ORIGINAL ARTICLE

Safety and performance of a synthetic sealant patch aimed to prevent postoperative pancreatic fistula after distal pancreatectomy (SHIELDS) – Prospective international multicenter phase II study

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Abstract

Objective: The incidence for clinically relevant postoperative pancreatic fistulas (CR-POPF) in distal pancreatectomy (DP) ranges up to 25%. None of the available sealants significantly reduce CR-POPF. A new biodegradable sealant patch was able to reduce POPF and to achieve bleeding control in a preclinical porcine DP model. The aim of this first-in-human study was to assess the safety and performance of the sealant patch.

Methods: In this multicenter, single-arm study, 40 patients undergoing distal pancreatectomy were prospectively enrolled from 8 centers. Following surgical resection, the transection plane was closed according to the standard of care and manually covered with the sealant patch. As primary endpoint the incidence of CR-POPF up to 30-days postoperatively was evaluated. The secondary endpoints included the assessment of complications and device usability.

Results: Among 40 patients after distal pancreatectomy, CR-POPF occurred in 7 (17.5%) up to postoperative day 30. No type C POPF was observed. There was no intraoperative bleeding observed after patch application.

Conclusion: The results of this international phase II study demonstrate promising results of a new sealant patch regarding the rate of CR-POPF. Randomized studies are now needed to confirm the superiority of the current patch as compared to the best current practice.

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Background and aims

Postoperative pancreatic fistulas (POPF), defined as the postoperative leakage of pancreatic enzyme-rich fluid into the abdominal cavity, are the main contributors to postoperative morbidity and mortality after pancreatic resections.[1] The international study group of pancreatic surgery (ISGPS) has reached a consensus regarding the definition and grading of POPF.[2] According to precise definitions the actual incidence remains high with up to more than 30% after pancreatic resections in general.[3] In distal pancreatectomy (DP), the incidence

[a] Deceased.

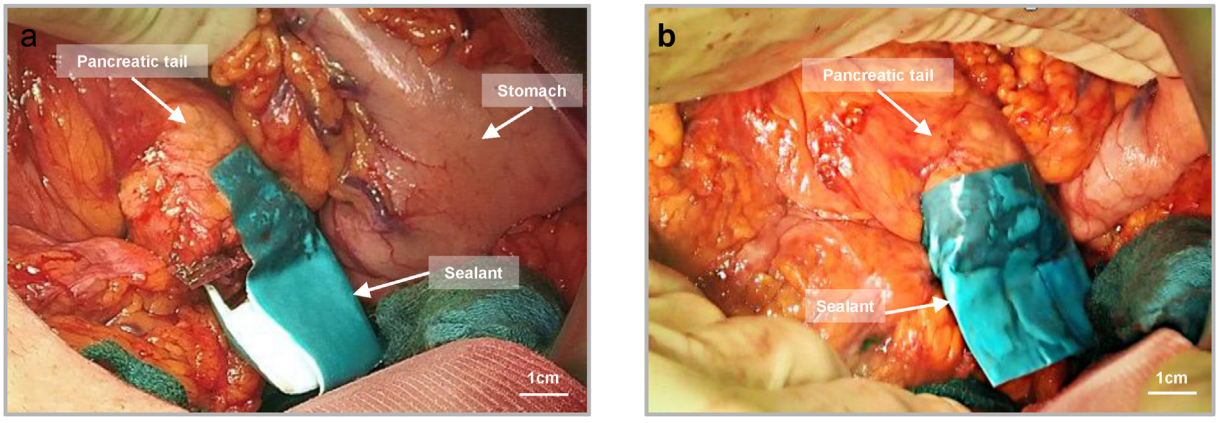

Figure 1 Application of the sealant at the pancreatic transection plane (a) After transection (in this case with a reinforced stapler), the pancreatic remnant is covered with the ACTISEAL® sealant (b) In order to fully cover the transection plane, a second sealant is applied

of clinically relevant fistulas (CR-POPF; type B and C according to the ISGPS) ranges up to 25%.[3–5] Short-term consequences include delayed gastric-emptying, intra-abdominal abscess formation and post-pancreatectomy hemorrhage. In particular CR-POPF correlate strongly with long-term morbidity and mortality, prolonged hospital stays, re-admissions and increased costs.[6] Importantly, the presence of CR-POPF delays adjuvant therapy and contributes to decreased overall survival in oncological patients.[7]

