



# PMA P130023 Cohera Medical TissuGlu®

General and Plastic Surgery Devices Advisory Panel  
August 1, 2014



# P130023 Review Team

Janette Alexander, MD: Clinical Review

Ying Yang, PhD: Statistical Review

Ozlem Topaloglu, PhD: Epidemiology Review

George Mattamal, PhD: Chemistry Review

Kelley Burrige, PhD: Chemistry Review

Laura Whare, BS: GMP Review

Dolores Bernato, RN/MN: Bioresearch Monitoring Review

Joseph Nielsen, PhD: Lead and Biocompatibility Review



# FDA Presentation

Introduction and preclinical studies: Joe Nielsen, PhD

Clinical study design and results: Janette Alexander, MD

Statistical plan and results: Ying Yang, PhD

Post-Approval study: Ozlem Topaloglu, PhD

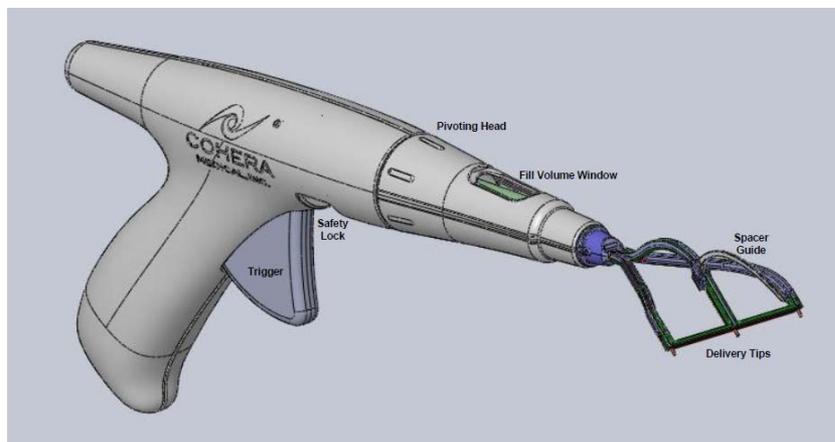
Panel questions: Joe Nielsen, PhD

# Device Description

TissuGlu® is a new tissue adhesive consisting of a polyurethane pre-polymer generated by reacting trimethylolpropane with lysine di-isocyanate ethyl ester. The polymer polymerizes *in situ* upon contact with moisture.

TissuGlu® is provided in a hand-held disposable delivery device containing 5 mL of adhesive.

The adhesive is delivered in drops onto planar tissue surfaces. The applicator delivers 3 linear drops of adhesive, at an average drop volume of 25-40 microliters.

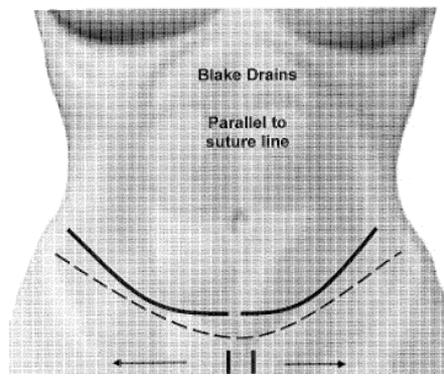


# Indications for Use

TissuGlu® Surgical Adhesive is indicated for the approximation of tissue layers where subcutaneous dead space exists between the tissue planes in large flap surgical procedures such as abdominoplasty.

FDA seeks Advisory Committee input on whether the clinical data provides a reasonable assurance of safety and effectiveness for abdominoplasty surgeries.

Additional large flap surgical procedures: mastectomy, inguinal lymph node dissection, transverse rectus myocutaneous flap reconstruction, latissimus dorsi flap reconstruction, and potentially post-bariatric body contouring operations.



# TissuGlu® Specifications

Key TissuGlu® specifications include:

viscosity

shear strength

gel point

residual crosslinker

Sterility

Endotoxin

Shelf life

# Biocompatibility

TissuGlu® passed the following biocompatibility studies:

- Cytotoxicity
- Intracutaneous Reactivity
- Sensitization
- Acute Systemic Toxicity
- Hemolysis
- Subcutaneous Implantation
- Rabbit Pyrogen test USP <151>
- LAL endotoxin testing USP <85> and <161>

# Biocompatibility/Toxicity

- 13-week subchronic toxicity
- 6 and 12-month chronic toxicity studies
- Reproductive toxicity testing
- Genotoxicity: bacterial reverse mutation, mouse lymphoma, and *in vivo* micronucleus
- Carcinogenicity testing: transgenic rasH2 mouse tumorigenicity model

# *In Vivo* Degradation Study

Animal study conducted to evaluate the long-term degradation profile and biocompatibility of TissuGlu®.

Bilateral abdominal subcutaneous pockets were created using blunt dissection and electrocautery. Approximately 1.0 ml of TissuGlu® was applied drop wise onto the abdominal wall surface.

The most significant degradation of TissuGlu® occurred over the first 6-months of the study. The surrounding tissue matured to a fibrotic capsule that remained until the end of the 24-month study.

The failure of the TissuGlu® polymer to fully resorb over 24-months was considered a potential clinical safety concern, and prompted FDA's request for 12-months of follow-up in the first clinical study.

# Simulated Abdominoplasty Animal Model

A 3-week proof-of-concept animal study was conducted to evaluate the effectiveness of TissuGlu® in reducing the volume of postoperative wound exudates after a simulated abdominoplasty procedure.

Bilateral abdominal subcutaneous pockets were created using blunt dissection and electrocautery. Approximately 1.0 ml of TissuGlu® was applied drop wise onto the abdominal wall surface.

Results: Controls 690 mL exudate, TissuGlu® 44 mL exudate

Conclusion: TissuGlu® was effective in reducing exudate in simulated abdominoplasty canine model.

# Conclusions

The applicant has identified key product specifications.

The preclinical testing provides a reasonable assurance the TissuGlu® product will be biocompatible, and potential toxicity risks have been adequately characterized.

Animal evaluation in a model approximating device use in humans indicated TissuGlu® worked as intended.



