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Prospective Cohort Study

## Outcomes of a new slowly resorbable biosynthetic mesh (Phasix™) in potentially contaminated incisional hernias: A prospective, multi-center, single-arm trial



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## ABSTRACT

**Background:** Resorbable biomaterials have been developed to reduce the amount of foreign material remaining in the body after hernia repair over the long-term. However, on the short-term, these resorbable materials should render acceptable results with regard to complications, infections, and reoperations to be considered for repair. Additionally, the rate of resorption should not be any faster than collagen deposition and maturation; leading to early hernia recurrence. Therefore, the objective of this study was to collect data on the short-term performance of a new resorbable biosynthetic mesh (Phasix™) in patients requiring Ventral Hernia Working Group (VHWG) Grade 3 midline incisional hernia repair.

**Materials and methods:** A prospective, multi-center, single-arm trial was conducted at surgical departments in 15 hospitals across Europe. Patients aged  $\geq 18$ , scheduled to undergo elective Ventral Hernia Working Group Grade 3 hernia repair of a hernia larger than 10 cm<sup>2</sup> were included. Hernia repair was performed with Phasix™ Mesh in sublay position when achievable. The primary outcome was the rate of surgical site occurrence (SSO), including infections, that required intervention until 3 months after repair.

**Results:** In total, 84 patients were treated with Phasix™ Mesh. Twenty-two patients (26.2%) developed 32 surgical site occurrences. These included 11 surgical site infections, 9 wound dehiscences, 7 seromas, 2 hematomas, 2 skin necroses, and 1 fistula. No significant differences in surgical site occurrence development were found between groups repaired with or without component separation technique, and between clean-contaminated or contaminated wound sites. At three months, there were no hernia recurrences.

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**Conclusion:** Phasix™ Mesh demonstrated acceptable postoperative surgical site occurrence rates in patients with a Ventral Hernia Working Group Grade 3 hernia. Longer follow-up is needed to evaluate the recurrence rate and the effects on quality of life. This study is ongoing through 24 months of follow-up.

## 1. Introduction

Incisional hernia (IH) is a frequent complication after abdominal surgery, with incidences varying from 10 to 20% [1], and can be more than 30% in high-risk patients, such as patients with a Body Mass Index (BMI) over 30 kg/m<sup>2</sup> [2,3]. Patients with IH score lower in the areas of physical functioning, cosmetic, and body image components of health-related quality of life questionnaires [4]. Surgical hernia repair is often needed as a result; some 350,000 ventral hernia repairs are done each year in the United States alone [5].

Incisional hernias used to be repaired with sutures only. However, multiple studies have shown that repair with synthetic mesh leads to significantly fewer recurrences compared to primary suture repair [1, 6–8]. However, permanent synthetic mesh has also been associated with chronic inflammation, pain, adhesions, and fistulae [6,9]. With a reported infection rate of about 5%, synthetic meshes are more prone to infection than biological tissue-derived materials [10]. This could pose a problem in potentially contaminated hernias like Ventral Hernia Working Group (VHWG) Grade 3 hernias (Table 1) [11]. The success of the mesh repair is jeopardized by potential contamination, which is caused by complicating factors such as previous wound infection, the presence of a stoma or violation of the gastro-intestinal tract.

Due to this potential contamination in VHWG Grade 3 hernias, it may be desirable that no foreign material remains in the body: that the mesh is resorbed. An alternative to permanent synthetic mesh, such as biological tissue-derived materials, may be considered. It is hypothesized that biological meshes have a higher ability to resist infection, have a milder inflammatory response, and cause more orderly collagen deposition than permanent synthetic meshes [12–14]. However, these biological materials are costly, and have not fulfilled all expectations related to their possible advantages.

