A multi-center, randomized, controlled, single blinded, parallel-group study evaluating the clinical performance and safety of LiquiBand FIX8® versus control for hernia mesh fixation and peritoneal closure in groin hernia repair.

Clinical Evaluation of LiquiBand FIX8®

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Overview

Laparoscopic hernia mesh fixation has become more commonplace worldwide for abdominal herniorrhaphy since first demonstrated in the early 1990's [1] [2]. Mesh fixation by this technique typically requires the use of a mechanical fastener, such as suture or a screw-like tack to physically attach the mesh to the abdominal wall. While providing strong fixation, permanent metal fasteners have been associated with high instances of chronic pain and other complications. Absorbable fasteners have been more recently developed as alternatives to permanent devices, however chronic pain continues to be an issue due to the associated penetration of abdominal tissues [2]. Surgical adhesives have recently been promoted as an alternative to mechanical fasteners due to their strong adhesive properties, without tissue penetration. These adhesives have been used as alternatives to other penetrative wound closure methods such as sutures and staples in topical wound closure since the late 1990's [3]. Most commonly formulated from cyanoacrylate polymers, these adhesives rapidly polymerize in contact with moisture on the skin to bond opposing sides of a wound forming an effective and durable wound closure. The LiquiBand FIX8® device incorporates a similar cyanoacrylate adhesive formulation, packaged in a laparoscopic delivery instrument to provide internal mesh and peritoneal tissue fixation as opposed to topical wound closure. LiquiBand FIX8® obtained CE-marking for approval in the European Union in 2014 for inguinal hernia mesh fixation and is now approved for peritoneal closure in addition to other indications. In addition to the EU, LiquiBand FIX8® is approved for use in multiple other countries worldwide including Australia, Canada, Israel and the United Arab Emirates. Independent evaluations of the LiquiBand FIX8® device have found it to be safe and effective for hernia mesh fixation and peritoneal closure, and although the authors stated the low occurrence of complications, the limited scope of these studies did not include a detailed review of post-operative pain [4] [5] [6] [7] [8] [9] [11]. In this study, further evaluation of the clinical performance and safety of the LiquiBand FIX8® device is proposed, including the detailed assessment of any long term post operative pain and other complications experienced by study subjects.

CLINICAL INVESTIGATION SUMMARY

Study Title: A multi-center, randomized, controlled, single blinded, parallel-group study evaluating the clinical performance and safety of LiquiBand FIX8® versus control for hernia mesh fixation and peritoneal closure in groin hernia repair.

Investigational Device: LiquiBand FIX8® Hernia Mesh Fixation Device

Device Description: The device consists of:

a) n-butyl-2-cyanoacrylate adhesive monomer, in liquid form, supplied in a thin-walled, sealed glass vial; and,

b) a surgically invasive, laparoscopic 5mm diameter cannula, with a handle at the proximal end incorporating a loading chamber, filter, piston chamber and trigger. The distal tip of the device is open to allow the adhesive to be dispensed from it.

The device is designed to be used in conjunction with a 5 mm diameter laparoscopic port sleeve. Both the cyanoacrylate adhesive in the glass vial and the surgically invasive delivery device are supplied sterile, for single use only.

Indication for Use: The LiquiBand FIX8® device is intended for use in laparoscopic surgical repair of groin (femoral and inguinal) hernias, achieved through the fixation of prosthetic mesh to the abdominal wall and the approximation of peritoneum.

Design: Prospective, two-arm, randomized, single blinded, multi-center study.

Purpose: To demonstrate the efficacy and safety of LiquiBand FIX8® for groin hernia repair.

Objectives: Primary:

1. To compare the improvement in pain following groin hernia repair by LiquiBand FIX8® to control device as measured by Visual Analog Scale (VAS) at baseline (worst pain experienced within 1 month of screening visit) and at six months post hernia repair.

Secondary:

1. To evaluate the incidence of hernia recurrence in patients following laparoscopic (TEP and TAPP) hernia repair using LiquiBand FIX8® or control device at 6 months post hernia repair.
2. To compare the use of LiquiBand FIX8® to control device for mesh fixation at time of surgery.
3. To compare the use of LiquiBand FIX8® to control devices for the approximation of the peritoneum (TAPP repairs only) at time of surgery.
4. To evaluate the quality of life experienced by subjects following groin hernia repair by LiquiBand FIX8® or control as measured by the Carolinas Comfort Scale (CCS) at baseline (prior to surgery), and at 1 week, 2 weeks, 1 month, 3 months, 6 months, 9 months and 12 months following surgery.

