Statistical Analysis Plan
for
final analysis

Version 4.0

Study:	A Prospective, Multi-Center Study of Phasix™ Mesh for Ventral or Incisional Hernia Repair
Study-ID:	DVL-HE-011
Sponsor / Contact:	Davol Inc. Subsidiary of C. R. Bard, Inc. 100 Crossings Boulevard Warwick, RI 02886
Evaluation:	FGK Clinical Research GmbH
FGK code	3234
Version:	4.0 of August 07, 2018
Previous versions:	1.0 of August 18, 2014 2.0 of December 17, 2015 3.0 of September 21, 2017

Revision history

Version	Author	Date	Reason for Revision
1.0	A. Petri	18AUG2014	
2.0	A. Petri	17DEC2015	• New protocol version 2.0 of September 03, 2014: The study criteria were broadened by allowing subjects with multiply-recurrent hernia repair (not to exceed 3 recurrences) instead of first-recurrent hernia repair. The changes are effective for sites that approve this protocol change. Sites without an approval proceed according to protocol version 1.4. • Some additions to a few tables and listings were made. • Minor modifications as phrasings and correction of typos. • Additional analyses and changes in planned analyses requested by sponsor • The by-gender analysis should be performed for primary and secondary endpoints only (section 4 tables in Appendix A) as requested by sponsor. • The calculation of the defect ratio based on the area of an ellipse implemented. • The safety parameter “Procedure related adverse events by time intervals” will also be analyzed by gender. • The signature page was updated. • For analyses by time intervals, the intervals are explicitly defined based on the visit windows. • Listings of hernia recurrence and SSIs should rather be displayed by time intervals than on visit dates. • For the allocation of hernia recurrence to the defined time intervals in the tables the start date of the corresponding AE should be used and for the allocation of surgical site infection to the defined time intervals in the tables the date of SSI as documented on the SSI log page should be used. • All listings with information about several visits should be sorted by visit date per subject so that unscheduled visits are displayed in chronological order according to the visit dates. • New protocol version 3.0 of August 03, 2015: 12 month extension of the study and additional per-protocol analysis set. • A data review before final analysis added to classify protocol deviations and define the analysis sets. • The combination of sites with few subjects

Version	Author	Date	Reason for Revision
			for subgroup analysis by site is defined because the enrollment period had finished. • The two primary endpoints (hernia recurrence rate and the surgical site infection rate) as well as the rate of reoperations due to index hernia repair are analyzed by disjointed time intervals (Post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months – 30 months/ > 30 months – 36 months) instead of cumulative time intervals post device placement (Until Month 1/ Until Month 3/ Until Month 6/ Until Month 12/ Until Month 18/ Until Month 24/ Until Month 30/ Until Month 36). • Some specifications were added.
3.0	A. Petri	21SEP2017	• Based on sponsor's review of TLGs ("dry run"), changes in the SAP 2.0 were requested: - In the presentation of frequency tables special missing values, as 'not done', 'unknown', 'not applicable', 'not documented', should not be merged to the value 'missing' but be presented separately. - Some tables should be stratified by gender and visit instead of by visit and gender. - Some listings should be reduced to the "yes"-cases (e.g. SSI=yes). - Some footnotes to tables/listings were added/ modified and variables to listings were added in Appendix A. - Specifications added, typos corrected. - Surgical Procedure time should be calculated in minutes instead of hours. • Ying Wan signs the SAP instead of Aimin Feng. • Criterion (Index hernia repair/ Phasix™ Mesh cut through or a piece of the Phasix™ Mesh removed during a surgery) for exclusion from PP set added. • For the hernia recurrence rate, SSI rate and rate of reoperation due to the index hernia repair an overall rate is added to the rates per time interval.
4.0	A. Petri	07AUG2018	• New protocol version 4.0 of October 30, 2017: 24 month extension of the study. The changes are effective for sites that approve this protocol change. Sites without an approval proceed according to protocol version 3.0. Visit window for 36 month visits changed

Version	Author	Date	Reason for Revision
			from Day 1090 ± 30 days post device placement to Day 1095 ± 30 days post device placement. • Some specifications were added. • The following terminology was modified: - “Defect ratio” was changed to “Ratio of mesh size to defect size” and - “Screened subjects” was changed to “Enrolled subjects”.

Table of Contents

List of Abbreviations

In the following abbreviations are listed as used within this statistical analysis plan or which might occur within the tables, listings and graphs outputs:

AE	Adverse event
ATC	Anatomical therapeutic chemical classification
BMI	Body mass index
CCS	Carolinas comfort scale™
CDC	US centers for disease control and prevention
CI	Confidence interval
Cm	centimeter
COPD	Chronic obstructive pulmonary disease
CS	Clinically significant
CST	Component separation technique
CT	Computed tomography
eCRF	Electronic case report form
EoS	End of study
ET	Early termination
FU	Follow-up
ICF	Informed consent form
ITT	Intention-to-treat
MCS	Mental component summary
MedDRA	Medical dictionary for regulatory activities
mITT	modified intention-to-treat
MRI	Magnetic resonance imaging
MSE	Missing score estimation
N	Number of subjects
NA	Not applicable
NCS	Not clinically significant
OP	Operation
OTC	Over the counter
PCS	Physical component summary
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SF-12®	12-item short form
SSI	Surgical site infection
TLG	Tables, listings, graphs
UV	Unscheduled visit
V	Version
VAS	Visual analog scale
WHO-DD	World health organization drug dictionary

1 General

This Statistical Analysis Plan (SAP) was defined by the Sponsor and the responsible Statistician. It is based upon the Study Protocol (version 4.0 of October 30, 2017) and contains detailed description of the statistical methods described therein.