A more recent development in surgical prostheses is biosynthetic mesh. Biosynthetic mesh made from poly-4-hydroxybutyrate (P4HB) has the advantage of having mechanical strength comparable to traditional polypropylene mesh [15], and might therefore result in low recurrence rates when used for incisional hernia repair. Additionally, it resorbs over 12–18 months [15,16], leaving no foreign material behind in the body. However, this P4HB mesh retains only 70% of its strength after 12 weeks [15,17,18], possibly causing early hernia recurrence due to early breakdown of the mesh. Also its ability to resist infection in potentially contaminated sites (such as VHWG grade 3 hernias) remains understudied. For such a new and promising mesh to be considered for repair, postoperative complication and infection rates should be collected. The objective of this study was therefore to collect additional data on the short-term performance of a P4HB synthetic mesh (Phasix™) in patients requiring VHWG Grade 3 midline incisional hernia repair.

**Table 1**

Ventral Hernia Working Group grading system: assessment of risk for surgical site occurrences [11].

Grade 1	Grade 2	Grade 3	Grade 4
Low Risk	Co-morbid	Potentially contaminated	Infected
Low risk of complications	Smoker	Previous wound infection	Infected mesh
No history of wound infection	Obese	Stoma present	Septic dehiscence
	Diabetic	Violation of the GI tract	
	Immunosuppressed		
	COPD		

COPD: chronic obstructive pulmonary disease, GI: gastro-intestinal.

## 2. Methods

### 2.1. Study design

This prospective, single-arm, multicenter trial was conducted at surgical departments in 15 hospitals across Europe. The trial protocol has been previously published [19] and can be found on clinicaltrials.gov (NCT02720042). Patients aged 18 years or older and scheduled to undergo elective VHWG Grade 3 hernia repair of a midline incisional hernia larger than 10 cm<sup>2</sup> were asked to participate in the trial. Patients with a BMI over 35 kg/m<sup>2</sup>, peritonitis, HIV, liver cirrhosis, or chemotherapeutic medication were excluded. An elaborate overview of exclusion criteria has been previously published [19].

The protocol was reviewed and approved by the Institutional Review Boards or Health Authorities of all participating centers. All participants gave written informed consent prior to any study procedures being conducted. The study has been reported following the STROCSS criteria [20].

### 2.2. Procedures

The participants were registered in an online database with a personal, unique trial code. Final eligibility of a patient, with regard to the hernia-specific and intraoperative exclusion criteria, was determined during surgery.

All eligible patients underwent open ventral hernia repair. The Phasix™ Mesh had to be placed in a retro-rectus (sublay) position. Onlay placement was allowed only when retro-rectus placement could not be achieved. The Phasix™ Mesh was fixated with slowly resorbable sutures. The specific type of suture and fixation pattern were left to the discretion of the surgeon, along with the use of component separation technique (CST), when considered appropriate. The mesh was positioned to overlap the defect on all edges by at least 5 cm. It was recommended to the surgeons to fixate the mesh at approximately 5–6 cm-intervals around the periphery of the mesh. All skin incisions were closed with staples or sutures.

After surgery, patients were treated per hospitals' standard protocol. Patients were invited for follow-up visits on three points in time: after drain removal or at hospital discharge, 1 month after surgery, and 3 months (±14 days) after surgery. During these follow-up visits – as well as before surgery – patients underwent physical examination by a medical doctor.

### 2.3. Outcomes

The primary outcome was surgical site occurrence (SSO) that required any type of medical or surgical intervention. SSOs were assessed by physical examination at each study visit through 3 months (±14 days). SSO was defined as hematoma, seroma, surgical site infection (SSI) [21], wound dehiscence, skin necrosis and fistula. As a secondary endpoint, the hernia recurrence rate up until 3 months was assessed.

### 2.4. Statistical analysis

Since VHWG grade 3 hernia patients are rare, it was chosen to use a sample of convenience. Seventy-five patients were deemed sufficient to evaluate the performance of Phasix™ Mesh. This means that at an estimated SSO rate at 3 months of 37% [22–25], the accuracy will be 11% (i.e. half of the 95% Confidence Interval width of the estimated SSO

rate, is 11%). Eighty-five participants were included due to an anticipated attrition rate of approximately 10%.

