implant devices with tissue/bone contact of permanent duration (>30 days). The results of the tests are summarized in Table 1 below. The biocompatibility studies were performed in accordance with the Federal Good Laboratory Practices Regulations (21 CFR § 58), ISO 10993 and FDA's Blue Book memorandum G95-1 "Use of ISO-10993 Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." The preclinical testing provides a reasonable assurance that TissuGlu[®] Surgical Adhesive will be biocompatible when used as intended. All of the results summarized in table 1 are acceptable.

Table 1: TissuGlu[®] Surgical Adhesive Biocompatibility Testing Summary

Type of Test	Test Method	Result
Cytotoxicity	Agarose overlay using L-929 mouse fibroblast cells per ISO 10993-5:1999 Tests for <i>in vitro</i> cytotoxicity	Non-toxic
Cytotoxicity	MEM elution using L-929 mouse fibroblast cells per ISO 10993-5:1999 Tests for <i>in vitro</i> cytotoxicity	Non-toxic
Sensitization	Guinea pig maximization sensitization test (saline and cottonseed oil extracts) per ISO 10993-10:2002 Tests for irritation and delayed-type hypersensitivity	No sensitization
Irritation	Intracutaneous irritation test (saline and cottonseed oil extracts) per ISO 10993-10:2002 Tests for irritation and delayed-type hypersensitivity	Non-irritant
Acute toxicity	Acute systemic injection test (saline and cottonseed oil extracts) per ISO 10993-11:2006 Tests for systemic toxicity	Non-toxic
Implantation	Subcutaneous implantation test (2 weeks) per ISO 10993-6:2007 Tests for local effects after implantation	Slight irritant
Sub-chronic toxicity	13-week implantation and toxicity study in rabbits per ISO 10993-6:2007(E) Tests for local effects after implantation and ISO 10993-11:2006 Tests for systemic toxicity	Non-irritant No systemic effects
Chronic toxicity	26-week implantation and toxicity study in rabbits per ISO 10993-6:2007(E) Tests for local effects after implantation and ISO 10993-11:2006 Tests for systemic toxicity	Slight irritant No systemic effects
Chronic toxicity	52-week implantation and toxicity study in rabbits per ISO 10993-6:2007(E) Tests for local effects after implantation and ISO 10993-11:2006 Tests for systemic toxicity	Non irritant No systemic effects
Pyrogenicity	Materials mediated rabbit pyrogen per ISO 10993-11:2006 Tests for systemic toxicity	Non-pyrogenic

Hemolysis	Hemolysis test per ISO 10993-4:2002 Selection of Tests for Interaction with Blood and ASTM F756 (2008) Standard practice for assessment of hemolytic properties of materials	Non-hemolytic
Genotoxicity	Bacterial mutagenicity test (Ames assay) using five Salmonella strains (saline and DMSO extracts) per ISO 10993-3: 2003 Tests for genotoxicity, carcinogenicity and reproductive toxicity	Non-mutagenic
Genotoxicity	<i>In vitro</i> mouse lymphoma assay (saline and DMSO extracts) per ISO 10993-3: 2003 Tests for genotoxicity, carcinogenicity and reproductive toxicity	Non-mutagenic
Genotoxicity	<i>In vivo</i> mouse micronucleus assay (saline and cottonseed oil extracts) per ISO 10993-3: 2003 Tests for genotoxicity, carcinogenicity and reproductive toxicity	Non-mutagenic
Carcinogenicity	6 month carcinogenicity study of TissuGlu [®] in RasH2 transgenic mice per ISO 10993-1: (2003), ISO 10993-2 (2006), and ISO 10993-6:2007.	Non-carcinogenic
Reproductive toxicity	Surgical study for the effects of TissuGlu [®] on embryo-fetal development in rats per International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines (Section 4.1.3.)	No developmental toxicity
Degradation	24-month degradation study of TissuGlu [®] in beagles	No systemic effects

B. *In vitro* Performance Testing

TissuGlu[®] Surgical Adhesive has been tested and characterized through physical and chemical analysis (Table 2). All of the results summarized in table 2 are acceptable.