The SAP describes prospectively the analyses to be performed on study data. It was finalized prior to data base lock.

This is a post-market, prospective, multi-center, open-label study designed to collect additional data on safety, performance and effectiveness of Phasix™ Mesh for primary ventral or incisional or multiply-recurrent hernia repair in subjects with a higher level of risk. Subjects at high risk are defined as having one or more of the following co-morbidity conditions: body mass index (BMI) between 30-40 kg/m^2, active smokers, chronic obstructive pulmonary disease (COPD), diabetes mellitus, immunosuppression, coronary artery disease, chronic corticosteroid use, serum albumin less than 3.4 g/dL, advanced age or renal insufficiency. Subjects who receive a Phasix™ Mesh implant will be followed for 60 months with follow-up visits conducted at 1, 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months following surgery. At the 30, 42 and 54 month visit a telephone contact should be scheduled with the subject. If the investigator determines the responses provided by the subject demands a physical examination be conducted, a clinic visit will be scheduled.

This clinical study is projected to enroll up to 120 subjects at approximately 16 US sites. The sample size of 120 subjects is based on potential adequacy of data to meet the study objectives. No formal sample size calculation was performed.

The two primary endpoints are hernia recurrence rate and surgical site infection (SSI) rate. There is no formal statistical hypothesis for this post-market study with a single treatment condition.

2 Primary and Secondary Variables

2.1 Primary Variables

The two primary parameters for this study are:

- Hernia recurrence rate
- Surgical site infection (SSI) rate

2.2 Secondary Variables

The following secondary parameters will be analyzed:

- Pain - Visual Analog Scale (VAS)
- Device related adverse event incidence
- Rate of reoperation due to the index hernia repair
- Quality of life assessments (Carolinas Comfort Scale™ and SF-12® - 12-item short form health survey)
- Surgical procedure time as measured from incision to closure (skin to skin)
- Length of stay

2.3 Safety Variables

- Physical examination
- Adverse events (AEs)
- Device failure, malfunctions and defects
- Concomitant pain medication

2.4 Other Relevant Variables

- Protocol deviations

3 Statistical Analysis Sets

3.1 Intention-to-treat Set

The intention-to-treat (ITT) set consists of all enrolled subjects who have signed the informed consent form (ICF).

3.2 Modified Intention-to-treat Set

The modified ITT (mITT) set is defined as those subjects in the ITT set in whom Phasix™ Mesh has been implanted.

3.3 Per-protocol Set

All subjects of the mITT will also be included in a per-protocol (PP) set if they do not violate any major protocol criteria. Protocol deviations will be identified and classified for each subject during a data review (see section 4.8).

The violation of any inclusion or exclusion criterion is a priori defined to have a “major” grade and will lead to an exclusion from the PP set. If for a subject the Phasix™ Mesh was cut through or a piece of the Phasix™ Mesh was removed during a surgery not related to the index hernia repair, the subject will be excluded from the PP set as well. The inclusion and exclusion criteria as defined in the latest protocol version will be decisive irrespective which protocol version at time of subject’s enrollment was effective or if a new protocol version was approved by the site.

3.4 Additional subgroup analysis

Where appropriate, subgroup analysis (based on the mITT set) may be performed for the two primary parameters if enough subjects within the subgroups allow further insight to the data. Following subgroups are subject to further interest:

- Gender: Male versus female subjects
- Centers: Study sites with ≤ 5 subjects in the mITT set will be combined to one site.
- Pre-operative diagnosis: ‘Primary ventral or incisional hernia’ versus ‘recurrent ventral or incisional hernia’ (regardless of first-recurrent or multiple-recurrent hernia) versus ‘Other’ (if applicable). Other pre-operative diagnoses, which are multiple recurrences as documented on the protocol deviation form, will be allocated to the subgroup ‘recurrent ventral or incisional hernia’ and not kept in subgroup ‘Other’.
- Surgical procedure performed with ‘Retro-rectus with CST’, ‘Retro-rectus without CST’, ‘Onlay placement with CST’, ‘Onlay placement without CST’ and ‘Other’.

The ‘by gender’ analysis will be performed for all primary and secondary parameters and for the analysis of procedure related AEs by time intervals.

The subgroups of ‘Surgical procedure performed’ will additionally be considered in the analyses of device and procedure related AEs by time intervals.