# ***TissuGlu***

## **P130023**

**Clinical Review**

**Janette Alexander, MD**

**PRSB1/DSD/ODE/CDRH**

# Proposed Indication for Use

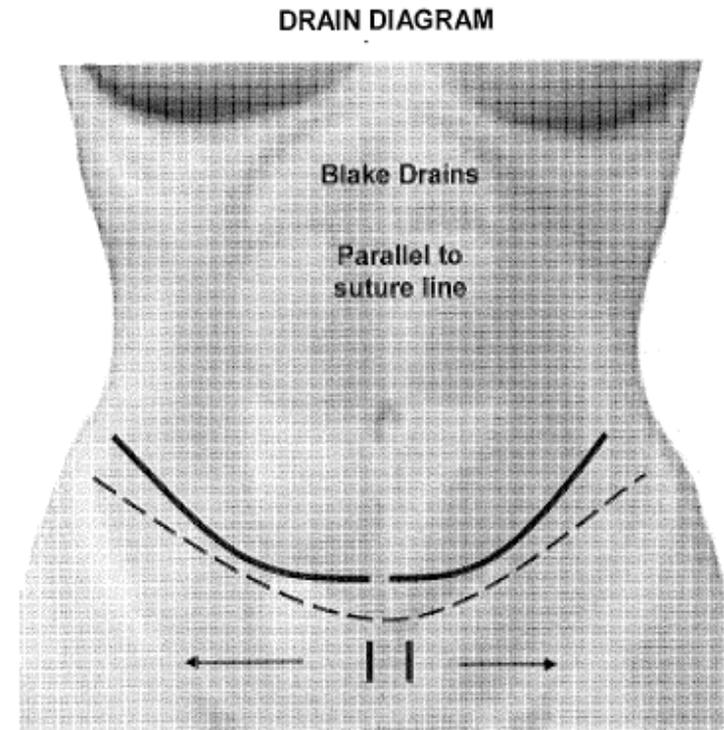
TissuGlu® Surgical Adhesive is indicated for the approximation of tissue layers where subcutaneous dead space exists between the tissue planes in large flap surgical procedures such as abdominoplasty.

# History

- Pilot study #1- Drains vs Drains+TissuGlu
- Pilot Study #2- TissuGlu only, weight loss vs non-weight loss
- Pivotal study #1- Drains vs Drains+TissuGlu
- Pivotal study #2- Drains vs TissuGlu
- OUS post-market use
  
- **All of the controlled clinical studies were performed in abdominoplasty**

# Abdominoplasty

- Standard procedure
  - Large surface area
- Necessity for drains
  - Wound dehiscence
  - Persistent seroma
- Differences with TissuGlu
  - Up to 5cc in droplets
  - Hold in place
  - Time to cure – 30-45 minutes



# Pilot Study #1

## TissuGlu® compared to Standard Wound Closure

- **Primary endpoint - days to drain removal**
- 21 patients with drains (control), 19 patients with drains plus TissuGlu
- Inclusion: BMI  $\leq$  30
- Drain removal when  $<$  30ml/24 hrs
- Patients were seen daily until drain removal

# Pilot Study #1 N=40

## Results

### Drains vs Drains+TissuGlu

	TissuGlu® N=19	Control N=21
Time to drain removal (days)	2.9 ± 1.35	3.7 ± 1.5
Total drainage volume (mL)	208.7 ± 138.2	303.5 ± 240.8
Adverse events	14 events in 8 subjects	18 adverse events in 10 subjects

# Pilot Study #1

## Conclusions

N=40

- A trend of decrease in time to drain removal
- No significant difference in adverse events

# Pilot Study #2

## TissuGlu only, Weight loss vs non-Weight loss

- A safety study examining the use of TissuGlu® without drains in non-weight-loss and weight-loss patients.
- Prospective, open-label, multi-center study in which all subjects were treated with standard wound closure techniques plus TissuGlu® without drains.
- Subjects were followed for 60 days post-surgery

# Pilot Study #2

(no drains)

- 16 non-weight loss patients (BMI  $\leq 28$ )
- 15 weight loss patients (BMI  $\leq 28$  plus  $> 15\%$  prior weight loss)

## Feasibility Trial 2 results

	non-weight loss	weight loss
mean number of seroma aspirations	1.6 (0-10)	3.5 (0-7)

# Pilot Study #2 Results, cont

## No drains

	non-weight loss- N=16	weight loss N=15
mean cumulative aspiration volume (mL)	156.7	537.5
Seroma aspirations	28	53
necrosis	3	1
Infected seroma	2	2

# Pilot Study #2

## Weight loss vs Non-weight loss

### Conclusions

- Small study results suggest the need for more postoperative fluid aspirations and higher rates of postoperative adverse events (seromas) in patients who had a history of weight loss
- Panel discussion of relevance requested

# Pivotal Study #1

## Drains vs Drains+TissuGlu

- Prospective, Randomized, Controlled, Single-blind, Multicenter US Clinical Trial
- 150 abdominoplasty patients
- Randomized 2:1
  - Drains plus TissuGlu
  - Drains only
- Patients were blinded
- Follow-up for 12 months

# Endpoints, pivotal study #1

## Drains vs Drains+TissuGlu

- Primary endpoint – mean time to reach criteria for drain removal (<30ml/24hrs)

### Secondary endpoints

cumulative wound drainage

additional clinic visits

duration of hospital stay

number and type of complications

number and type of additional procedures

Patient Reported Pain, Physical component and Mental component scores

# Inclusion Criteria

- Good health
- BMI  $\leq$  35
- Scheduled for abdominoplasty
- Weight loss patients were allowed

# Results

## Primary Effectiveness Analysis: Time to Last Drain Removal in days

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



# Safety Results

	SWC+Drains (N=50)		SWC +Drains and TissuGlu® (N=100)		P-value
	Events	Subjects	Events	Subjects	
Seroma Formation	11	9/50 (18.0%)	24	23/100 (23.0%)	0.5326
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
Wound Complication	2	2/50 (4.0%)	4	4/100 (4.0%)	1.0000

# Pivotal Study #1

## Weight loss analysis – Secondary endpoint

<b>Population</b>	<b>SWC+ Drains # subjects</b>	<b>SWC+Drains+ TissuGlu # subjects</b>	<b>All subjects</b>
Intent to Treat	50	100	150
Weight Loss only	18	36	54
Non-weight loss only	32	64	96

# Pivotal Study #1 Results

## Cumulative wound drainage (mean)

	SWC+ Drains	SWC + Drains+ TissueGlu
Total wound drainage (ml) +/-SD	622 +/- 689	640 +/- 784
Weight loss (ml) +/-SD	834 +/- 779	848 +/- 1104
Non weight loss (ml) +/-SD	502 +/- 614	522 +/- 499

# Pivotal Study #1

## Drains vs Drains+TissuGlu

### Conclusions

- Study did not meet success criteria for shortening time to drain removal.
- Weight loss patients had more wound drainage
- Pivotal study 1 only provides 12 month safety data