Despite various mitigation strategies the incidence of CR-POPF remains high after pancreatic resections, in particular after DP, illustrating the need for a new innovative approach.[8] None of the available tissue sealants or haemostatic devices with sealing capabilities are able to reduce CR-POPFs when used as adjunct to standard closure. In fact, the surgical community is forced to accept CR-POPF as an unpreventable complication after pancreatic resections in a significant proportion of patients, which clearly underlines the unmet need.[9] Therefore, a new bioresorbable tissue sealant patch (ACTISEAL®) has been developed to reduce the incidence and severity of CR-POPF in combination with haemostatic abilities (Fig. 1).[10] Within a previous work, strong adhesion to the pancreatic surface and resistance of the sealant patch against pancreatic juice was demonstrated. In a preclinical porcine DP model, the sealant patch was able to reduce POPF and indicated a better performance when compared to the control group.[10]

The beforementioned reasons, the standardized surgical approach in DP, as well as the relatively low morbidity and mortality compared to pancreatic head resections, formed the basis to evaluate the newly developed sealant patch in this model. The aim of this first-in-human study was to evaluate safety and performance in two groups: DP and liver resections. The present work will focus on the results obtained in DP.

Methods

Study design and participants

The SHIELDS trial is a multicenter prospective, single-arm phase II study, to evaluate the safety and performance of the ACTISEAL® sealant patch (Fig. 2). Eligible patients had to be $\geq$ 18 years old and undergo DP for any indication, through an open or hand-assisted laparoscopic approach. Participants were required to be able and willing to comply with all study procedures and follow-up examinations outlined within the written consent form. Hospitals were allowed to participate only after having obtained local or national ethics approval. Patients were excluded if there were known hypersensitivities to the components of ACTISEAL®. Other exclusion criteria included a known pregnancy or breast feeding, presence of an active infection, use of double anti-coagulation or presence of peritoneal dialysis. Patients were excluded as well if they participated in any investigational drug- or device study within 30 days prior to screening. Intraoperatively, patients were excluded if a multivisceral resection was conducted (except resection of the spleen) or when an anastomosis (e.g. an enteric anastomosis) was necessary during the procedure. A maximum usage of three sealant patches (size 10 × 5 cm) was allowed.

The study was conducted in accordance with the principles described in the International Conference on Harmonisation Good Clinical Practice. All patients provided written informed consent prior to enrollment. The trial was preregistered at clinicaltrials.gov (NCT04024956).