3.5 Assignment of Analysis Sets to Analysis

The mITT set will be considered the primary analysis. All analyses are based on the mITT set. In-/ exclusion criteria (where applicable with reason for failure to meet eligibility criteria), subjects per study site, applicable protocol version and demographics (listing only) will be presented for the ITT set. Adverse events of subjects in the ITT set but not in the mITT set

will be listed as well. The primary and secondary variables will additionally be analyzed using the PP set (including the subgroup analyses by gender but no further subgroup analyses).

4 Statistical Evaluation

The measured data at 'screening and baseline' visit will be used as baseline value. No imputation of missing baseline values will be applied.

The following visit notation will be used for table, listing, and graph presentation:

Notation used in the database specification/ paper case report form	Notation used for table, listing and graph presentation and in the SAP
Screening and Baseline	Baseline
Day of Surgery (Day 0)	Surgery (Day 0)
Post-Operative One Month FU (30 +/- 7 days)	Month 1
Post-Operative 3 Month FU (90 +/- 30 days)	Month 3
Post-Operative 6 Month FU (180 +/- 30 days)	Month 6
Post-Operative 12 Month FU (365 +/- 30 days)	Month 12
Post-Operative 18 Month FU (545 +/- 30 days)	Month 18
Post-Operative 24 Month FU (730 +/- 30 days)	Month 24
Post-Operative 30 Month FU (910 +/- 30 days)	Month 30
Post-Operative 36 Month FU (1095 +/- 30 days)	Month 36
Roll-in Visit (Re-consent)	Roll-in
Post-Operative 42 Month FU (1275 +/- 30 days)	Month 42
Post-Operative 48 Month FU (1460 +/- 30 days)	Month 48
Post-Operative 54 Month FU (1640 +/- 30 days)	Month 54
Post-Operative 60 Month FU (1825 +/- 30 days)	Month 60
Unscheduled Visit 1	UV 1
Unscheduled Visit 2	UV 2
> Unscheduled Visit 2	> UV 2
End of Study Page	EoS

Time window deviations will not be considered for statistical analyses.

If unscheduled visits (UVs) are not numbered according to the chronological order of the visit dates, the numbering of the UVs will be adapted for analysis. For example, if UV 4 was performed before UV 3 according to the visit dates, the UVs will be renumbered (UV 4 will get the number UV 3 and UV 3 will be UV 4). In the footnote of the listing with the visit data (see listing 1.1.2) subjects concerned will be described.

Values assessed during unscheduled visits will be listed but not used in summaries with exception of the primary endpoints. The information from UVs concerning hernia recurrence

and SSI will be included in the analysis of the primary endpoints, physical examination and rate of reoperation due to index hernia repair. Data which are gathered in the log pages (e.g. adverse event form, device failure/ malfunctions/ defects form, mesh infection form) contain information from UVs anyway.

All listings with information about several visits will be sorted by visit date per subject so that unscheduled visits are displayed in chronological order according to the visit dates.

In analyses where time intervals will be used, they are based on the following visit windows (calculated from date of surgery at Day 0):

Visit	Visit Window	Interval	
		Term	**Days**
1 month	Day 30 ± 7 days	Post OP – 1 month	**0-37 days**
3 month	Day 90 ± 30 days	>1 month – 3 months	**38-120 days**
6 month	Day 180 ± 30 days	>3 months – 6 months	**121-210 days**
12 month	Day 365 ± 30 days	>6 months – 12 months	**211-395 days**
18 month	Day 545 ± 30 days	>12 months – 18 months	**396-575 days**
24 month	Day 730 ± 30 days	>18 months – 24 months	**576-760 days**
30 month	Day 910 ± 30 days	>24 months – 30 months	**761-940 days**
36 month	Day 1095 ± 30 days	>30 months – 36 months	**941–1125 days**
42 month	Day 1275 ± 30 days	>36 months – 42 months	**1126-1305 days**
48 month	Day 1460 ± 30 days	>42 months – 48 months	**1306-1490 days**
54 month	Day 1640 ± 30 days	>48 months – 54 months	**1491-1670 days**
60 month	Day 1825± 30 days	>54 months – 60 months	**1671 days - end of study**

4.1 Dispositions of Subjects and Analysis Sets

Disposition of subjects and analysis sets

Subjects per analysis sets, per center, per applicable protocol version and per visit, violation of inclusion and exclusion criteria (incl. intraoperative in-/ exclusion criteria), and the status at end of study (incl. reason for early termination) will be shown. If there are subjects that changed the study center during the study, they will be analyzed with the site where the surgery at Day 0 took place.

4.2 Demographics and Other Covariates

Demographic data

Demographic data (age, gender, ethnicity, race, body height, body weight at baseline, body mass index (BMI)) at baseline will be tabulated.