5. To compare levels of pain experienced following laparoscopic (TEP and TAPP) groin hernia repair by LiquiBand FIX8® or control device, as measured by VAS at discharge, and at 1 week, 2 weeks, 1 month, 3 months, 6 months, 9 months and 12 months following surgery.
6. To evaluate the safety of LiquiBand FIX8® and control device for groin hernia repair by comparing incidence of all adverse events in patients post laparoscopic groin hernia repair.

Number of patients: 284 (142 per treatment arm)

Investigational centers: Up to 10 investigational centers will be recruited for this study, including the following institutions:

1. University of Kentucky
2. The Ohio State UniversityPrisma Health – Upstate
3. Overlake Medical CenterCleveland Clinic
4. Prisma Health – Upstate
5. Overlake Medical Center
6. Cleveland Clinic

Study Hypothesis

The study hypothesis is that the LiquiBand FIX8® device is non-inferior to a tack-based control device (AbsorbaTack™) for the laparoscopic (TEP and TAPP) repair of groin hernia. Non-inferiority will be demonstrated in a primary efficacy endpoint of improvement (decrease) of pain scores, measured by Visual Analog Scale (VAS), between baseline (worst pain experienced within 1 month of screening visit) and 6 months post-operatively.

INCLUSION/EXCLUSION

Inclusion Criteria

1. Patients who meet all the following criteria at the time of enrollment may be included:
2. Is male or female, ≥22 years of age
3. Is willing and able to give written informed consent
4. Has a primary or recurrent groin hernia (unilateral or bilateral, inguinal or femoral)
5. Is currently scheduled and eligible for TAPP or TEP laparoscopic groin hernia repair (inguinal or femoral)
6. Hernia mesh to be used at the time of surgery is at least 4" x 6" in size and is one of the following;
    - **a.** 3D Max™ Mesh (Bard Inc.)
    - **b.** 3D Max™ Light (Bard Inc.)
    - **c.** Parietex™ 2D (order code starting with TEC) Flat Sheet Mesh (Medtronic)
    - **d.** Parietex™ 3D (order code starting with TET) Flat Sheet Mesh (Medtronic)
7. Is willing and able to comply with the protocol assessments at time of surgery and during the post surgical follow up period

Exclusion Criteria

1. Patients who meet any one of these criteria will be excluded from the investigation:
2. Has a hernia type not suitable for laparoscopic hernia repair as determined by the Investigator (i.e. strangulated)
3. Subject has a recurrent groin hernia previously repaired laparoscopically, has an anatomical defect or had prior surgical procedures that in the opinion of the Investigator prevents access to the pre-peritoneal space for TAPP or TEP laparoscopic hernia repair
4. Is pregnant or actively breastfeeding
5. Has a known sensitivity to cyanoacrylate or formaldehyde,D&C Violet No.2 dye or any component of LiquiBand FIX8® or control device
6. Has an active or potential infection at the surgical site or systemic sepsis
7. Hernia mesh to be used at surgery is less than 4"x6" in size, or not one of the types of mesh listed in Inclusion Criteria #5.
8. Cannot tolerate general anaesthesia
9. Has any significant or unstable medical or psychiatric condition that, in the opinion of the Investigator, would interfere with his/her ability to participate in the study.
10. Is currently enrolled in another clinical study or undergoing treatment with another investigational drug or device.