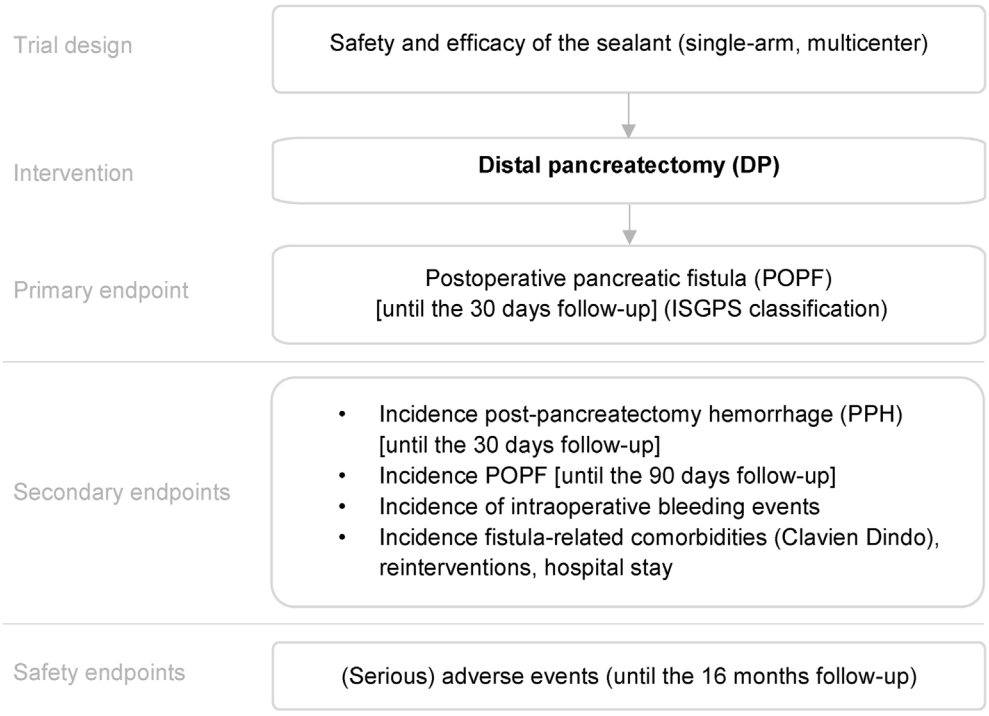

Figure 2 Trial design

Role of the funding source

The funders of the study (Polyganics BV) participated in study design. They had no role in conduction of surgeries, data collection, analysis, interpretation of results or manuscript writing. All authors had full access to all data in the study and the corresponding author had the final responsibility for the decision to submit the collected data.

Intervention

ACTISEAL® is a thin, bioresorbable, flexible patch with two layers: an adhesive layer (depicted as white foam) and a protective barrier layer (blue colored; Fig. 1). Both layers are made of biodegradable polyurethane. The white foam layer is incorporated with an adhesive component, which is placed on the pancreatic transection surface and reacts with amines in the tissue in a moist environment, forming covalent bonds between the device and the tissue. The blue colored protective barrier layer forms a watertight seal, intended to reduce pancreatic or blood leakage.

DP and stump closure was performed according to local standards. There were no exclusion criteria regarding the indication for DP; all types of indications were present e.g. malignancy or cystic neoplasms. Prior to application of the sealant patch, the pancreatic stump was rinsed with physiological saline. ACTISEAL® was then placed over the pancreatic stump, fully covering the resection surface. If necessary, the device could be tailored by cutting it into the right shape or a second device could be applied. Light pressure was applied for a minimum of 1 min. In case of dislocation of ACTISEAL®, it should be removed and replaced by another ACTISEAL®. Drain placement was according to local standards of each center and not obligatory within this study.

All surgeons were trained prior to the study and were informed as well to record all surgeries by video, to be able to assess bleeding rates and correct application of the devices.

Postoperatively, on day 1, day 3 and at discharge, a regular physical examination including inspection of the wound, assessment of lipase and amylase levels and blood tests was required. If drains were not placed at all or removed earlier, assessment of lipase and amylase levels was no longer required.

Outcomes

The main objective of the study was to evaluate safety and performance in reducing postoperative leakage of pancreatic fluid by using ACTISEAL® in patients undergoing elective distal pancreatectomy.

For the distal pancreatectomy group, the primary endpoint was the incidence of postoperative CR-POPF (according to the ISGPF classification) within the 30 days follow-up.[2] The grading of CR-POPF was done by the participating centers using the electronic case report form. In patients, where no drain was placed, CR-POPF was diagnosed through the events, which classify CR-POPF grade B or grade C, e.g. percutaneous or endoscopic drainage of fluid collections, angiographic procedures for bleeding or reoperation. Drainage of fluid collections

also enabled the investigators to measure amylase and lipase levels in the collected fluids.