Medical history

The proportion of subjects with hypertension, diabetes, immunosuppression, renal disease, cardiovascular disease, history of myocardial infarction, history of stroke, lung disease, cancer history, chemotherapy within last 12 months, pre-operative use of chronic corticosteroids, prior abdominal incisions, abdominal aortic aneurysm, history of post surgical infections, malnutrition, connective tissue disorder, alcohol abuse, cigarette smoking, drug abuse or other significant medical history will be tabulated (including frequencies of

specifications where available). Subjects with prior abdominal incisions will be listed separately including location and reason of prior abdominal incisions. From that listing a medical expert of the sponsor will determine the number of prior abdominal incisions per subject. The frequencies for the number of prior abdominal incisions will be added to the medical history table.

Pre-operative diagnoses and hernia assessment

Pre-operative diagnosis, mesh used for repair in case of recurrence, previous component separation technique if mesh was used, the location of hernia, size of hernia, intake of prescription or over the counter (OTC) medications for treatment of pain and the pre-study conditions of the subject will be descriptively summarized. The pre-study conditions (high risk criteria) will be presented as documented in the eCRF, where multiple entries per subject are possible, and broken down by each high risk criteria.

For sites without or subjects enrolled before approval to protocol version 2.0 (where only first time recurrent repairs are allowed and not multiply-recurrent repairs), when the index repair is a first time recurrence, the question ‘If hernia recurrence, specify’ receives the value 1 (= number of recurrence) and primary repairs receive the value 0. For subjects with greater than the per protocol (version before 2.0) allowed number of hernia recurrences (documented as 'other' pre-operative diagnosis with a specification on the protocol deviation form), the type (recurrent incisional or ventral hernia) and the number of hernia recurrences are incorporated into the 'pre-operative diagnosis' and 'if hernia recurrence, specify’ variables. These composite variables are used throughout the analyses (see also subgroup analysis in section 3.4 above).

4.3 Surgery

Surgical diagnoses and hernia assessment

Frequency tables for administration of prophylactic antibiotics (yes/no), surgical procedure (retro-rectus with CST/ retro-rectus without CST/ onlay placement with CST/ onlay placement without CST/ other), component separation technique (CST) performed (Ramirez, open technique/ posterior technique/ endoscopic, minimally invasive technique/ open or endoscopic technique + combinations), technique (without CST) performed (Rives-Stoppa/ open perforator preserving/ other + combinations), swiss cheese configuration (multiple discreet hernias) (yes/no) and for any reportable adverse events (yes/no) will be presented. Defect length (cm) and defect width (cm) will be summarized descriptively. Concomitant procedures will be tabulated as well.

Phasix™ Mesh device implant

Frequency tables for size of mesh used (7.6 cm round/ 10.2 cm x 15.2 cm/ 15.2 cm x 20.3 cm/ 20.3 cm x 25.4 cm/ 25.4 cm x 30.5 cm), method of perimeter fixation (mechanical/ suture), if suture fixation, device type (absorbable monofilament / non-absorbable monofilament/ absorbable multifilament/ non-absorbable multifilament), if recurrent, was mesh explant necessary (yes/no), wound closed (yes/no), method of closure (fascia closed/ hernia sac closed/ other), was fascia re-approximated (yes/no) and was skin fully closed (yes/no) will be presented. The number of fixation points will be summarized descriptively.

The ratio of mesh size to defect size will be calculated as mesh size ([½ length x ½ width] x pi in cm², calculation is based on the area of an ellipse) divided by the defect size ([½ defect

length x ½ defect width] x pi in cm², calculation is based on the area of an ellipse). Summary statistics will be presented for the ratio of mesh size to defect size.

Surgical drains

A frequency table will show if a drain was placed (yes/no) and the number of drains (0/ 1/ 2/ ...). The placement, location and tube duration will be tabulated by drain number.

4.4 Analysis of Primary and Secondary Variables

No formal hypothesis will be stated and statistically tested. All primary and secondary variables will be analyzed using descriptive methods. Any statistical testing, if performed, will be considered exploratory and will be based on a two-sided 5% significance level. No adjustment for multiple testing will be done. The primary and secondary variables will additionally be analyzed using the PP set (including the subgroup analyses by gender but no further subgroup analyses).

Changes from baseline will be calculated as follows:

Absolute change = post-baseline/ post procedure result – baseline result

In the following the details on the specification, definition, or calculation of the primary and secondary variables will be given.

4.4.1 Analysis of Primary Variables

Hernia recurrence rate

Hernia recurrence rates will be assessed by physical examination at each study visit through 60 months. A recurrent hernia will be defined as any hernia identified or confirmed by the investigator, during any study follow-up visit, in approximately the same position as the hernia repaired in the study procedure. Potential hernias identified via incidental magnetic resonance imaging (MRI) or computed tomography (CT) scan will be evaluated by the operating surgeon for clinical significance and confirmation of hernia recurrence.

Hernia recurrence (after surgery including UVs) is defined as follows:

- The question “Is there any evidence of hernia recurrence in the same location as the index procedure per physical exam?” is answered with “yes”

or

- the question “Is there any evidence of hernia recurrence in the same location as the index procedure by any other means?” is answered with “yes”.