Data from all patients in whom Phasix™ Mesh was implanted were analyzed, through an intention-to-treat principle. No missing value imputation methods were applied. Patient and hernia characteristics were summarized with frequency counts and percentages, or with the mean and standard deviation (SD). Information on follow-up is given through median and interquartile range (IQR), and the primary endpoint is reported with a 95% confidence interval (CI).

### 3. Results

In total, 85 patients were enrolled in the study between March 2016 and April 2017. In one patient, a different type of mesh was implanted. Therefore, 84 patients were included in the analysis. All but 1 patient attended their follow-up visits up to and including the 3-month visit (median follow-up 90 days, interquartile range 85–99 days).

#### 3.1. Patients and follow-up

Baseline characteristics are listed in Table 2. The mean age in males was 63.3 years (SD 12.8) and in females 61.3 years (SD 11.9). The mean BMI in males was 27.4 kg/m<sup>2</sup> (SD 3.6) and in females 28.3 kg/m<sup>2</sup> (SD 4.6). Twenty-five patients (29.8%) had other significant medical history not listed in Table 3, such as an intersphincteric fistula, Crohn’s disease, pancreatitis, depression, hip replacement, cholecystectomy, or post-traumatic stress syndrome, among others.

#### 3.2. Hernia and surgery characteristics

Sixty-eight patients (81%) were operated on for a primary incisional hernia, 9 patients (10.7%) were operated for a first-time recurrence, and for 7 patients (8.4%) it was a repair of ≥second-time recurrence. Of the 16 patients (19.1%) who were operated on for incisional hernia recurrence, 10 (11.9%) had a previously placed mesh that needed to be explanted.

Reasons for VHWG 3 classification were previous wound infections in 51 patients (60.7%), stoma presence in 24 patients (28.6%), violation of gastro-intestinal (GI) tract in 6 patients (7.1%), small bowel resection with anastomosis in 1 patient (1.2%), take down of ileostomy with ileocolonic anastomosis in 2 patients (2.4%), cholecystectomy in 1 patient (1.2%), creation of stoma in 3 patients (3.6%), or other reasons in 4 patients (4.8%). One patient was proven to be contaminated with extended spectrum beta-lactamase bacteria, but did not meet any of the criteria for a VHWG grade 3. After inclusion, two patients were considered to have Grade 4 hernias instead of Grade 3 due to the presence of an active infection (1; 1.2%) and a fistula (1; 1.2%). However, they remained included in the analyses.

**Table 2**  
Baseline characteristics (mean (SD) or n (%)).

	N = 84
Gender	
Male (%)	51 (60.7)
Female (%)	33 (39.3)
Age, years (SD)	62.5 (12.4)
BMI, kg/m <sup>2</sup> (SD)	27.8 (4.0)
History of post-surgical infection (%)	60 (71.4)
Hypertension (%)	39 (46.4)
Smoking (%)	39 (46.4)
Cancer history (%)	35 (41.7)
Lung disease (%)	19 (22.6)
Cardiovascular disease (%)	19 (22.6)
Diabetes Mellitus (%)	12 (14.3)
Renal disease (%)	12 (14.3)
Chronic pain (%)	10 (11.9)

Kg/m<sup>2</sup>: kilogram per square meter, SD: standard deviation, BMI: Body Mass Index.

**Table 3**

Hernia characteristics (mean (SD) or n (%)): size, site contamination according to CDC classification, and surgical methods.