Secondary endpoints were the occurrence of intra-operative bleeding (classified according to the validated intraoperative bleeding scale[11] as well as the incidence of postoperative bleeding (PPH), the incidence of leak-associated comorbidities (classified according to the Clavien-Dindo Scale,[12] re-interventions, transfusions, hospital stay, mortality and ease of use and application of ACTISEAL®. Patients were followed up at postoperative day 30, 90 and 180 to evaluate the long-term incidence of postoperative pancreatic juice leakage and safety. The safety endpoint was the incidence of (serious) adverse events. Last patient follow-up was scheduled at 16 months.

Data collection and follow-up

Preoperatively, baseline data such as clinical history, previous surgery and medication were collected. Intraoperative data including surgical technique, type of stump closure, exact application time points of the ACTISEAL® and bleeding according to the intraoperative bleeding scale were collected at the date of surgery. On day 1, day 3 and upon discharge data on physical status, blood tests regarding signs of inflammation and samples from the drains (testing for amylase and lipase as well as hemoglobin levels) were collected. Postoperative complications, length of drain-in-situ and length of hospital stay were registered at discharge. Patients were asked to participate in a personal follow-up (day 30 and day 90) and in a telephone follow-up (day 180 and after 16 months) and data were collected regarding physical status, laboratory results and adverse events. Trial data were recorded using an electronic database hosted by IQVIA (clinical research organisation).

Statistical analysis

Sample size calculation was based on the results in pre-clinical studies with respect to device performance. In addition, sample size calculation was based on values retrieved from the literature, namely a rate of POPF of 29%[2,13] for pancreas and bile leakage 15%[14] for the liver group.

In summary, the aim of this study is to evaluate whether a leakage rate of 10% is achievable among both groups.

For sample size calculation, the Clopper-Pearson method is used to calculate a 95% confidence interval (CI) around the 10% leakage rate. A confidence interval with an upper limit of 22% clinically relevant leakages was chosen, based on the average leakage percentage in the literature for liver and pancreas (as mentioned above). This can be achieved with a sample size of 70 patients, with a 95% CI ranging from 4.1% to 19.5%. Taking into account a maximum of 12.5% lost-to-follow-up within 30 days postoperatively, the total sample size is 80 patients, resulting in 40 patients in the pancreas group.

We performed an analysis in which we compared all possible outcomes within the chosen CI range (4.1%–19.5%) with the assumed 10% leakage rate. It was found that if the number of clinically relevant leakages is higher than expected, as long as the maximum is 17%, the confidence interval will contain the assumed 10% (CI: 9.1%–27.9% of 17%) and the study will be considered successful.

Reflecting on the different nature of pancreatic and hepatic surgery with regard to patients' profile as well as risk and nature of complications, the device performance was evaluated separately for liver and pancreas. The present work focuses on the results obtained in DP. Data are depicted as mean values and standard deviation or alternatively absolute numbers and percentage of whole population. The subgroup analyses are considered exploratory.

Results

Patient characteristics

From September 2020 to October 2021, 80 patients were recruited in 8 European centers for HPB surgery from 5 countries, of which 40 underwent DP. Sex was well balanced with 52.5% female patients. Median age at time of trial enrolment was 62.5 years (standard deviation (SD) ±13). The mean body mass index (BMI) of the participants' cohort was 25.21 kg/m2 (SD ± 4.06). Regarding the indication for surgery, there were more patients with a suspected pancreatic adenocarcinoma and lesions due to chronic pancreatitis, than cystic or premalignant lesions. See Table 1 for baseline characteristics.