ENDPOINTS

Table 1: Primary and Secondary Efficacy and Safety Endpoints of the Investigational Study	
Primary Efficacy 1	Effectiveness of LiquiBand FIX8® will be assessed and compared to treatment with AbsorbaTack™ in subjects requiring laparoscopic (TEP and TAPP) hernia repair. Success will be determined by improvement in pain not inferior to control device as measured by a VAS value (0 = no pain to 10 = most pain imaginable) from baseline (worst pain experienced within 1 month of screening visit) to six months post hernia repair.
Secondary Efficacy 1	The incidence of hernia recurrence in patients following laparoscopic (TEP and TAPP) groin hernia repair by LiquiBand FIX8® or control (AbsorbaTack™) will be assessed by physical examination at 2 weeks, 3 months, and 6 months and evaluated following the 6 month timepoint. Suspected hernia recurrence will also be evaluated at any time following surgery and up to the 12 month follow up visit if reported by the subject. Suspected hernia recurrence will be confirmed by ultrasound imaging following physical examination.
Secondary Efficacy 2	LiquiBand FIX8® will be required to successfully fix hernia mesh in patients undergoing TEP and TAPP laparoscopic groin hernia repair, at a rate non-inferior to control device (AbsorbaTack™) in order to meet this end point. Successful mesh fixation would not require any additional fixation by alternate fixation device. Unsuccessful mesh fixation is defined as requiring the use of an alternative fixation device or additional procedure to achieve adequate fixation.
Secondary Efficacy 3	LiquiBand FIX8® will be required to successfully approximate the peritoneum in patients undergoing laparoscopic TAPP hernia repair, at a rate non-inferior to control devices in order to meet this end point. Successful peritoneal closure would not require any additional fixation by alternate fixation device or additional procedure. Unsuccessful peritoneal closure is defined as requiring the use of an alternative fixation device or additional procedure to achieve adequate fixation. Investigators in the study will be able to use AbsorbaTack™, sutures or staples for closure of the peritoneum.
Secondary Efficacy 4	Quality of Life will be assessed by completion of the Carolinas Comfort Scale (CCS) Questionnaire prior to surgery and at 1 week, 2 weeks, 1 month, 3 months, 6 months, 9 months and 12 months following laparoscopic (TEP and TAPP) groin hernia repair. CCS scores at each timepoint will be compared between the LiquiBand FIX8® and control (AbsorbaTack) treatment groups.
Secondary Efficacy 5	Evaluation of pain will be measured by VAS (0 = no pain to 10 = most pain imaginable) at baseline (pre-surgery), at discharge, and at 1 week, 2 weeks, 1 month, 3 months, 6 months, 9 months and 12 months post surgery.
Secondary Safety 1	The incidence of all adverse events whether or not determined to be related to the LiquiBand FIX8® device or control device (AbsorbaTack™) will be assessed intraoperatively, at discharge, and at each follow-up visit throughout the study, or for cause at any time in the follow up period.

SCHEDULE OF STUDY ASSESSMENTS

Study design and schedule of assessments. (Shaded columns represent assessments performed in-clinic, non-shaded for remote visits).

	Pre-Surgery	Surgery	Discharge	Post-Surgery Visits							Unscheduled visit
Visit	1	2	3[3]	4	5	6	7	8	9	10	N/A
Day / Month	≤21 Days	Day 0	Day 0 or 1	Day 7	Day 14	Month 1	Month 3	Month 6	Month 9	Month 12	N/A
Visit Window (Days)				±3	-3 / +6	±7	±14	-21 / +14	-21 / +14	-21 / +14	N/A
Informed Consent	X										
Inclusion/ Exclusion	X										
Pregnancy Test (if applicable)		X[1]									
Medical History	X										
Analgesics usage	X	X[1]	X	X	X	X	X	X	X	X	X
Demographics	X										
Vital Signs (HR/BP/T/Ht/Wt)[4]	X	X[1]	X		X		X	X			X
Randomization[5]		X[2]									
Hernia Information (type & size)	X	X[2]									
Use of Investigational or control device		X[2]									
Number of Investigational or control device applications		X[2]									
Photograph following mesh fixation		X									
Photograph following peritoneal closure[6]		X									
Clinician evaluation of hernia repair & PE[7]					X		X	X			X
Subject Pain (0-10 VAS) Assessment	X		X	X	X	X	X	X	X	X	
Subject QOL Assessment	X			X	X	X	X	X	X	X	
AE Evaluation		X[2]	X	X	X	X	X	X	X	X	X

[1]Immediately prior to surgery

[2]During surgery

[3]At discharge post-surgery, either on same day as surgery or next day post-surgery according to standard of care

[4]Height only required at Pre-surgery visit. Unless Pre-surgery (Visit 1), Surgery (Visit 2) and Discharge (Visit 3) occur on the same date, weight should be obtained for each separate visit. Vital signs may be obtained remotely at Month 3 and 6 visits as volunteered by subjects using their own devices as available (e.g. thermometer, weight scales, smart wearable technology)

[5]Patient must be blinded to the randomized device

[6]Photograph following peritoneal closure only required for TAPP repairs

[7]Suspected hernia recurrence will be confirmed by ultrasound imaging following physical examination

STATISTICAL CONSIDERATIONS

Statistical Hypotheses

Statistical methods are presented below.

Primary Endpoint: Effectiveness of LiquiBand FIX8® will be assessed and compared to treatment with AbsorbaTack™ in subjects requiring laparoscopic (TEP and TAPP) hernia repair. Success will be determined by improvement in pain not inferior to control device as measured by a VAS value (0 = no pain to 10 = most pain imaginable) from baseline (worst pain experienced within 1 month of screening visit) to six months post hernia repair.