Hernia defect	N = 84
Length in cm (SD)	12.1 (5.7)
Width in cm (SD)	8 (3.5)
Size in cm <sup>2</sup> (SD)	109.2 (87.9)
<i>CDC Wound Class – Preoperative Assessment</i>	
Clean (%)	1 (1.2)
Clean-contaminated (%)	46 (54.8)
Contaminated (%)	37 (44.0)
<i>CDC Wound Class – Assessment at Device Implant</i>	
Clean (%)	35 (41.7)
Clean-contaminated (%)	38 (45.2)
Contaminated (%)	10 (11.9)
Dirty/Infected (%)	1 (1.2)
<i>Surgical details</i>	
Retro-rectus with CST (%)	48 (57.1)
Retro-rectus without CST (%)	35 (41.7)
Onlay, with CST (%)	1 (1.2)
Concomitant procedures (%)	52 (61.9)
<i>In case of CST</i>	
Ramirez/open technique (%)	13 (27.1)
Posterior CST (%)	16 (33.3)
Endoscopic/minimally invasive technique (%)	12 (25.0)
Combination of techniques	7 (14.6)

SD: standard deviation, CST: component separation technique.

Hernia characteristics can be found in Table 3. One of these characteristics is the CDC wound classification [21]. This is not to be confused with the VHWG grading system; with the CDC wound classification, the wound site is assessed as either clean, clean-contaminated, contaminated, or infected. The frequency of the use of CST is shown, because CST use in the treatment for incisional hernia repair might lead to more post-operative surgical complications compared to a Rives-Stoppa technique. Concomitant procedures included, among others, lysis of adhesions, relocation of a colostomy, hemicolectomy, removal of excess skin, or Hartmann reversal. All hernias were located in the midline.

#### 3.3. SSO rate

The primary outcome measure, SSO rate, is listed in Table 4. In total, 22 patients (26.2%; 95% CI: 17.2%–36.9%) developed 32 SSOs. Four of the SSOs (12.5%) required hospitalization, 3 required surgical intervention (9.3%), 1 required an ultrasound examination before drainage (3.1%), 1 required a vacuum assisted closure device (3.1%), 2 were resolved by aspiration (6.3%), 1 superficial excision of necrotic tissue took place (3.1%), and twenty SSOs (62.5%) could be managed with

**Table 4**

SSO rates, split up for the use of component separation technique and preoperative CDC wound class assessment.

	Total (n = 84)	with CST (n = 49)	without CST (n = 35)	Contam. (n = 37)	Clean-contam. (n = 46)
Patients with SSO (%)	22 (26.2)	13 (26.5)	9 (25.7)	9 (23.7)	13 (28.9)
Total SSO	32	20	12	15	17
SSI	11	8	3	6	5
Wound dehiscence	9	6	3	5	4
Seroma	7	4	3	3	4
Hematoma	2	–	2	–	2
Skin necrosis	2	2	–	–	2
Fistula	1	–	1	1	–

SSO: surgical site occurrence, SSI: surgical site infection, CST: component separation technique, Contam.: contaminated, Clean-contam.: clean-contaminated.

either medication, wound care, or drainage alone.

Patients with SSOs were stratified for the use of CST and for either contaminated or clean-contaminated wound sites. With regard to the difference of SSO development per sex, among men 19.6% developed an SSO, compared to 36.4% among women.

A total of 90 adverse events (AE) were experienced by 43 patients (51.2%). SSOs were also considered AEs. AEs that were not SSOs, were, for example, postoperative ileus, hypokalemia, or pneumonia. In 2 patients, the AE was considered to be possibly device-related; these were a seroma and a parastomal hernia recurrence. In the other patients the AE was not device-related. Of the 90 AEs, 28 were serious adverse events (SAE), in 16 patients (19.0%), all of which were classified as not device-related. One Phasix™ Mesh had to be explanted due to the patient's development of fecal peritonitis two days after surgery. No clinical hernia recurrences of the hernias repaired with Phasix™ Mesh occurred within 3 months.