Table 2: *In vitro* Performance Testing

Test	Method	Result
Gel point	Gel point evaluated using rheometer to determine the crossover point of the elastic and viscous component during curing in the presence of moisture	11.74 min (8.5-15.0 min)
Volumetric swelling	Volumetric expansion of cured adhesive due to fluid absorption was measured upon exposure to saline	27.6% expansion
Heat evolution during curing	Exotherm measured during curing in the presence of moisture using a biological tissue substrate heated to approximately 37°C	$\Delta T < 3^{\circ}\text{C}$ during curing
Shear strength	Shear strength evaluated with lap shear method using biological tissue substrate	32.6 N (22-47 N)
T-peel strength	T-peel strength evaluated using biological tissue substrate	0.36 – 0.92 N
Tensile strength	Tensile strength evaluated using biological tissue substrate	12.9 – 21.8 N*

* Tensile strength could not be effectively evaluated by the test method due to failure of the cyanoacrylate bond between the tissue substrate and the fixture.

Filled and assembled devices are sterilized using a validated gamma irradiation sterilization process. The production sterilizer adheres to the requirements of ISO 11137-1:2006 for the development, validation, and routine control of the sterilization of medical devices by radiation. The minimum dose of 25 kGy was validated according to ANSI/AAMI/ISO 11137-2:2012 Sterilization of health care products—Radiation—Part 2: Establishing the sterilization dose—Method Vdmax25. The validation demonstrated that this dose achieves a Sterility Assurance Level (SAL) of 10⁻⁶ for TissuGlu[®] Surgical Adhesive.

Stability data have been collected through 12 months at 25°C/ 60% relative humidity. At each time point, product was evaluated for conformance with functional and chemical specifications. Conformance with all specifications was confirmed.

C. *In vivo* Performance Testing

Seroma Prevention in the Canine Abdominoplasty Model

A canine study was conducted to evaluate the short-term effectiveness of the TissuGlu[®] adhesive for reducing the occurrence and volume of postoperative wound exudates after a simulated abdominoplasty procedure. Eight animals were included in the three-week study. Two bilateral abdominal subcutaneous pockets (10x15cm) were created using blunt dissection and electrocautery. One pocket on each dog was treated with approximately 1.0 ml of TissuGlu[®] applied drop wise by syringe in a 4 x 6 array onto the abdominal wall surface within the pocket. The control side received no treatment prior to standard closure of the incision. After application of the adhesive, the upper flap of skin was repositioned and the incision was closed using standard surgical techniques. Drainage of serous fluid by needle aspiration was performed as medically necessary and the volume of fluid aspirated was recorded. At 3 week necropsy, the animals were euthanized and the volume of serous fluid was recorded from each side and added to the volume aspirated prior to sacrifice. Tissue from the surgical sites was harvested for histological analysis. On the control side, seroma formation was observed in all eight animals, with a range of 167 mL to 2731 mL and an average of 690 mL of total fluid collected. The TissuGlu[®] treated side showed a range of 0 mL to 129 mL with an average of 44 mL of total fluid collected.

X. SUMMARY OF CLINICAL INFORMATION

Four studies (two feasibility and two pivotal studies) were conducted (Table 3). The applicant performed two pivotal clinical studies to establish a reasonable assurance of safety and effectiveness of abdominoplasty with TissuGlu® for the approximation of tissue layers where subcutaneous dead space exists between the tissue planes in abdominoplasty in the US under IDE # (G100128 and G120245). Data from these clinical studies were the basis for the PMA approval decision. A summary of the clinical studies is presented below.

Table 3: Summary of Clinical Studies

Clinical Study	Study Design	Objective	Number of Sites	Subjects (Study Duration)
EU Feasibility Study 1 (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)
EU Feasibility Study 2 (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)
Pivotal clinical 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)
Pivotal clinical 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)

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.

Objectives

- To determine the effectiveness of the TissuGlu® device to reduce post-operative drainage thereby allowing earlier drain removal in subjects undergoing an abdominoplasty procedures.
- To document the type and duration of adverse events associated with TissuGlu® use in abdominoplasty procedures.
- Evaluate the performance of the TissuGlu® dispensing device.

Study Design: Patients were enrolled and treated between May 2012 and September 2013. There were 5 investigational sites. 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 $\alpha=0.025$ 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.

$H_0: \mu_T \geq \mu_S$

$H_a: \mu_T < \mu_S$

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

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.