If a hernia recurrence occurs, a corresponding adverse event has to be documented. The start date of the corresponding AE is used to determine the time point of hernia recurrence. The rate of hernia recurrence will be classified in time intervals (as defined in section 4 above): post OP – 1 month, > 1 month – 3 months, > 3 months – 6 months, > 6 months – 12 months, > 12 months – 18 months, > 18 months – 24 months, > 24 months – 30 months, > 30 months – 36 months, > 36 months – 42 months, > 42 months – 48 months, > 48 months – 54 months, > 54 months – 60 months. The time of a hernia recurrence is calculated as start date of the corresponding AE minus date of device placement (surgery at Day 0). In case of more than one hernia recurrence per subject in an interval, the recurrences are counted only once per interval. In case a scheduled visit was not performed but the subject had a visit afterwards, the total number of subjects will not be reduced for the concerned time interval as the subject is still in study. If no information is available that a hernia recurrence occurred until the missed visit, no hernia recurrence is assumed for that time interval. The total number of subjects per time interval will be reduced by the number of subjects discontinued in a time interval if the time interval was not completed (according to the predetermined time windows). However, if a hernia recurrence occurred in a not completed interval the subject is counted for that interval. The date of completion or discontinuation from the end of study

page or the last visit date if the subject was lost to follow up will be used to determine the study duration of each subject since surgery at Day 0. In addition to the recurrence rates per time interval, the overall hernia recurrence rate will be calculated considering the time from post OP to end of study irrespective of the individual study duration. In case of more than one hernia recurrence per subject, the recurrences are counted only once.

Exact two-sided 95% confidence intervals (CIs) for hernia recurrence = “yes” using the SAS procedure PROC FREQ with option BINOMIAL will be calculated per time interval and overall.

The hernia recurrence rates by time intervals (visit) and overall will additionally be presented by the subgroups described in section 3.4 above (for subgroup ‘gender’ with 95%-CIs and for subgroups ‘center’, ‘pre-operative diagnosis’ and ‘surgical procedure’ without 95%-CIs).

Additionally, a Kaplan-Meier analysis for time from surgery to hernia recurrence will be performed and graphically displayed. Subjects without hernia recurrence will be censored at the last date at which they were known to have no hernia recurrence (i.e. date of completion or discontinuation from the end of study page or the last visit date if the subject was lost to follow up).

The time to event (first time of hernia recurrence as defined above) will be calculated as date difference (in days) between date of surgery (Day 0) and start date of the corresponding AE when a hernia recurrence occurred first time.

Kaplan-Meier analysis (tables and curves) will also be performed for the subgroups defined in section 3.4 above. Median time will be compared between the male and female subjects using the log-rank test. If the sample size is too low to perform an adequate valid log-rank test, the test results will not be presented.

SSI rate

Infections at the surgical site will be assessed by physical examination at each study visit through 60 months. If an infection is suspected, a routine culture, obtained via each site’s standard protocol, should be obtained to determine cell count and type (i.e. yeast, gram positive or gram negative bacteria or other). If genus and species of the culture are identified as part of the routine practice at the site, that information should be recorded. Classification will follow the US centers for disease control and prevention (CDC) guidelines for superficial and deep surgical site infections (see Appendix 3 of the study protocol).

A SSI (after surgery including UVs) is defined as follows:

The question “Is there any evidence of a surgical site infection in the same location as the index procedure?” is answered with “yes”.

If a SSI occurs, the SSI has to be documented on the SSI log page. The date of surgical site infection from the SSI log page is used to determine the time point of the SSI. The SSI rate will be analyzed analogously to the hernia recurrence rate (see above) with rates of SSI in time intervals (post OP – 1 month, > 1 month – 3 months, > 3 months – 6 months, > 6 months – 12 months, > 12 months – 18 months, > 18 months – 24 months, > 24 months – 30 months, > 30 months – 36 months, > 36 months – 42 months, > 42 months – 48 months, > 48 months – 54 months, > 54 months – 60 months) and the overall SSI rate considering the time from post OP to end of study (incl. exact two-sided 95% CIs for SSI = “yes”), Kaplan-Meier analysis for time (days) from surgery to first time when a SSI occurred and subgroup

analyses. In case of more than one SSI per subject in an interval, the SSIs are counted only once per interval.

A frequency table will show the type of SSIs (superficial/ deep).

4.4.2 Analysis of Secondary Variables

Pain – VAS

Subjects complete the pain VAS with 0 cm = no pain to 10 cm = severe pain at baseline and at all post procedure visits. The pain VAS length (cm) and its absolute change from baseline will be described with summary statistics by visit. In case of subjects with chronic pain as documented in other significant medical history, summary statistics by visit and its absolute change from baseline will be presented additionally without these subjects. The results of pain VAS of UVs will be listed only.

Device related adverse event incidence

Adverse events that are possibly or definitely related to device are considered. In case of a missing classification of the relationship to device a relation to the device is assumed. A frequency table will be prepared displaying the number of subjects and percentage of subjects with at least one event and number of events with event = device related AE.