# Pivotal Study #2

## Drains vs TissueGlu

- Prospective Randomized, Controlled, Multicenter Non-inferiority Study
- Compares Standard Wound Closure Technique with Drains (control) to Standard Wound Closure Techniques Plus TissueGlu® and No Drains (test) in Abdominoplasty

# Pivotal Study #2

## Drains vs TissueGlu

The primary endpoint of the study was the number of post-operative invasive treatments:

- 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

Seroma was to be diagnosed and aspirated by the presence of a palpable fluid wave

# Panel input requested

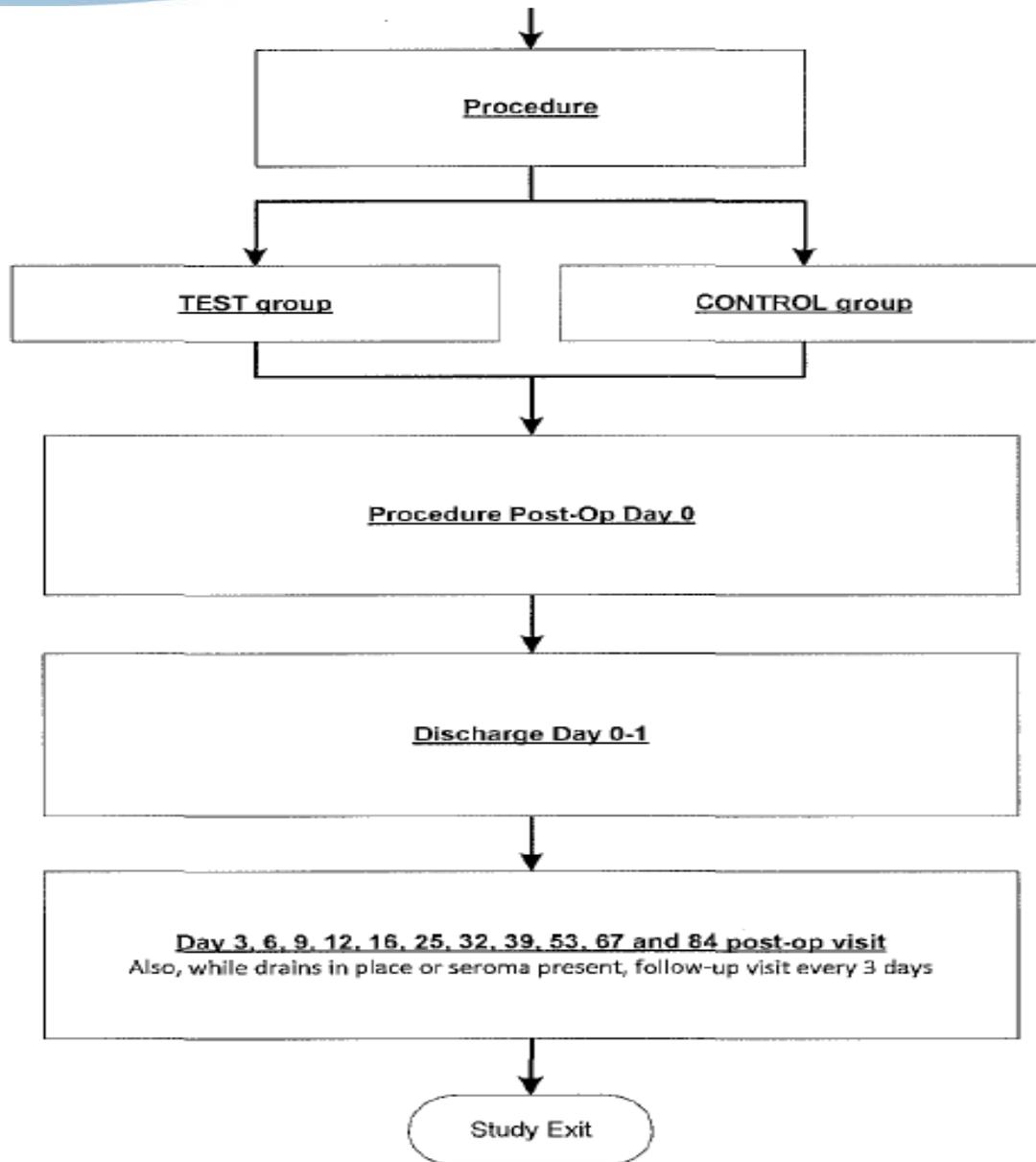
- During the trial design phase, a clinical judgment was made that a clinical benefit exists if up to two aspirations are needed compared to placement and removal of two drains in abdominoplasty surgery.
- You will be asked to comment on whether you agree with this clinical judgment, and whether the insertion and removal of drains is clinically comparable to needle aspirations.

# Secondary Endpoints

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

# Study Design

- 130 subjects
- Randomized intra-operatively 1:1
- 5 investigational US sites



# Inclusion Criteria

- Body Mass Index (BMI)  $\leq 28$ , healthy patients
- Surgical incision of at least 20 cm in length as part of elective abdominoplasty
- $\leq$  ASA2

# Exclusion criteria

- Prior bariatric or weight loss surgery
- Lost  $\geq 15\%$  of maximum lifetime bodyweight (excluding pregnancy weight gain)
- 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
- Previous abdominoplasty

# Demographics

There were no notable differences in demographics between the TissuGlu and control patients.

# Subject Accounting

Disposition	Drains	TissuGlu	All
Completed study	62	64	126
Withdrew consent	1	0	1
Lost to followup	0	2	2
Other	1	0	1

# Safety Outcomes, pivotal study #2

## Surgical Site Complications

	SWC + Drains		SWC + TissuGlu		P-value
	Events	Subjects	Events	Subjects	
Seroma	9	8/64 (12.5%)	22	18/66 (27.3%)	0.048
Dehiscence	0	0%	2	2/66 (3%)	0.4962
Skin necrosis	0	0%	1	1/66 (1.5%)	1.0
Hematoma	1	1/64 (1.6%)	3	3/66 (4.5%)	0.62
Wound complication	0	0%	1	1/66 (1.5%)	1.0

# Non-Serious Device-related Adverse Events

	SWC + TissuGlu N=66	
	Events	Subjects
Hematoma	2	2 (3%)
Seroma	18	16 (24%)
Wound dehiscence	2	2 (3%)
Wound infection	1	1 (1.5%)
<b>Total</b>	<b>23</b>	<b>21 (31.8%)</b>

# Wound Dehiscence Patients

- Two tissuGlu patients had wound dehiscence
  - 05-003 duration 47 days, resolved
  - 05-009 duration > 48 days, unresolved at study completion