1. Inclusion/Exclusion Criteria

Enrollment in the pivotal clinical study 1 was limited to patients who met the following inclusion criteria:

Inclusion

- Be at least 18 years of age;
- Have a BMI ≤ 35 ;
- \leq 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.

Patients were not permitted to enroll in pivotal clinical study 1 if they met any of the following exclusion criteria:

- 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 scarring;
- 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.

2. 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.

3. Clinical endpoints

With regards to 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.

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

With regards to 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.

B. Accountability of PMA Cohort

At the time of database lock, of 150 patients enrolled in PMA study, 148 patients are available for analysis at the completion of the study, the 1-year post-operative visit.

Table 4: 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

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an abdominoplasty study performed in the US. 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.

Table 5: Demographics and medical history:

	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%)	
Ethnicity			
Hispanic or Latino	2/50 (4.0%)	5/100 (5.0%)	1.0000
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%)	1.0000
Asian	2/50 (4.0%)	5/100 (5.0%)	1.0000
Black or African American	11/50 (22.0%)	21/100 (21.0%)	1.0000
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) (46.7,69.2,112.5)	0.7093
Height (cm)	162.4 ± 6.5 (50) (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 (°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 variables and Count/N (Percent) for categorical variables. P-values are from Wilcoxon test for continuous variables and Fisher's Exact test for categorical variables.

D. Safety and Effectiveness Results

1. Effectiveness Results

The analysis of effectiveness was based on the cohort of patients evaluable at the time of drain removal. Key effectiveness outcomes are presented in tables 6 and 7. 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®.

Table 6: Primary Effectiveness Results (Intent-to-treat population)

	SWC + Drains (N= 50)	SWC + Drains and TissueGlu® (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

Table 7: Cumulative Wound Drainage Output

	SWC + Drains (N=50)	SWC + Drains and TissueGlu® (N=100)	P-value
Total Wound Drainage	622.1 ± 689.4 (50) (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) (26.0,438.5,5023.0)	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.

2. Safety results:

The analysis of safety was based on the cohort of 148 patients available for the 12- month evaluation. The key safety outcomes for this study are presented below in tables 8 to 13. Device related adverse effects are reported in tables 9 and 10.

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 TissueGlu® treatment group (Tables 11 and 12). 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. See table 10 for comparison of wound complication adverse events in the control and TissueGlu® treatment groups.

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. Table 15 lists the un-resolved adverse events reported in the study.

Table 8: Wound Complications

	SWC + Drains		SWC + Drains and TissuGlu®		P-value
	Events	Subjects	Events	Subjects	
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.

Table 9: Serious Device-Related Adverse Events

	SWC + Drains and TissuGlu® (N=100)	
	Events	Subjects
102-Hematoma	2	2 (2.0%)
108-Seroma 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

Table 10: 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

Table 11: 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.

Table 12: 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.

Table 13: 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
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

Pivotal Clinical Study 2

A Pivotal, Prospective Clinical Investigation for a Randomized, Controlled, Multicenter Non-inferiority Study Comparing Standard Wound Closure Technique with Drains (control) to Standard Wound Closure Techniques Plus TissuGlu® and No Drains (test) during Abdominoplasty

Objectives:

- To establish that the use of TissuGlu® Surgical Adhesive is a safe and effective alternative to drains (standard of care) for fluid management following abdominoplasty.
- To evaluate the impact of TissuGlu® Surgical Adhesive on post-operative invasive treatments, and seroma formation.
- To evaluate the impact of TissuGlu® Surgical Adhesive on post-operative subjective satisfaction and quality of life.
- To document the type and duration of adverse events associated with TissuGlu® use during an abdominoplasty procedure as an alternative to drains.

Study Design: Patients were enrolled and treated between March 2013 and September 2013. There were 5 investigational sites. This clinical study was a pivotal, prospective 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. The study included 130 subjects randomized 1:1 across 5 investigational sites. 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. Blake drains and placement locations were standardized among sites.

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.