The statistical hypothesis is:
H_0: $\delta_T - \delta_C \geq 0.9$[21, 22]
H_1: $\delta_T - \delta_C < 0.9$ [21, 22],
where δ is the change from baseline (worst pain experienced within 1 month of screening visit) to 6-month on VAS for the appropriate treatment group.

Secondary Endpoints: To assess efficacy and safety outcomes following TAPP or TEP laparoscopic groin hernia (femoral and inguinal) repair by LiquiBand FIX8® compared to AbsorbaTack™ by evaluating the following:

- Recurrence rate in subjects following laparoscopic (TEP and TAPP) groin hernia repair by LiquiBand FIX8® or control (AbsorbaTack™) at 2 weeks, 3 months, 6 months, and 12 months.
  The statistical hypothesis for the recurrence rate at 6 months is:
  H_0: $q_T - q_C \geq 10\%$[25]
  H_1: $q_T - q_C < 10\%$[25],
  where q is the recurrence rate at 6 months for the appropriate treatment group.
- Rate of successful hernia mesh fixation in subjects undergoing TEP and TAPP laparoscopic groin hernia repair.
  The statistical hypothesis is:
  H_0: $p_C - p_T \geq 10\%$
  H_1: $p_C - p_T < 10\%$,
  where p is the rate of successful hernia mesh fixation at time of surgery for the appropriate treatment group.
- Rate of successful peritoneal closure in subjects undergoing laparoscopic TAPP hernia repair.
  The statistical hypothesis is:
  H_0: $\pi_C - \pi_T \geq 15\%$
  H_1: $\pi_C - \pi_T < 15\%$,
  where π is the rate of peritoneal closure at time of surgery for the appropriate treatment group.
- Quality of Life assessed by the Carolinas Comfort Scale (CCS) Questionnaire prior to surgery and at 7 days, 14 days, 1 month, 3 months, 6 months, 9 months and 12 months following laparoscopic (TEP and TAPP) groin hernia repair.

Population for Analysis

The following subject populations will be created:

- Intent-to-Treat (ITT): All enrolled subjects. ITT analysis will be per randomized group irrespective of the treatment actually received.
- Per Protocol (PP): All ITT subjects excluding those with major protocol violations. PP analysis will be per actual treatment group which is the same as the treatment initially randomized.
- As the PP analysis is more conservative for non-inferiority hypothesis, all hypotheses will be tested with the PP population. ITT analysis will also be performed for all hypotheses, as the primary analysis for the primary endpoint, and the supportive analysis for secondary endpoints with non-inferiority hypothesis.

Statistical Analysis

General Approach

The primary efficacy endpoint will be tested for non-inferiority of treatment to control with a predefined non-inferiority margin of 0.9 on the VAS scale. Confounding factors for the pain score including analgesic use or other pain management therapies will be measured at screening and all follow up visits, and compared between treatment arms to ensure proper balance within each site. The study will be claimed successful if both PP and ITT analyses on the primary efficacy endpoint showed significance at 0.025. Once the hypothesis tests succeed for both analysis sets on the primary efficacy endpoint, key secondary endpoints will be compared between treatments sequentially in a non-inferiority manner. The following sequential analysis approach will be taken:

- Primary non-inferiority on the PP set; if significant at one-sided alpha=0.025, and
- Primary non-inferiority on the ITT set; if significant at one-sided alpha=0.025, then proceed to key secondary endpoints detailed in Section 3.1.
- Secondary non-inferiority on the PP set on Hernia Recurrence rate in subjects following laparoscopic (TEP and TAPP) groin hernia repair by LiquiBand FIX8® or control (AbsorbaTack™) at 6 months, at one-sided alpha=0.025.
- Secondary non-inferiority on the PP set on Rate of successful hernia mesh fixation in subjects undergoing TEP and TAPP laparoscopic groin hernia repair; if significant at one-sided alpha=0.025, then
- Secondary non-inferiority on the PP set on Rate of successful peritoneal closure in subjects undergoing laparoscopic TAPP hernia repair; if significant at one-sided alpha=0.025, then

The family-wise type I error will therefore be controlled at 0.025.

Summary statistics will consist of the number and percentage of responses in each category for discrete variables, and the mean, median, standard deviation (SD), minimum, and maximum for continuous variables. One-sided statistical tests will use a significance level of α = 0.025, and two-sided tests will use a significance level of α = 0.05.