# Serious Adverse Events device-related

- Four TissuGlu patients had placement of seven drains

	SWC + TissuGlu N=66	
	Events	Subjects
Hematoma	1	1 (1.5%)
Seroma	4	3 (4.5%)
Total	5	4 (6.1%)

# Serious Adverse Events, Non Device-related

	SWC + Drains		SWC + TissuGlu	
	Events	Subjects	Events	Subjects
Hematoma	1	1 (1.6%)	0	0
Ileus	0	0	1	1 (1.5%)

# Summary all Adverse Events Pivotal Study #2

## Drains vs TissuGlu

	SWC + Drains		SWC + TissuGlu	
	Events	Subjects	Events	Subjects
Seroma	9	8/64 (12.5%)	22	18/66 (27.3%)
Wound dehiscence	0	0	2	2/66 (3%)
Skin necrosis	0	0	1	1/66 (1.5%)
Hematoma	1	1/64 (1.6%)	3	3/66 ( 4.5%)
Wound complication	0	0	1	1/66 (1.5%)

# Combined Table of Adverse Events (Both Pivotal Trials)

Adverse event	Control (N=114), events	Control (N=114), subjects	TissuGlu (N=166), events	TissuGlu (N=166), subjects	P-value
Cellulitis	3	2 (1.8%)	1	1 (0.6%)	0.5687
<b>Hematoma</b>	1	1 (0.9%)	7	7 (4.2%)	0.1476
Infection	0	0 (0%)	1	1 (0.6%)	1.0000
<b>Seroma formation</b>	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	1	1 (0.9%)	6	5 (3.0%)	0.4063
Wound complication	2	2 (1.8%)	5	5 (3.0%)	0.7045
Wound dehiscence/separation	12	9 (7.9%)	15	15 (9.0%)	0.8299
Wound infection	0	0 (0%)	1	1 (0.6%)	1.0000
<b>Infection: all</b>	4	3 (2.6 %)	9	8 (4.8%)	0.5338

# Study Populations

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



# Primary Effectiveness Results

# Primary Effectiveness Endpoints (per-protocol N=103)

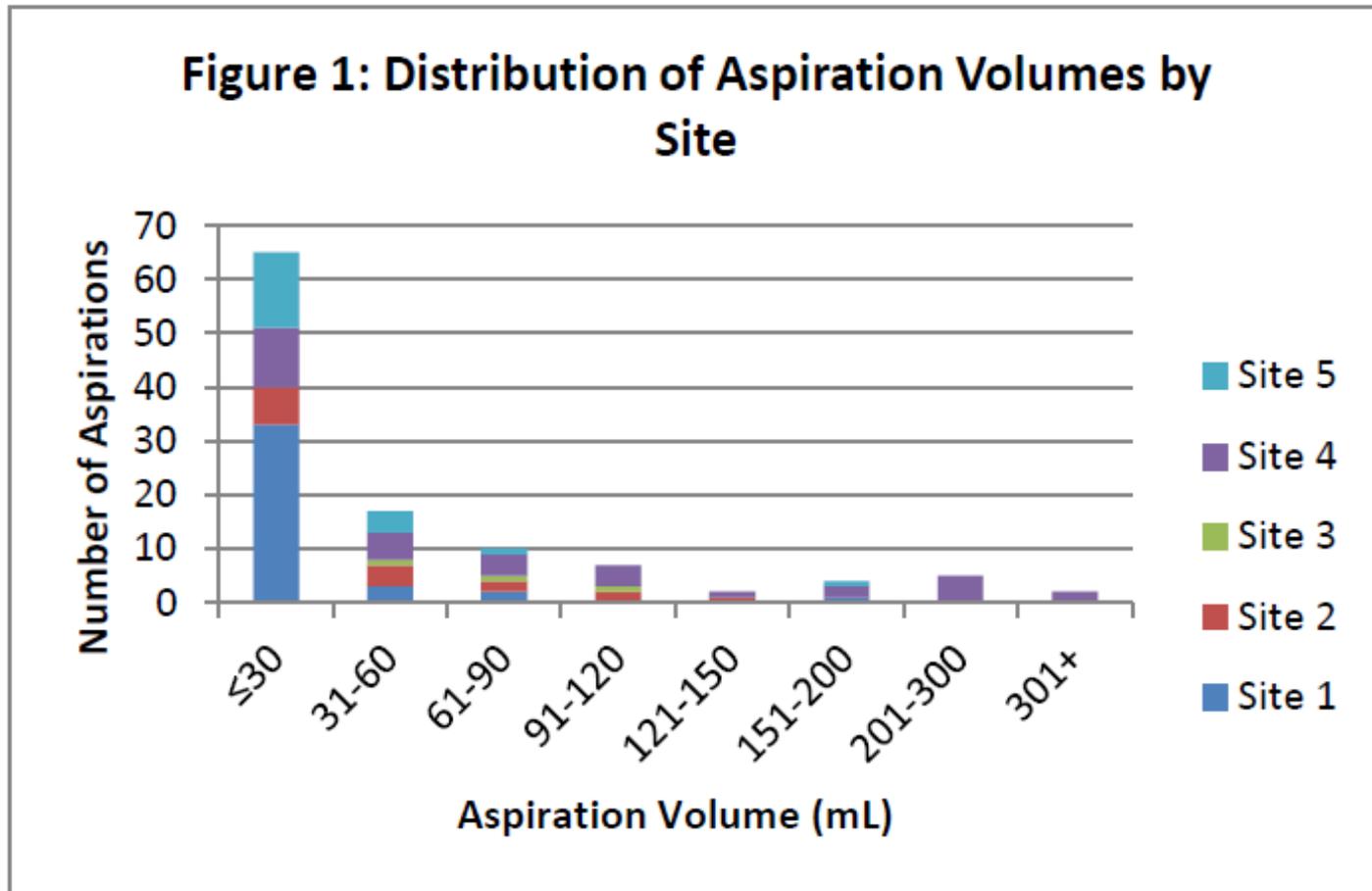
Number of post-operative invasive treatments	SWC + drains (n=52)	SWC + TissuGlu (n=51)
<b>Median</b>	2	0
Min, Max	2.0, 8.0	0, 4.0
<b>Mean (SD)</b>	2.2 (0.9)	0.2 (0.7)
Min, Max	2.0, 8.0	0, 4.0
<b>Number of needle aspirations</b>		
<b>Median</b>	0.0	0.0
Min, Max	0.0, 6.0	0.0, 4.0
<b>Mean (SD)</b>	0.2 (0.9)	0.2 (0.7)
Min, Max	0.0, 6.0	0.0, 4.0
<b>Removal of an in-dwelling drain</b>		
<b>Median</b>	2.0	0.0
Min, Max	2.0, 2.0	0.0, 0.0
<b>Mean (SD)</b>	2.0 (0.0)	0.0 (0.0)
Min, Max	2.0, 2.0	0.0, 0.0
<b>Total number of events</b>	104	0.0