Additionally, a frequency table grouped by Medical dictionary for regulatory activities (MedDRA) terms (system organ class (SOC) and preferred term (PT)) will be presented.

A frequency table for device related AEs by time intervals (OP/ post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months – 30 months/ > 30 months – 36 months/ > 36 months – 42 months/ > 42 months – 48 months/ > 48 months – 54 months/ > 54 months – 60 months) presenting the number of events only will be displayed stratified by the subgroups of ‘Surgical procedure performed’.

Rate of reoperation due to the index hernia repair

The rate of subjects with a post procedure reoperation due to the index hernia repair will be presented by time intervals (post OP – 1 month, > 1 month – 3 months, > 3 months – 6 months, > 6 months – 12 months, > 12 months – 18 months, > 18 months – 24 months, > 24 months – 30 months, > 30 months – 36, > 36 months – 42 months, > 42 months – 48 months, > 48 months – 54 months, > 54 months – 60 months) and overall considering the time from post OP to end of study analogously to the primary variables (but without 95% CIs, no Kaplan-Meier analysis and no subgroup analysis except presentation by gender).

All reoperations documented on the reoperation page are counted as reoperations due to the index hernia repair. The date of reoperation will be used to calculate the time interval since date of surgery (day 0). In case of more than one reoperation per subject in an interval, the reoperations are counted only once per interval. A frequency table will present the reasons for reoperation.

Carolinas comfort scale™ (CCS)

The CCS is a 23-item questionnaire that measures sensation of mesh, severity of pain and movement limitations in the following eight domains: laying down, bending over, sitting up, activities of daily living, coughing or deep breathing, walking, stairs and exercise. The CCS is completed by the subjects at baseline and at all post procedure visits.

A total score will be calculated by summing up the scores of all 23 questions. Additionally, the total score by the three scales “sensation of mesh”, “pain” and “movement limitations” will be calculated by summing up the concerned questionnaire items (sensation of mesh: questions 1a, 2a, 3a, 4a, 5a, 6a, 7a, 8a; pain: questions 1b, 2b, 3b, 4b, 5b, 6b, 7b, 8b; movement limitations: 2c, 3c, 4c, 5c, 6c, 7c, 8c).

CCS will be analyzed in accordance to the CCS user guide[1]. Computational algorithms including the handling of missing values are described in detail in the guideline. In summary, the following rules will be applied:

- Questions outcomes 0-5 will be used with lower scores indicating a more favorable health status.
- Not applicable or no response will be handled as missing values.
- Two or more outcomes ticked per question will be handled as missing value.
- If more than two questions are missing within any of the three scales (sensation of mesh, pain or movement limitations), the whole questionnaire will not be used.
  If less or equal to two questions are missing within any of the three scales (sensation of mesh, pain or movement limitations), the missing values will be replaced by the mean of the remaining items of the scale.
  An exception of the rule is made for this study at baseline due to the fact that many values concerning sensation of mesh are “not applicable” at baseline (pre-operative assessment). For example, subjects without recurrent hernia cannot answer the questions related to sensation of mesh at baseline. Therefore, at baseline the scale scores for “pain” and “movement limitations” will be calculated for all subjects nevertheless, if within any of the two scales (“pain” or “movement limitations”) are less or equal to two questions missing applying the aforementioned rule (missing values will be replaced by the mean of the remaining items of the scale).

The total score and the three scales scores “sensation of mesh”, “pain” and “movement limitations” will be calculated and descriptive statistics will be reported by visit. At baseline the scale score “sensation of mesh” and the total score will be calculated for subjects with recurrent hernia and used mesh in situ and for subjects with recurrent hernia but unknown if previous mesh is still in situ (see listing 2.4 ‘Pre-operative diagnoses’ in Appendix A of the SAP). The absolute change from baseline will be calculated for the two scale scores “pain” and “movement limitations” and descriptively summarized by visit for all subjects. In case of sufficient entries for sensation of mesh at baseline, the absolute change from baseline will be calculated for the scale score “sensation of mesh” and the total score in the subset of subjects with recurrent hernia and used mesh in situ and with recurrent hernia but unknown if previous mesh is still in situ.

The outcome of the 23 individual questions will be tabulated by visit using both a frequency table and a table with basic statistics using the original answers of the subjects without replacement in case of missing values.

The calculated total score and the three scale scores of UVs and their change from baseline will be listed only.

SF-12® - 12 item short form health survey

The SF-12 is a multipurpose, 12-item health survey that measures eight domains of health: physical functioning, role limitations due to physical health (role-physical), bodily pain,

general health, vitality, social functioning, role limitations due to emotional problems (role-emotional), and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and mental health: the physical component summary (PCS) and mental component summary (MCS). The SF-12 is completed by the subjects at baseline and at all post procedure visits.

The SF-12 domains and summary measures will be calculated using the QualityMetric Health Outcomes™ Scoring Software 4.5 applied to the SF-12v2 Health Survey using the 2009 U.S. general population t-scores. Missing score estimation (MSE) is included in the software.