The non-inferiority of SWC plus TissuGlu® without drains (test) relative to SWC with drains (control), consists of a between-group comparison of the number of invasive treatments. The non-inferiority hypotheses that were tested are as follows:

H0: MT-MC \geq d

H1: MT-MC < d

where MT is the location parameter for the distribution of number of invasive treatments for the test arm, MC is the location parameter for the distribution of number of invasive treatments for the control arm, and d is the non-inferiority margin of 1. A one-sided 97.5% confidence interval is constructed for the Hodges-Lehmann estimate of location shift between the two groups (MT - MC). The upper bound of the confidence interval was compared to a delta of 1 (d=1). An upper bound value less than 1 leads to rejection of the null hypothesis, thus SWC plus TissuGlu® without drains is considered non-inferior to SWC with drains in the number of invasive treatments.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal clinical study 2 was limited to patients who met the following inclusion criteria

- Male or female ≥ 18 years of age
- Provide a 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 willing to follow guidelines related to resumption of daily activities
- Agree not to schedule any additional elective surgical procedures that involves 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
- \leq ASA2 - American Society of Anesthesiologists Physical Classification System (2=subject with mild systemic disease)
- Have a Body Mass Index (BMI) ≤ 28

Patients were not permitted to enroll in the pivotal clinical study 2 if they met any of the following exclusion criteria:

- Pregnancy or lactation
- Previous abdominoplasty
- Prior bariatric or weight loss surgery
- Lost $\geq 15\%$ 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 anticoagulation 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

2. Follow-up Schedule

Subjects were required to attend follow-up visits at days 3, 6, 9, 12, 16, 25, 32, 39, 53, 67, and 84.

3. Clinical Endpoints

With regards to 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

With regards to 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.

B. Accountability of PMA Cohort

At the time of database lock, of 130 patients enrolled in PMA study, 126 patients are available for analysis at the completion of the study, the 12-week post-operative visit.

Table 14: Subject Accounting

Disposition	SWC + Drains	SWC + TissueGlu®	All Subjects
Enrolled	64	66	130
Completed Week 1 Visit			
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

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an abdominoplasty study performed in the US.

Table 15: Study Populations

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

Table 16: Demographics and Medical History: There were no notable differences in demographics between the TissuGlu® and control patients. Like pivotal study 1, most all of the subjects enrolled were female.

	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%)	1.0000
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	45/64 (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 (%)	4.2 ± 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 (51.5%)	0.6042
Any Surgical History	53/64 (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)	75.1 ± 9.4 (66) (56.0,76.5,97.0)	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 variables and Count/N (Percent) for categorical variables. P-values are from Wilcoxon test for continuous variables and Fisher's Exact test for categorical variables.

D. Safety and Effectiveness Results

1. Effectiveness results

The analysis of effectiveness was based on the cohort of patients evaluable at the 12-week time point. Key effectiveness outcomes are presented in tables 17 to 18. The primary effectiveness criteria for the study, a comparison of invasive procedures, was met for both the per protocol and intent-to-treat populations (Tables 17 and 18).

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.

Table 17: 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.