Analysis of the Primary Efficacy Endpoint

To test change from baseline (worst pain experienced within 1 month of screening visit) to 6-month on VAS between LiquiBand FIX8® and AbsorbaTack™, a general linear model (ANCOVA) will be run using SAS Proc GLM, with the treatment arm and laparoscopic repair technique (TAPP or TEP) as covariates. (SAS Institute Inc. NC USA). A p-value of < 0.025 will be considered evidence that LiquiBand FIX8® is not inferior to the AbsorbaTack™. 95% confidence interval will be calculated for the difference on changes from baseline (screening visit) to 6-month visit on VAS between LiquiBand FIX8® and AbsorbaTack™. This endpoint will be assessed when the enrollment is completed, i.e., when 148 subjects have been enrolled in the TAPP cohort, and there are at least 226 evaluable subjects with 6-

month data for change from baseline to 6-month on VAS. Tipping point analysis will also be performed to evaluate the impact of missing data.

Analysis of the Secondary Endpoints

The following safety and clinical outcomes will be evaluated.

The safety and clinical outcomes assessments include:

1. Hernia recurrence up to 12 months following surgery.
2. Hernia mesh fixation at time of surgery.
3. Approximation of the peritoneum at time of surgery (TAPP repairs only).
4. Quality of Life following groin hernia repair as measured by Carolinas Comfort Scale at baseline and at 7 days, 14 days, 1 month, 3 months, 6 months, 9 months and 12 months following laparoscopic (TEP and TAPP) groin hernia repair.
5. Subject pain following groin hernia repair as reported by VAS at screening, discharge and at 7 days, 14 days, 1 month, 3 months, 6 months, 9 months and 12 months following surgery.
6. Rate of device and procedure-related adverse events reported throughout the duration of the study.

To test the secondary endpoints #1, 2, and 3, a binomial non-inferiority test will be run using SAS Proc Freq with the Farrington-Manning method on the PP set. A p-value of < 0.025 from the binomial non-inferiority test will be considered evidence that LiquiBand FIX8® is not inferior to AbsorbaTack™. Confidence interval on the difference of the rates will be reported and non-inferiority is indicated if the upper limit of the confidence interval is less than the non-inferiority margin. ITT analyses will be performed for the three secondary endpoints with hypothesis statements as supporting sensitivity analyses.

Bibliographical References

[1]	L. S. Schultz, J. N. Graber and D. F. Hickok, “Early results with laparoscopic inguinal herniorrhaphy are promising,” *Clin Laser Mon,* vol. 8(7), pp. 103-105, July 1990 .
[2]	E. Reynvoet and F. Berrevoet, “Pros and cons of tacking in laparoscopic hernia repair,” *Surg Technol Int,* vol. 25, pp. 136-140, November 2014.
[3]	A. J. Singer, J. E. Hollander, S. E. Valentine, T. W. Turque, C. F. McCuskey and J. V. Quinn, “Prospective, Randomised, Controlled Trial of Tissue Adhesive (2-Octylcyanoacrylate) vs Standard Wound Closure Techniques for Laceration Repair,” *Acad Emerg Med,* vol. 5, no. 2, pp. 94-99, February 1998.
[4]	V. Calu, R. Parvuletu, M. Oun and A. Miron, “TAPP laparoscopic repair for inguinal hernia using glue fixation - our initial experience,” in *European Association for Endoscopic Surgery, 24th Annual Congress*, Amsterdam, Netherlands, 2016.
[5]	B. Dauser, A. Szyszkowitz, G. Seitinger, R. H. Fortelny and F. Herbst, “A novel glue device for fixation ofmesh and peritoneal closure during laparoscopic inguinal hernia repair: short and medium-term results,” *Eur Surg,* pp. DOI 10.1007/s10353-016-0450-0, 2016.
[6]	M. Ertem, H. Gok and E. Ozveri, “MRI visible meshes and non-invasive fixation,” in *European Hernia Society, 39th Annual International Congress*, Vienna, Austria, 2017.
[7]	R. Mittermair, G. Jenic, R. Kolenik and C. Sorre, “TAPP surgery with mesh fixation and peritoneal closure using n-butyl-2-cyanoacrylate (LiquiBand®FIX8TM) - initial experience,” *Eur Surg,* pp. DOI 10.1007/s10353-015-0367-z, 2015.
[8]	P. Wilson, “TAPP Repair: To glue or not to glue?,” in *British Hernia Society, 9th Annual Conference*, Newcastle, UK, 2016.
[9]	J. Schmidt, “Fixation of Titanizedmesh with N-Butyl-Cyanoacrylate (Nbca) Using a Novel Device: Biocompatibility and Short Term Results in Laparoscopic Hernia Repair,” *JSM Gen Surg Cases Images,* vol. 2, no. 2, pp. 1026-1029, 2017.