Operative details

The majority of the DP procedures were performed via an open approach (92.5%) whereas 7.5% were performed as a minimally

Table 1 **Patient characteristics** (n = 40)

Variable	Incidence
Sex	
Female (n; %)	21 (52.5)
Male (n; %)	19 (47.5)
Age (mean; ±SD)	62.5 (±13)
BMI (mean; ±SD)	25.21 (±4.1)
Smokers (n; %)	8 (20.0)
Comorbidities (n; %)	32 (80.0)
Cardiovascular (n; %)	24 (35.0)
Diabetes (n; %)	10 (25.0)
Oncologic (n; %)	12 (30.0)
Gastroesophageal reflux (n; %)	1 (2.5)
Musculoskeletal (n; %)	2 (5.0)
Autoimmune disease (n; %)	1 (2.5)
Other (n; %)	21 (52.5)
Diagnosis	
Pancreatic adenocarcinoma or pancreatitis (n; %)	28 (70.0)
Ampullary, duodenal, cystic, islet cell, etc. (n; %)	12 (30.0)

Table 2 **Operative details** (n = 40)

Variable	Incidence
Operative approach	
Open approach (n; %)	37 (92.5)
Hand-assisted approach (n; %)	3 (7.5)
Closure technique	
Handsewn closure (n; %)	13 (32.5)
Stapled closure (n; %)	21 (52.5)
Reinforced stapled closure (n; %)	0
Combination of suturing/stapling (n; %)	3 (7.5)
Other	3 (7.5)
Duration of surgery in minutes (mean; ±SD)	248.2 (±99.1)
Duration of sealant application in minutes (mean; ±SD)	12.7 (±12.9)
Numbers of sealants applied (mean; ±SD)	2 (±0.53)

invasive hand-assisted surgery. The primary method for pancreatic stump closure was stapling in 21 cases (52.5%), followed by sutures used in 13 cases (32.5%), and a combination of sutures and stapling in the remaining patients. The mean duration of surgery amounted to 248.2 min (SD ± 99.1). Within the procedure, the mean duration of sealant patch application was 12.7 min (SD ± 12.9) for all of the applied sealant patches. The mean number of patches applied was two (SD ± 0.53) (Table 2). Additional sealants or glues were not used in any cases.

Primary endpoint

The rate of CR-POPF was 7 of 40 patients (17.5%) up to postoperative day 30 (Table 3). Noteworthy, no type C POPF was observed. The patients were classified as a type B leakage due to persisting peripancreatic drainage over 3 weeks (n = 2; 5%), endoscopic intervention and drainage of leak associated fluid collections (n = 3; 7.5%) and due to a clinically relevant change in management (n = 2; 5%) (supplemental table 2). These changes in management included somatostatin analogues and parenteral nutrition in one case of an associated delayed gastric emptying. An additional 12 patients (30.0%) had a biochemical leak without clinical relevance, yielding a total of 19 cases (47.5%) of POPF of any grade (Table 3). There was no difference in the occurrence of CR-POPF regarding the technique of stump closure prior to sealant patch application (supplemental table 4).

Table 3 **Primary endpoint.** POPF within the 30 days follow-up (n = 40)

Variable	Incidence
CR-POPF (30 days follow-up; n; %)	7 (17.5)
Type B (n; %)	7 (17.5)
Type C (n; %)	0
Biochemical leak (30 days follow-up; n; %)	12 (30)

Secondary endpoints

The incidence of CR-POPF remained unaltered within the 90 days follow-up (Table 4). Leak-associated comorbidities were seen in 19 patients (47.5%) at the 30 days follow-up (Table 4). Regarding the Clavien Dindo Classification the comorbidities seen in these patients were in 4 cases ≥ Grade III (10%). Bleeding was categorized using the validated intraoperative bleeding scale by Lewis et al.[11] Before device application the majority of patients (57.5%) had a grade I bleeding. Directly after device application 92.5% had no bleeding. Transfusion of blood products intraoperatively was required in 2 participants (5.0%). A total of 3 patients (7.5%) had a postoperative bleeding event in less than 24h after surgery. Peripancreatic drains were removed on average after 13 days (SD ± 24.3 days); in patients with a type B leakage on average after 36.6 days (SD ± 42.6 days), in patients with a biochemical leak on average after 6.8 days (SD ± 2.3 days).