#### 4. Discussion

Phasix™ Mesh demonstrated acceptable postoperative SSO rates for VHWG Grade 3 incisional hernia repair in the short term. An SSO rate of 26% is rather low in this patient population. The reported SSO rate in VHWG grade 3 hernias when synthetic mesh is used, is between 6% and 55% [22,25–29]. The 6% comes from a study in which only 17 patients with VHWG grade 3 were included, and the SSO rate was assessed after 30 days, whereas in this trial, the SSO rate was assessed after 90 days [26]. All other studies reporting an SSO rate in VHWG grade 3 patients treated with synthetic mesh, report rates over 30% [22,25,27–29]. Studies describing the use of synthetic meshes in contaminated settings (not reporting a VHWG grade), observe similar results to ours. One large retrospective study of 100 patients using lightweight polypropylene mesh showed a 26.2% SSO rate in clean-contaminated cases, and 34% in contaminated cases. Also the SSI rate in this study was slightly higher than ours, with 14% within 30 days [30].

Only few studies have reported the SSO incidence in VHWG grade 3 patients after repair with biological mesh. One study reports a 63% SSO rate in patients with either VHWG grade 3 or 4 [31]. Another study compared Permacol®, Surgisis®, and Alloderm®, rendering an SSO rate of 25%–40% [32]. However, no information on contamination of the hernia site was reported in that study. A recent systematic review on biologic versus synthetic mesh in clean-contaminated hernias found overall surgical site complication rates of 44% in the nonabsorbable synthetic group, and 50% in the biologic group [33].

As described above, comparison of the SSO rate between studies is difficult, since many different factors play a role in studies, such as type of mesh used, the use of a component separation technique, study type (prospective or retrospective), and the timeframe used to detect SSOs. However, the P4HB biosynthetic mesh from this study seems to show acceptable short-term results.

An interesting finding was the difference in SSO development between men and women in the study. Women tended to develop SSOs more often than men (36.4% vs 19.6%). This difference in SSO might be explained by the use of CST between men and women; CST was used in 40% of men and in 75% of women that developed an SSO. There was no difference in contamination of the surgical site between men and women. However, due to the small study sample, no conclusions can be drawn upon the difference in SSO rate between the sexes.

As we did an intention-to-treat analysis, two patients were included in the analysis while actually having a VHWG grade 4 surgical site. These patients both contributed to the SSO rate, with both developing a postoperative wound infection (SSI) and wound dehiscence. The actual SSO rate in VHWG grade 3 patients would therefore be slightly lower.

From the results, it can also be confirmed that smoking seems to be a risk factor for the development of a superficial or deep infection. Many included patients were smokers, and 7 of the 11 patients that developed an SSI were current or past smokers (63.6%).

#### 4.1. Limitations

A methodological limitation of the study is the absence of a control group. However, all comparison options have their own drawbacks. First, no standard treatment is registered for VHWG Grade 3 hernias. Because 15 hospitals in Europe participated, it would be insufficient to use the standard treatment per hospital as a control group. This would lead to very heterogeneously treated patients and different results, not suitable for the comparison with the performance of the Phasix™ Mesh. Second, permanent synthetic mesh could have been used in a control group, because it reduces recurrences when compared to suture closure or closure with the aid of biological mesh [34,35]. However, due to the potential contamination in VHWG Grade 3 hernias, synthetic mesh could lead to a high infection and potential removal rate [36,37]. Last, using biological mesh in the control group is also not ideal. Biological mesh has the advantage of having a high salvage rate when infected [38,39], but renders a higher recurrence rate than repair with synthetic mesh [35].

Another methodological limitation might be the partially standardized procedure for incisional hernia repair in this study. Multiple centers in multiple countries across Europe participated. Every center or every surgeon has different regulations, habits, and preferences. Because of the patient population, some centers use CST more often than others. CST use in the treatment for incisional hernia repair might lead to more postoperative surgical complications, compared to exclusive use of a sublay technique (24% vs. 11.1%) [40]. However, the SSO rates for both patients treated with and without CST were not significantly different in the present study. This finding might be explained by the fact that all patients were treated in experienced hernia centers across Europe, and that some freedom in the surgical protocol should be allowed to provide the most fitting repair for every individual patient.