Table 18: 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†		

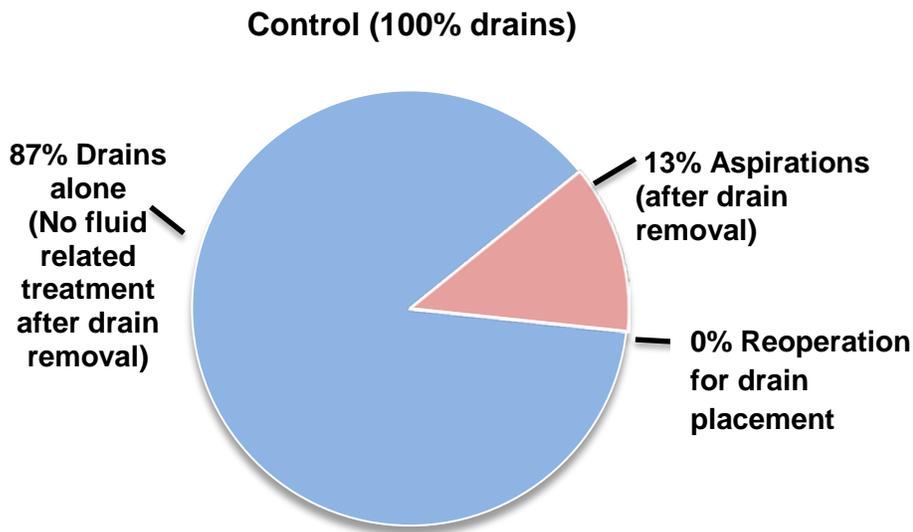
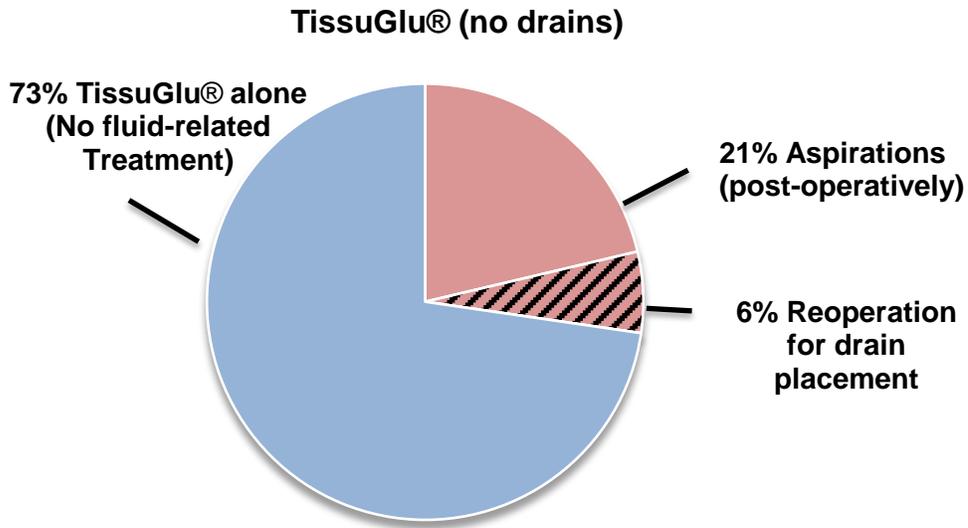
1 The Hodges-Lehman estimate of location shift and exact one-sided upper 97.5% confidence limit are presented.

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 effectiveness 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, and 6% receiving reoperation for drain placement 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.

Table 19: 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 measures. The analyses of these outcomes are descriptive with no formal hypothesis testing. Table 22 and 23 summarize the post-operative questionnaire results through follow-up for the SWC+Drains and SWC+ TissuGlu® groups, respectively. 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.

Table 20: 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%	52.5%	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	9.7%	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%

Table 21: 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=65)	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%

2. Safety

The analysis of safety was based on the cohort of patients available for the 12-week evaluation. The key safety outcomes for this study are presented below in tables 22 to 28. Device related adverse effects are reported in tables 23 to 24.

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 (Table 25). 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 (Table 26). There was one serious adverse event (hematoma) in the control group (Table 27).

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.

Table 22: Aspiration Volumes Early in the trial, overly aggressive treatment of the TissuGlu® no drain group led to aspirating seromas frequently and at low volumes.

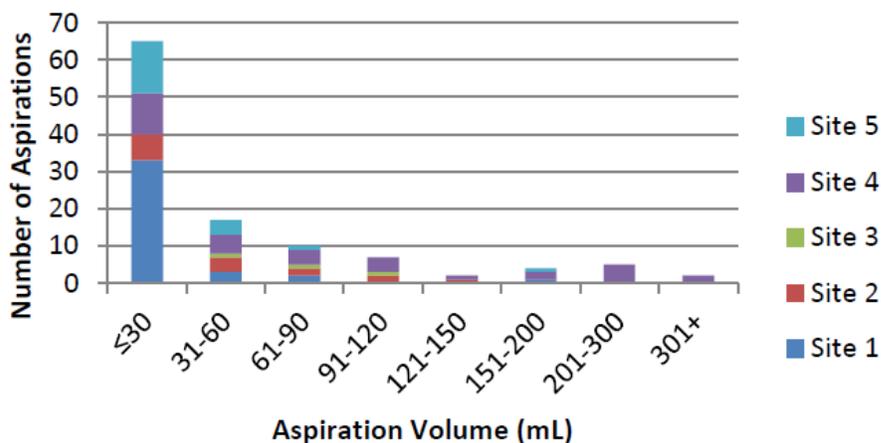


Table 23: Serious Device-related Adverse Events The serious hematoma in the TissuGlu® group was classified as “possibly device related”. This patient had the left lateral gutter opened, and the hematoma was evacuated and all oozing points were cauterized with electrocautery. Two drains were placed and 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).