# Primary Effectiveness Analysis

## (intent-to-treat N=130)

Number of post-operative invasive treatments	SWC + drains (n=64)	SWC+TissuGlu (n=66)
<b>Median</b>	2	0
<b>Mean (SD)</b>	2.4 (1.2)	1.8 (3.8)
<b>Min, Max</b>	2.0, 8.0	0, 17.0
<b>Total number of events</b>	152	119
<b>Needle Aspiration</b>		
<b>Median</b>	0.0	0.0
<b>Mean (SD)</b>	0.4 (1.2)	1.7 (3.7)
<b>Min, Max</b>	0.0, 6.0	0.0, 17.0
<b>Total number of events</b>	24	112
<b>Removal of an in-dwelling drain</b>		
<b>Median</b>	2	0
<b>Mean (SD)</b>	2.0 (0.0)	0.1 (0.4)
<b>Min, Max</b>	2.0, 2.0	0, 2.0
<b>Total number of events</b>	128	7

# Aspiration Volumes



# Secondary Endpoint Results

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

# Total wound drainage, Cumulative drain volume, and Aspiration volume

	<b>SWC+drains N=64</b>	<b>SWC+TissuGlu N=66</b>
Total wound drainage	411 ml	97 ml
Cumulative drain volume	397 ml	--
Aspiration volume	14.9 ml	97 ml

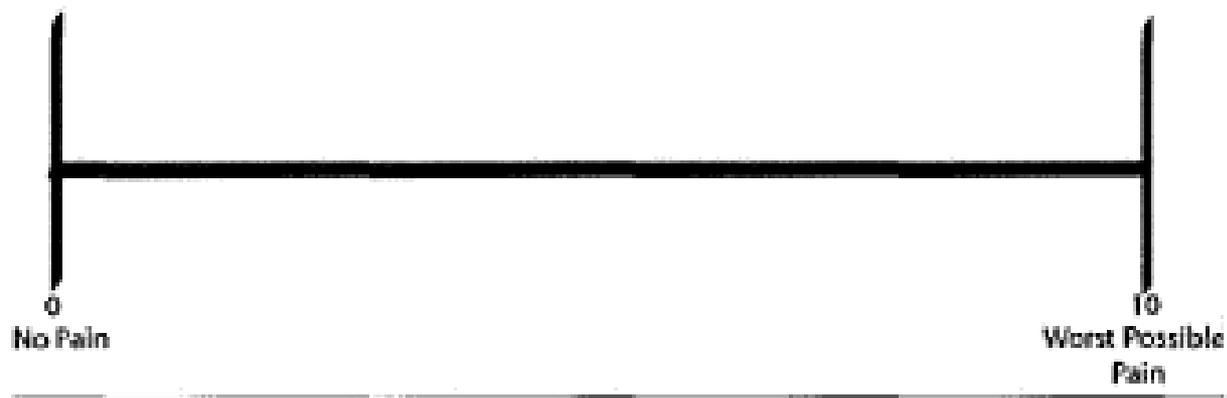
# Cumulative days of invasive treatment (days with drains in and days aspirated)

	SWC+ Drains	SWC + TissuGlu
Days to drain removal	6.9	--
Number of aspirations	0.4	1.7
Cumulative days of invasive treatment	7.3	1.6

# Pt Reported Outcomes

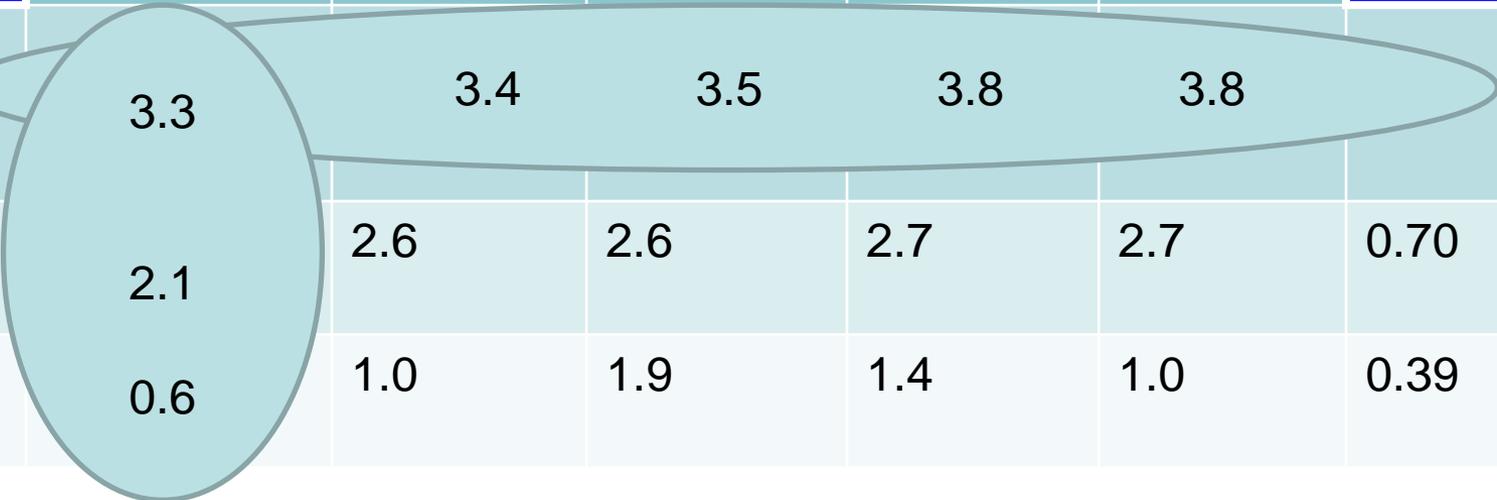
- VAS Pain Score
- Quality Metrics Health Survey SF-8 Score
  - Physical component
  - Mental component
- Activity Questionnaire

# VAS Pain Score



# VAS Pain Results

	Drain site	Surgical site		Overall Abdominal		P-value
	SWC+drains	SWC+ Drains	SWC+ TissuGlu	SWC+ Drains	SWC+ TissuGlu	
Day 3	3.3	3.4	3.5	3.8	3.8	
Day 6	2.1	2.6	2.6	2.7	2.7	0.70
Day 16	0.6	1.0	1.9	1.4	1.0	0.39





**SF-8 Questionnaire**

# SF-8 Score

1. Overall, how would you rate your health during the past 24 hours?

Excellent	Very good	Good	Fair	Poor	Very Poor
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>	<input type="checkbox"/> <sub>6</sub>

2. During the past 24 hours, how much did physical health problems your usual physical activities (such as walking or climbing stairs)?