The SF-12 domains and summary measures and their absolute change from baseline will be descriptively tabulated by visit. SF-12 domains and summary measures and their absolute changes from baseline will be calculated for UVs with performed SF-12 as well but will only be listed.

Surgical procedure time as measured from incision to closure (skin to skin)

The surgical procedure time (minutes) of the index procedure is calculated as time of skin closure complete minus time of first incision. Summary statistics will be presented for surgical procedure time.

Length of stay

The length of hospital stay (days) at index procedure is calculated as date of hospital discharge (index procedure, documented at Month 1 visit) minus date of hospital admission (documented at surgery (day 0)). The length of hospital stay will be descriptively tabulated.

4.5 Safety Analysis

Physical examination

The frequencies of changes in the physical examination since baseline will be shown for all post procedure visits (incl. unscheduled visit) using shift tables for the body systems “abdomen” and “skin”. The categories of the findings (normal/ abnormal) and the specification if abnormal (clinically significant/ not clinically significant) will be summarized for the shift tables in “normal”, “abnormal – NCS” and “abnormal – CS” with NCS = not clinically significant and CS = clinically significant.

The absolute change from baseline of body weight and BMI will be summarized descriptively.

Adverse events (AEs)

In this study, an AE is defined as any undesirable clinical event occurring in the abdominal space including the lower abdominal, inguinal and pubic regions (including the skin), as well as any other undesirable clinical events judged to be related to the study device or surgical procedure regardless of anatomical region.

AEs will be coded by using MedDRA version 16.1.

AEs will be tabulated by system organ class (SOC) and preferred term (PT) (MedDRA). The number of entries, as well as the number and rate of affected subjects will be reported.

Serious AEs (SAEs) and AEs with a causal relationship to the procedure (relationship to procedure is definitely related or possibly related; in case of a missing classification of the relationship to procedure a relation to the procedure is assumed), and AEs by severity are presented separately. A frequency table for procedure related AEs by time intervals (OP/

post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months – 30 months/ > 30 months – 36 months/ > 36 months – 42 months/ > 42 months – 48 months/ > 48 months – 54 months/ > 54 months – 60 months) presenting the number of events only will be displayed stratified by the subgroups 'gender' and 'Surgical procedure performed'. Device related AEs are described in section 4.4.2 "Analysis of Secondary Variables" above.

A listing with high risk criteria (pre-study conditions) combined with AE information will be prepared additionally with the following variables: Total high risk criteria, What are the pre-study conditions the subject has, Total procedure related AEs, Total device related AEs, Total procedure related SAEs, Total device related SAEs and SAE term sorted by the total high risk criteria from high to low. Here AEs with causal relationship to procedure or device are displayed only.

Documented AEs of subjects who do not have Phasix™ Mesh implanted (subjects of ITT set but not included in the mITT set) will be listed separately.

Device failure, malfunctions and defects

The investigator records if the surgical mesh device used in the study procedure failed to meet its performance specifications whether due to mechanical failure, malfunction or defects. Device failure, malfunctions or defects will be tabulated by the failure code.

Pain medication

All current pain medication is captured at baseline. Hernia associated pain medication is captured at 12, 24, 36, 48 and 60 months. All documented pain medication will be coded by world health organization drug dictionary (WHO-DD) and will be tabulated by anatomical therapeutic chemical classification (ATC) level 1, level 4 and WHO-DD preferred term.

A frequency table by Month 1, Month 3, Month 6, Month 18, Month 30, Month 42 and Month 54 visit (Month 30, 42 and 54 only if clinic visits were performed) will be presented showing the intake of prescription or OTC medications for treatment of pain related to hernia repair (yes/no) including the classification in "non-narcotic" and "narcotic" if "yes".

4.6 Analysis of Other Relevant Variables

Protocol deviations

The proportion of subjects with any protocol deviation will be tabulated.

4.7 Missing Values

No missing value imputation methods will be applied. For handling of missing values in the quality of life assessments (CCS and SF-12®) see section 4.4.2.

4.8 Data Base Closure and Data Review

A data base closure will be performed prior to the analysis. All parameters will be checked, as specified in the data validation plan, and all queries resolved before data base closure and analysis.

A data review will be conducted prior to data base closure to check for protocol deviations and to allocate the subjects to the analysis sets. At least the following items will be discussed:

- Informed consent form signed (date subject signed informed consent is documented)
- Phasix™ Mesh implantation
- Any violation of inclusion/exclusion criteria
- Subjects for which the index hernia repair/ Phasix™ Mesh was cut through or a piece of the Phasix™ Mesh was removed during a surgery not related to the index hernia repair (for example documented as other action taken on the AE form)
- Reasons for premature discontinuation
- Protocol deviations as captured in the eCRF on the protocol deviation log page

If required, critical data/ analysis issues can additionally be discussed (e.g. review reasons for reoperations, SSIs and hernia recurrences).