Table 24: 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).

Table 25: 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

Table 26: 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 - Pncumonia	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

Table 27: Serious Adverse Events: Seroma Formation (Both Pivotal Trials)

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

Table 28: Combined Table of Adverse Events (Both Pivotal Trials)

Adverse event	Control (N=114)		TissuGlu® (N=166)		P-value*
	# events	# subjects	# events	# subjects	
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	5	5 (4.4%)	8	8 (4.8%)	1.0000
Other Abdominal	4	4 (3.5%)	7	7 (4.2%)	1.0000
Other GI event	2	2 (1.8%)	5	4 (2.4%)	1.0000
Other neurologic	1	1 (0.9%)	0	0 (0%)	0.4071
Other pulmonary	1	1 (0.9%)	1	1 (0.6%)	1.0000
Other renal	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
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.

See individual adverse event tables for definition of “other” events.

Financial Disclosure

The Financial disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study 1 included 6 primary Clinical Investigators. The pivotal clinical study 2 included 5 primary Clinical Investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

C. SUMMARY OF SUPPLEMENTAL 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 as 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 fluid management is required to prevent seroma formation in abdominoplasty patients. *Andrades , et al., Plast Reconstr Surg. 2007 120(4):935-951.*

C. Feasibility study 1: Safety and preliminary efficacy study evaluating TissuGlu[®] compared to Standard Wound Closure for abdominoplasty procedures, with days to drain removal as the primary endpoint. The study was an open-label, prospective, randomized, multicenter study with two treatment group (standard wound care (SWC) closure technique versus SWC closure technique plus TissuGlu[®] treatment). The objectives of the clinical investigation were to determine the safety of the TissuGlu[®] device used during abdominoplasty procedures, to obtain a preliminary assessment of the efficacy of the TissuGlu[®] device in reducing post-operative drainage thereby allowing earlier drain removal in patients undergoing an abdominoplasty procedure, to examine the performance of the delivery method, and to evaluate potential device-related complications.

42 subjects were screened for inclusion into the study and 40 subjects were randomized with 20 subjects receiving standard of care treatment and 20 subjects receiving standard of care + TissuGlu® treatment. Subjects scheduled for at least one full thickness surgical incision of at least 20 cm in length as part of an elective standard abdominoplasty procedure. Subjects were excluded from the study with any of the following major criteria: obesity, as defined by BMI >30, current active tobacco use, including smokeless (chewing) tobacco, known blood clotting disorder, and current diagnosis of diabetes. Each patient had two drains placed during surgery to permit monitoring of fluid output. The drain removal criteria used for the study was established as less than 30 ml of fluid measured in a 24 hour period. Clinical assessments were performed during the hospital stay, at discharge from the hospital (day 2), daily (by healthcare professional) until day of final drain removal, at 14 days (± 3 days), 30 days (± 3 days) and 90 days (± 3 days) post operatively.

Results: All adverse events were categorized as either unlikely or not related to the device. A total of 5 serious adverse events occurred to 5 subjects (2 serious adverse events in 2 subjects in the standard of care + TissuGlu® group and 3 serious adverse events in 3 subjects in the standard of care group). The time to drain removal for the second drain showed a 27% decrease in time to drain removal (Table 4).

Table 29: Feasibility Trial 1 results

	TissuGlu®	Control	p-value
Time to drain removal (days)	2.9 ± 1.35	3.7 ± 1.5	p=0.13
Total drainage volume (mL)	208.7 ± 138.2	303.5 ± 240.8	p=0.14
Adverse events	14 events in 8 subjects	18 adverse events in 10 subjects	

D. Feasibility study 2: A safety study examining the use of TissuGlu® without drains in non-weight-loss and weight-loss patients. The clinical investigation was a prospective, open-label, single armed, multi-center study in which all subjects were treated with standard wound closure techniques plus TissuGlu® without drains. No control subjects were included in this clinical investigation. Subjects were followed for 60 days post-surgery. The objective of this study was to evaluate the safety and efficacy of the TissuGlu® device without a fluid drainage system in abdominoplasty.