Not at all	Very little	Somewhat	Quite a lot	Could not do physical activities
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

3. During the past 24 hours, how much difficulty did you have doing daily work, both at home and away from home, because of your physical health?

None at all	A little bit	Some	Quite a lot	Could not do daily work
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

4. How much **bodily** pain have you had during the past 24 hours?

None	Very mild	Mild	Moderate	Severe	Very Severe
▼	▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>	<input type="checkbox"/> <sub>6</sub>

5. During the **past 24 hours**, how much energy did you have?

Very much	Quite a lot	Some	A little	None
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

6. During the **past 24 hours**, how much did your physical health or emotional problems limit your usual social activities with family or friends?

Not at all	Very little	Somewhat	Quite a lot	Could not do social activities
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

7. During the **past 24 hours**, how much have you been bothered by **emotional problems** (such as feeling anxious, depressed or irritable)?

Not at all	Slightly	Moderately	Quite a lot	Extremely
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

8. During the **past 24 hours**, how much did personal or emotional problems keep you from doing your usual work, school or other daily activities?

Not at all	Very little	Somewhat	Quite a lot	Could not do daily activities
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

# SF-8 Health Survey, Physical Component Scores

Physical component score	SWC+ Drains	SWC+ TissuGlu
Baseline	57.4	57.2
Day 3	31.9	30.8
Day 6	38.2	39.0
Day 25	51.1	52.3



# Activity Questionnaire

## Activity Questionnaire

THIS PAGE IS TO BE COMPLETED BY THE SUBJECT

1. How many hours were you out of bed and mobile yesterday?

0-1	1-3	3-5	5-8	8+
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

2. How many hours did you spend out of your home yesterday?

0-1	1-3	3-5	5-8	8+
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

3. Have you returned to your normal work or activity schedule?

Yes	No
▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>

4. Check the appropriate box (all that apply) if you performed this activity yesterday?

Took a shower	Walked up stairs	Drove a car	Lifted something heavy	Exercised
▼	▼	▼	▼	▼
<input type="checkbox"/> <sub>1</sub>	<input type="checkbox"/> <sub>2</sub>	<input type="checkbox"/> <sub>3</sub>	<input type="checkbox"/> <sub>4</sub>	<input type="checkbox"/> <sub>5</sub>

**Table 16: Quality of Life Measures: Mean and Median Days to Activity**

Variable	TissuGlu (n=66) Mean (Median)	Control (n=64) Mean (Median)
Days to return to work	23.5 (14.0)	26.3 (18.0)
Days to showering	5.2 (5.0)	9.4 (6.0)
Days to climbing stairs	9.0 (5.0)	12.7 (6.0)
Days to driving	12.6 (10.0)	13.7 (10.0)
Days to lifting heavy objects	38.4 (32.0)	42.0 (36.5)
Days to exercising	42.7 (36.5)	43.1 (38.5)



# Activity

	Returned to normal work		Took a shower	
	TissuGlu	Drains	TissuGlu	Drains
Day 3	0.0%	0.0%	<b>47.7% N=31</b>	<b>28.1% N=19</b>
Day 6	7.7% (5pts)	7.9% (5pts)	<b>83.3% N=55</b>	<b>65.6% N=43</b>
Day 9	21.2%	20.6%	92.4% (62 pts)	81.3% (54 pts)
Day 12	<b>46.9% N=31</b>	<b>39.3% N=25</b>	95.5%	90.6%
Day 16	<b>58.7% N=39</b>	<b>45.2% N=30</b>	93.9%	96.9%

# Patient Reported Outcome Summary

- Trend to quicker showering, climbing stairs and return to normal schedule with TissuGlu
- No difference in pain
- No difference in Physical Component Scores

# Panel input requested

- The patient reported outcomes were not designed to show statistical significance; however, the results appear to show a difference in some of the postoperative functional outcomes including days to showering and days to return to work.
- The first clinical study included patients with previous weight loss surgery and  $BMI \leq 35$ . The second clinical study limited patient inclusion to patients with less than 15% lifetime weight loss and  $BMI \leq 28$ .

# Post Market OUS Experience

- TissuGlu® Surgical Adhesive received CE Marking approval in September of 2011, and been used in other large flap cases including:
  - **Latissimus dorsi flap reconstruction**
  - **No-Drain Mastectomy without Immediate Reconstruction**
  - **Inguinal Lymph Node Dissection**

# OUS Experience

- Latissimus dorsi flap for sternal reconstruction-  
Retrospective review

- 14 patients – TissuGlu + drains
- 10 patients – drains

Mean time to drain  
removal

TissuGlu – 19days  
Control – 24 days

- Mastectomy 27 patients

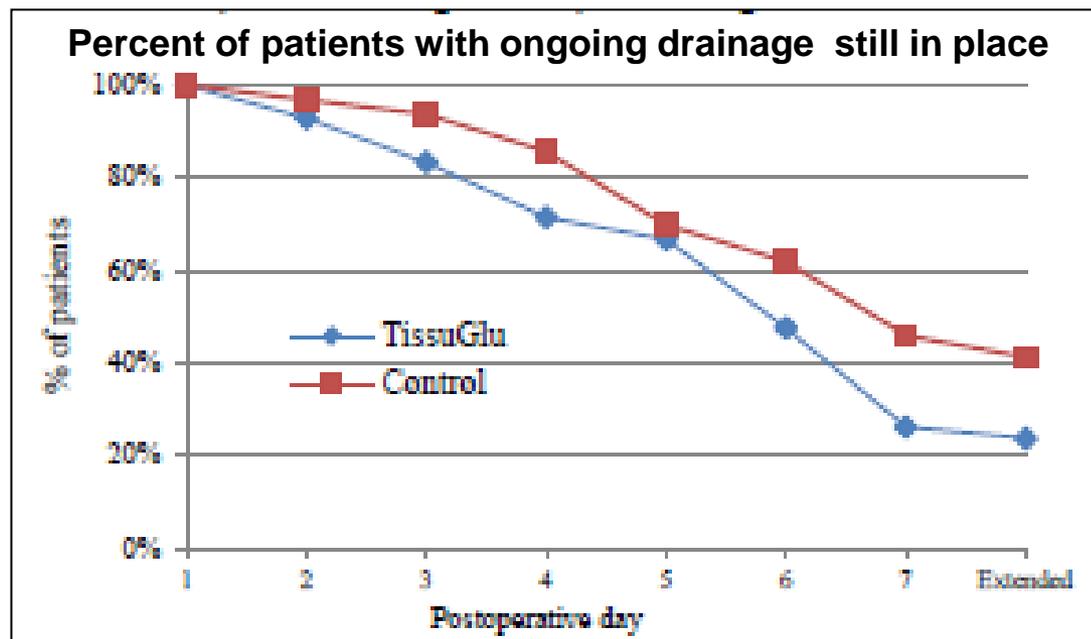
- Axillary dissection - 4 patients
- Sentinel Node biopsy – 9 patients
- Mastectomy only – 14 patients