These evaluations and assessments will be done together and in agreement with the Sponsor, however FGK will provide the Sponsor with the appropriate subject listings (as defined in Appendix A to the SAP). Data review can be done via a telephone conference or in writing.
After data review minutes (including the affiliation of subjects to the ITT, mITT and the PP set) have been signed by both the Sponsor and FGK, data base closure will be performed.

4.9 Miscellaneous

For qualitative variables the frequencies (absolute and relative) are calculated. If no further remark is given in the description of the tables following format will be used for all tables with qualitative variables:

	Y-variable(s) (e.g., subgroups)					
	Category 1		Category 2		Total	
X-variable(s)	N	%	N	%	N	%
category 1						
category 2						
missing						
Total		100.0		100.0		100.0

For this standard format the description of the tables in Appendix A determines only the X- and Y-variables. If another format of table is described in the details to the tables, the real design will be determined by the technical possibilities within SAS and may not look identical to the provided example. However, all information as displayed will be included.

Quantitative parameters will be described by declaring the number of non-missing values (N), number of missing values (missing), mean value (mean), standard deviation (SD), minimum, 1st quartile, median, 3rd quartile, and maximum. In the description of the tables this will be denoted by „basic statistics“.

If not stated differently, in the presentation of frequency tables special missing values, as ‘not done’, ‘unknown’, ‘not applicable’, ‘not documented’, will be presented separately as far as they occur. In tables with “basic statistics” they will be merged to ‘missing’. In the listings they will be displayed as captured in the eCRF.

The listings are always sorted by center and subject. All listings with information about several visits will be sorted by center, subject and visit date so that unscheduled visits are

displayed in chronological order according to the visit dates. If a different sorting order should be used for some listings this will be remarked separately. The variables for the special listings are explicitly given in the description of listings. All listings will be presented for the mITT set, if not stated differently.

Subjects enrolled but without Phasix™ Mesh implantation (e.g. withdrawal before implantation) will be considered in tables and listing describing subjects per analysis set, per study site, per applicable protocol version and inclusion/ exclusion criteria as well as in listings for subject demographics and adverse events.

The following title will be used for all generated tables, listings, and graphs:

DVL-HE-011: Phasix™ Mesh Page # of #

<Table/Listing/Graph NNN: Description of contents>

<Subtitle for description of contents - if applicable>

<Analysis set>

The numbering NNN of the tables/listings/graphs will be stated in the detailed description (Appendix A).

Following footnote will be used for all generated tables, listings, and graphs:

FGK GmbH, <Actual date> Author: <Author of program> Program: <Name of program>

The statistical evaluation will be performed using SAS version 9.3 or higher.

Additional analyses (e.g. further subgroup analyses) might be performed on an ad hoc basis, if deemed of further interest or indicated by the results of the final analysis.

5 Changes from Protocol

In the following any changes on statistical aspects as described in the protocol are given:

- In the study protocol, chapter 7.3, it is specified that demographics and baseline characteristics will be summarized using the ITT population. In this SAP it is planned to present the in-/ exclusion criteria (with reason for failure to meet eligibility criteria) and demographics (listing only) for the ITT set. Further baseline characteristics are not foreseen to be presented as they are not postulated to be documented in the eCRF (see study protocol, chapter 6.1.3, describing screening failures: “At a minimum, subject demographics and the reason for failure must be collected; …”).
- According to the study protocol, section 7.3, the primary endpoints of hernia recurrence rate and surgical site infections rate will be reported by visit. The calculation of rates at each time point will be based on available data at the time point. Missing data will not be imputed.
  In the SAP it is planned to present the respective rates in time intervals (Post OP – 1 month/ > 1 month – 3 months/ > 3 months – 6 months/ > 6 months – 12 months/ > 12 months – 18 months/ > 18 months – 24 months/ > 24 months – 30 months/ > 30 months – 36 months/ > 36 months – 42 months/ > 42 months – 48 months/ > 48 months – 54 months/ > 54 months – 60 months). In case a scheduled visit was not performed but the subject had a visit afterwards, the total number of subjects will not be reduced for the time interval as the subject is still in study. If no information is available that the event occurred until the missed visit, no event is assumed for that time interval.
- In the study protocol in section 6.4 'Table of study events' an early termination (ET) visit is mentioned together with an unscheduled visit what implies a separate ET visit. However, no separate ET visit is realized in this study, just last sequential visit is available with documentation of reason for withdrawal and date of discontinuation on end of study (EoS) page

6 Literature

1. *Carolinas Comfort Scale User Guide*. Carolinas Medical Center; Division of Gastrointestinal and Minimally Invasive Surgery.

7 Signatures

Statistician:	
Andrea Petri FGK Clinical Research GmbH Heimeranstr. 35 80339 München Germany	
Date (ddmmmyyyy)	Signature

Sponsor:	
Ying Wan C.R. Bard, Inc. Director of Biostatistics Murray Hill NJ 07974 USA	
Date (ddmmmyyyy)	Signature