31 subjects desiring abdominoplasty surgery were enrolled in 2 investigational centers in Germany (16 non-weight loss and 15 weight loss patients). At entry into this study, all

subjects were 18 years of age or older with a BMI \leq 28, in good general health with no conditions that would significantly impact wound healing and were scheduled for at least one full thickness surgical incision of at least 20 cm in length as part of an elective standard abdominoplasty procedure. Subjects were enrolled in the trial for a period of 60 days. The primary endpoint was safety of TissuGlu® in abdominoplasty surgery. Analysis focused on the number of wound complications: seroma formation, wound dehiscence, infection, skin necrosis and hematoma. Clinical assessments were performed pre-operatively, intra-operatively, during hospital stay (to be 1-2 nights), at discharge from hospital, at 5 days (\pm 1 days), 14 days (\pm 2 days), 30 Days (\pm 3 days) and 60, days (\pm 3 days).

Results: From the non-weight loss set (weight loss was $<$ 15% prior to TissuGlu® treatment), 7 subjects underwent one or more seroma aspirations. In the weight loss set (weight loss was \geq 15% prior to TissuGlu® treatment), 14 subjects underwent one or more seroma aspirations.

Seroma was the most frequently occurring AE (n=81), accounting for 83.5% of all AEs. Twenty (20) non-seroma type AEs occurred in this clinical investigation. Other reported events included hematoma (5.2% of all adverse events), impaired wound healing (1.0%), post-procedural hematomas (1.0%), pyrexia (2.1%), skin necrosis (4.1%) and wound dehiscence (2.1%).

Conclusions: The clinical study results suggest the need for greater postoperative fluid aspirations and higher rates of postoperative adverse events in patients who had a history of weight loss.

Table 30: Feasibility Trial 2 results

	non-weight loss	weight loss
mean number of seroma aspirations	1.6	3.5
mean cumulative aspiration volume (mL)	156.7	537.5
seromas	28 (34.6%)	53 (65.4%)
necrosis	3 (75.0%)	1 (25.0%)
Infected seroma	2 (50%)	2 (50%)

XI. PANEL MEETING RECOMMENDATION AND FDA’S POST-PANEL ACTION

A. Panel Meeting Recommendation

An advisory panel meeting was held on August 1, 2014. The General and Plastic Surgery Devices Panel voted 11-0-0 there is reasonable assurance TissuGlu® is safe, 6-5-0 there is a reasonable assurance TissuGlu® is effective, and 6-4-1 with one abstention the benefits of TissuGlu® outweigh the risks. The advisory panel unanimously agreed the pre-clinical and clinical evidence supported the safety of TissuGlu® in abdominoplasty procedures. Panel meeting summary:

<http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/GeneralandPlasticSurgeryDevicesPanel/UCM407227.pdf>

The advisory panel was divided on effectiveness with five panel members voting the clinical evidence did not provide a reasonable assurance of effectiveness. Panel members expressed concerns with the clinical trial design including the absence of a no-treatment control arm, the absence of a more objective method of seroma detection, and the use of a pre-determined number of invasive treatments in the control arm. In addition, Panel members noted the natural history of seromas following abdominoplasty is not well studied, and that seromas may either resolve on their own or form a chronic seroma cavity with or without the use TissuGlu®. Abdominoplasty is an aesthetic procedure and complications of seromas are not well tolerated in this population. Therefore, CDRH concluded a no-treatment control arm was not appropriate.

The advisory panel concluded there was not adequate data to support efficacy in obese or weight loss patients, and recommended including a warning that these patients may be at increased risk for seroma related complications. The advisory panel also concluded there was not adequate data to support efficacy in large flap surgeries other than abdominoplasty due to differences in wound geometry, shear forces, and lymphatic involvement.

B. FDA's Post-Panel Action

After the Advisory Panel meeting, FDA completed review of the product labeling and incorporated the Panel's recommendations into the labeling. These labeling changes included limiting the Indications for Use Statement to abdominoplasty, and adding warnings for the treatment of patients with BMI > 28 and weight loss patients, which have a propensity for fluid accumulation and may have an increased risk of seroma formation.

XII. CONCLUSIONS DRAWN FROM PRE-CLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the first pivotal study, 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 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 most 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.

XIII. CDRH DECISION

CDRH issued an approval order on February 3, 2015. The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facility has been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

3 APPROVAL SPECIFICATIONS

Directions for use: See Instructions for Use.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device Instructions for Use.

Post-approval Requirements and restrictions: See approval order.