- Axillary dissection – 2/4 aspirated one time
- +/-SLNB – 3/23 aspirated
- Aspiration volumes not provided

# Post Market Experience

## Inguinal Node Dissection

- Retrospective review of inguinal node dissection for melanoma
  - 39 patients - TissuGlu plus drains
  - 61 patients - control group of consecutive patients with drains



# Panel Questions

- In the pivotal clinical investigations, TissuGlu® was studied in abdominoplasty.
- In the post-market setting, TissuGlu® might be used in large flap surgical revisions in anatomic locations and in oncologic or infectious settings where other factors could influence product safety and effectiveness.
- Panel input is desired.

# Panel Questions

- The Advisory Committee will be asked to comment on whether the abdominoplasty clinical data collected from the pivotal clinical trials and non-peer reviewed case report data adequately supports the safety and effectiveness of the following additional large flap surgical procedures:
  - mastectomy
  - transverse rectus myocutaneous flap reconstruction
  - latissimus dorsi flap reconstruction
  - inguinal lymph node dissection

# Proposed Post-Approval Study

- Active postmarket surveillance study to monitor the device use and the device safety in large flap procedures



*Thank you*





# FDA Statistical Review: TissuGlu (P130023) Cohera Medical, Inc.

Ying Yang, Ph.D.

Office of Surveillance and Biometrics  
Center for Devices and Radiologic Health

# Outline

## **I. Pivotal study #1**

- Study design
- Effectiveness endpoint
- Results

## **II. Pivotal study #2**

- Study design
- Effectiveness endpoint
- Secondary effectiveness endpoints

# 1. Pivotal study #1

**TissuGlu+SWC+drains**

**vs.**

**SWC+drains**

- **Primary endpoint:** time to last drain removal (<30ml fluid per drain in 24 hours)

- **Study Design**

- randomized (2:1)
- superiority
- single-blinded (patients)

- **Follow-up**

- daily until drain removal
- days 14, 30, 60, 90, 6 months and 1 year

- **Hypothesis**

$$H_0: \mu_T \geq \mu_S \quad \text{vs.} \quad H_1: \mu_T < \mu_S$$

time to drain removal is shorter in TissuGlu+SWC+drains

$\mu_T$  = mean time to last drain removal in  
TissuGlu+SWC+drains

$\mu_S$  = mean time to last drain removal in SWC+drains

- **Sample size** :  $n_T=100$ ,  $n_S=50$

- **Calculation assumptions:**

- $\mu_T=3.23$  days,  $\mu_S=5.23$  days

- $\sigma=2.8$  days

- one-sided  $\alpha=0.025$ , power=98%

# Time to drain removal in days

	<b>TissuGlu+SWC+drains</b> (n=100)	<b>SWC+drains</b> (n=50)	<b>p-value</b> <b>(t-test)</b>
<b>Intent-to-treat (ITT)</b>			
Mean (SD)	6.7 (6.3)	6.6 (6.8)	0.54
Median	5	4	
Min, Max	1, 31	1, 29	

**Conclusion:** time to last drain removal is similar in both groups.

## 2. Pivotal study #2

**TissuGlu+SWC no drains**

**vs.**

**SWC+drains**

- **Primary endpoint:** number of post-operative invasive treatments, including
  - Removal of an in-dwelling drain
  - Needle aspiration to remove fluid from a clinically-diagnosed palpable seroma
  - Invasive action related to drain or drain wound
  - Reinsertion of a drain

- **Study Design**

- randomized (1:1)
- non-inferiority
- open-label

- **Followed-up**

- daily until drain removal
- days 3, 6, 9, 12, 16, 25, 32, 39, 53, 67, and 84.

- **Hypothesis**

$H_0: m_T - m_C \geq d$  vs.  $H_1: m_T - m_C < d$ ,

$m_T$  = location parameter for the distribution  
of invasive treatments in  
TissuGlu+SWC **no drains**

$m_C$  = location parameter for the distribution  
of invasive treatments in SWC **+  
drains**

$d=1$ , non-inferiority margin

- **Sample size:**
  - 62 patients per treatment
- **Calculation assumptions:**
  - difference in mean=0
  - common standard deviation=2.4
  - one-sided  $\alpha=0.025$ , power=80%

# Subject Accountability

	<b>TissuGlu +SWC no drains</b>	<b>SWC +drains</b>	<b>Total</b>
<b>Enrolled</b>	66	64	130
<b>Completed study</b>	64	62	126
<b>Discontinued</b>	2	2	4
<b>Withdrew consent</b>	0	1	1
<b>Lost to follow-up</b>	2	0	2
<b>Other reasons</b>	0	1	1

# Analysis populations

	<b>TissuGlu+SWC no drains</b>	<b>SWC + drains</b>	<b>Total</b>
<b>ITT</b>	66	64	130
<b>Protocol deviation</b>	15	12	27
<b>PP</b>	51	52	103



# Results(PP): Number of invasive treatments

	<b>TissuGlu + SWC no drains (n=51)</b>	<b>SWC + drains (n=52)</b>	<b>Median differ- ence</b>	<b>97.5% CI upper limit</b>
<b>Needle aspirations</b>				
Median	0	0	0.0	0.0
Mean (SD)	0.2 (0.7)	0.2 (0.9)		
Min, Max	0, 4	0, 6		
Total number of events	9	10		
<b>Removal of drains</b>	0	104		
<b>Total invasive treatments</b>				
Median	0	2	-2.0	-2.0
Mean (SD)	0.2 (0.7)	2.2 (0.9)		
Min, Max	0, 4	<b>2, 8</b>		
Total number of events	9	114		