#### 5. Conclusion and implications

Phasix™ Mesh demonstrated acceptable post-operative surgical site occurrence rates for VHWG Grade 3 incisional hernia repair. These results on infection and complications rates are valuable for the surgeon in the decision to use this new and promising type of mesh for hernia repair in this high-risk patient group. However, it remains to be studied whether hernia repair with Phasix™ Mesh causes lower recurrence rates and is more cost-effective than the use of biologics or permanent synthetics. Due to the high rate of obesity and comorbidities present in the studied population, the anticipated recurrence rate is high [2,3,41]. A low recurrence rate after longer follow-up would stimulate surgeons to consider the use of a biosynthetic mesh in potentially contaminated hernias. Cost-effectiveness analysis could also be valuable when long-term results are available, as recurrence and reoperation are both costly, but occur frequently later than only 3 months after surgery. Aside from complications, surgical site occurrences, and recurrences, the course of quality of life in patients receiving repair with Phasix™ Mesh should also be assessed. In short, information on the long-term performance of Phasix™ Mesh should be collected to make real recommendations regarding its use, but the early results are promising. This study is ongoing through 24 months of follow-up.

#### Ethical Approval

The protocol was reviewed and approved by the Institutional Review Boards or Health Authorities of all participating centers.

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## Author contribution

Study conception and design: Jairam, Jeekel.

Acquisition of data: van Rooijen, Kroese, Tollens, Jørgensen, de Vries Reilingh, Piessen, Köckerling, Miserez, Windsor, Berrevoet, Fortelny, Dousset, Woeste, van Westreenen, Gossetti, Lange, Tetteroo, Koch.

Analysis and interpretation of data: van Rooijen, Jeekel.

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Critical revision: Jairam, Kroese, Jeekel, Tollens, Jørgensen, de Vries Reilingh, Piessen, Köckerling, Miserez, Windsor, Berrevoet, Fortelny, Dousset, Woeste, van Westreenen, Gossetti, Lange, Tetteroo, Koch.

## Research Registration Number

1. *Name of the registry*: Clinicaltrials.gov

2. *Unique Identifying number or registration ID*: NCT02720042

3. *Hyperlink to your specific registration (must be publicly accessible and will be checked)*: <https://www.clinicaltrials.gov/ct2/show/NCT02720042?term=Phasix&cond=Incisional+Hernia&rank=5>.

## Guarantor

Prof. dr. J. Jeekel.

## Provenance and peer review

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## CRediT authorship contribution statement

**Mathilde M.J. van Rooijen**: Acquisition of data, Formal analysis, Drafting, of manuscript. **An P. Jairam**: Study concept. **Tim Tollens**: Acquisition of data, Critical revision. **Lars N. Jørgensen**: Acquisition of data, Critical revision. **Tammo S. de Vries Reilingh**: Acquisition of data, Critical revision. **Guillaume Piessen**: Acquisition of data, Critical revision. **Ferdinand Köckerling**: Acquisition of data, Critical revision. **Marc Miserez**: Acquisition of data, Critical revision. **Alastair C.J. Windsor**: Acquisition of data, Critical revision. **Frederik Berrevoet**: Acquisition of data, Critical revision. **René H. Fortelny**: Acquisition of data, Critical revision. **Guido Woeste**: Acquisition of data, Critical revision. **Henderik L. van Westreenen**: Acquisition of data, Critical revision. **Francesco Gossetti**: Acquisition of data, Critical revision. **Johan F. Lange**: Acquisition of data, Critical revision. **Geert W.M. Tetteroo**: Acquisition of data, Drafting, of manuscript, Critical revision. **Andreas Koch**: Acquisition of data, Critical revision. **Leonard F. Kroese**: Acquisition of data, Critical revision. **Johannes Jeekel**: Acquisition of data, Drafting, of manuscript, Critical revision.

## Declaration of competing interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijssu.2020.08.053>.

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