# Results(ITT): Number of invasive treatments

	<b>TissuGlu+SWC no drains (n=66)</b>	<b>SWC + drains (n=64)</b>	<b>Median differ- ence</b>	<b>97.5% CI upper limit</b>
<b>Needle aspirations</b>				
Median	0	0	0.0	0.0
Mean (SD)	1.7 (3.7)	0.4 (1.2)		
Min, Max	0, 17	0, 6		
Total number of events	112	24		
<b>Removal of drains</b>	<b>7</b>	128		
<b>Total invasive treatments</b>				
Median	0	2	-2.0	-2.0
Mean (SD)	1.8 (3.8)	2.4 (1.2)		
Min, Max	0, 17	<b>2</b> , 8		
Total number of events	119	152		

## Number of aspirations in Per Protocol and Intent to Treat Populations by treatment group

Site	TissuGlu + SWC <b>no drains</b>				SWC + <b>drains</b>			
	Per Protocol		Intent to Treat		Per Protocol		Intent to Treat	
	N	# aspirations	N	# aspirations	N	# aspirations	N	# aspirations
01	11	6	14	39	11	9	13	17
02	3	0	7	16	5	1	7	2
03	18	0	19	3	16	0	18	0
04	8	3	12	34	8	0	13	5
05	11	0	14	20	12	0	13	0
<b>Total</b>	<b>51</b>	<b>9</b>	<b>66</b>	<b>112</b>	<b>52</b>	<b>10</b>	<b>64</b>	<b>24</b>

- 103 aspirations in TissuGlu group were excluded from intent-to-treat population
- 14 aspirations in SWC+drain group were excluded from intent-to-treat population

# Assessment of the impact of missing data(ITT): worst case scenario

Total invasive treatments	TissuGlu+SWC <b>no drains</b> (n=66)	SWC <b>+drains</b> (n=64)	Median difference	97.5% CI upper limit
Median	0	2	-2.0	-2.0
Mean (SD)	2.2 (4.6)	2.4 (1.2)		
Min, Max	0, 17	2, 8		
Total number of events	148	152		

- ❖ TissuGlu+SWC **no drains**: imputed with the maximum observed number of invasive treatments per subject
- ❖ SWC **+ drains**: imputed with the observed number of invasive treatments at the time of last contact.



# Secondary endpoints

	<b>TissuGlu+SWC no drains (N=66)</b>	<b>SWC + drains (N=64)</b>
<b>Total wound drainage per patient (ml)</b>		
Mean (SD)	96.6 (270.1)	411.4 (366.6)
Median	0.0	306.5
(Min, Max)	(0.0, 1572.0)	(65.0, 2034.0)
<b>Cumulative drain volume per patient (ml)</b>		
Mean (SD)	--	396.5 (339.9)
Median	--	306.5
(Min, Max)	--	(65.0, 2034.0)
<b>Aspiration volume per patient (ml)</b>		
Mean (SD)	96.6(270.1)	14.9 (67.1)
Median	0.0	0.0
(Min, Max)	(0.0, 1572.0)	(0.0, 445.0)



## Secondary endpoints (Cont'd)

	<b>TissuGlu +SWC no drains (N=66)</b>	<b>SWC + drains (N=64)</b>
<b>Days to drain removal</b>		
Mean (SD)	--	6.9 (3.3)
Median	--	6.5
(Min, Max)	--	(2, 18)
<b>Number of seroma revisions</b>		
Mean (SD)	0.0 (0.1)	0.0 (0.0)
Median	0	0
(Min, Max)	(0, 1)	(0, 0)
<b>Cumulative days of invasive treatment</b>		
Mean (SD)	1.6 (3.4)	7.3(3.3)
Median	0.0	7.0
(Min, Max)	(0, 16)	(2, 18)

# Summary

- **Pivotal study #1** shows no statistically significant reduction in time to drain removal comparing TissueGlu+SWC+drains to SWC+drains.

## Summary (Cont'd)

- **Pivotal study #2** shows TissuGlu+SWC **no drain** is non-inferior to SWC+**drains** in terms of number of invasive treatments for both per protocol and intent-to-treat populations. **Please note:**
  - number of invasive treatments includes drain removal, a deterministic component that can be evaluated clinically.
  - Number of aspirations could be biased due to the open-label design and the fact that many aspirations were of small volume.

# Post-Approval Study (PAS) Considerations

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Division of Epidemiology  
Office of Surveillance and Biometrics

August 1, 2014

# Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket data submitted to the Agency and discussed today must stand on their own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate benefit/risk balance.

# Important Postmarket Issues

- What is the post-market device performance with regards to safety?
  - Additional comprehensive collection of peri-operative and post-operative AEs in the post-market setting
- What is the device performance in subgroups of patients?
  - Patients who have undergone bariatric surgeries
  - Patients with history of weight loss



## Applicant's Proposed PAS

Study Design	Active postmarket surveillance study
Objective	To continue monitoring of the distribution and the trends in the incidence of adverse events associated with the use of TissuGlu in large flap procedures
Patient population	Patients who undergo large flap procedures will be included.
Sample Size	10% of all commercial cases where TissuGlu is used.
Eligibility	Patients will be identified based on a random selection of distribution data and contact with the surgeon.

## Applicant's Proposed PAS (Cont.)

<p>Data to be collected</p>	<ul style="list-style-type: none"> <li>• Adverse events that are both MDR-reportable and MDR non-reportable or device complaints</li> <li>• Procedure type, concomitant procedures, use of drains and compression garment, user experience with the device use</li> </ul>
<p>Study Duration</p>	<p>2 years</p>
<p>Statistical Analysis</p>	<p>No formal statistical hypotheses will be tested.</p>

## FDA Assessment of Applicant's Proposed PAS

- Data to be collected: Procedure type, concomitant procedures, use of drains and compression garment, user experience with the device use, peri-operative and post-operative adverse events
- FDA recommends additional data collection such as volume of aspirations, time to resolution of seroma, secondary procedures and patient reported outcomes

The panel will be asked to discuss the appropriateness of the proposed safety data to be collected and whether there are any additional data needed

## FDA Assessment of Applicant's Proposed PAS (Cont.)

- Data will be collected on randomly selected 10% of all large flap procedures including abdominoplasty and similar procedures
- There is a need to evaluate device performance in subgroups of patients
  - Patients who have undergone bariatric surgery
  - Patients with history of weight loss

The panel will be asked to discuss the appropriate study to evaluate the device performance in subgroup of patients.