Within 90 days follow-up postoperative re-intervention for any reason was required in 7.5% (Table 4). The mean hospital stay was 11.5 days (SD ± 7.4 days); for patients with no fistula 9.4 days (SD + 4.3), for patients with a biochemical leak 10.5 days (SD + 7.3) and in patients with a type B leak 18.7 days (SD + 10.3; significantly different when compared to no leak; p = 0.009 using ordinary one-way ANOVA). In one patient, the patches detached, however in combination with a previous treatment with

Table 4 **Secondary endpoints.** Within the 90 days follow-up (n = 40)

Variable	Incidence
CR-POPF (90 days follow-up)	7 (17.5)
Type B (n; %)	7 (17.5)
Type C (n; %)	0
Biochemical leak (90 days follow-up; n; %)	12 (30)
Leak-associated comorbidities (n; %)	19 (47.5)
Clavien–Dindo	
Grade I (n; %)	12 (30)
Grade II (n; %)	3 (7.5)
Grade IIIa (n; %)	4 (10)
Grade IIIb (n; %)	4 (10)
Grade IVa (n; %)	0
Grade IVb (n; %)	0
Grade V (n; %)	0
Transfusion of blood products intraoperatively (n; %)	2 (5.0)
Postoperative bleeding events	
<24h after surgery (n; %)	3 (7.5)
>24h after surgery (n; %)	0
Postoperative re-intervention for any reason (n; %)	3 (7.5)
Mean hospital stay in days (mean; ±SD)	11.5 (7.4)
No leak (mean; ±SD)	9.41 (4.3)
Biochemical leak (mean; ±SD)	10.5 (7.3)
Type B (mean; ±SD)	18.71 (10.3)

hyperthermal intraperitoneal chemotherapy (HIPEC). The patient was withdrawn from the analysis as the detached patches were removed 9 days after surgery. There was no mortality until day 30. One patient was lost to follow-up due to death between the 30 and 90 days follow-up (2.5%). This patient passed away on day 44 from a gastrointestinal bleeding with hemorrhagic shock, which was clearly not related to the device.

Safety endpoints

At the 30 days follow-up 87 adverse events were reported within 31 patients (77.5%) (supplemental table 1). Nine of the named events were serious adverse events. In one patient, the patches detached, however in combination with a previous treatment with hyperthermal intraperitoneal chemotherapy (HIPEC). There were no signs of allergic reactions or infections related to ACTISEAL®.

Discussion

This is the first in human study to assess safety and performance of ACTISEAL® in patients receiving a distal pancreatectomy. Application of ACTISEAL® proved technically successful in all 40 patients and not associated with a prolonged operating time. In one case the sealant patch detached, most likely due to a simultaneous administration of intraperitoneal chemotherapy (HIPEC). The use of the sealant in combination with intraperitoneal chemotherapeutic drugs has not been tested. As it has been identified within this study, it will be included within the risk management.

The main finding was the relatively low rate of CR-POPF of 17.5% compared to other trials or larger cohorts, which evaluated the application of a sealant device (see Fig. 3). More particularly, the rate of CR-POPF was 27.4% in the FIABLE-trial, assessing a fibrin collagen patch, and 27.6% in the DISCOVER-trial, assessing additional coverage of the pancreatic remnant by an autologous patch.[15,16] Importantly, there was no type C POPF in our trial, which has been reported to occur in 3%–9% of patients undergoing DP.[3] This illustrates a shift towards pancreatic fistulas with a reduced clinical impact. Moreover, 4 out of 7 patients with a type B fistula were discharged without the need for further intervention. As a conclusion this might result in a reduction of morbidity and mortality, reduce the length of hospital stay and costs and thereby it might improve subsequent patient treatments, e.g. progression to adjuvant chemotherapy. Given the positive outcomes in DP, the effect of the sealant patch is potentially more pronounced in patients with partial pancreaticoduodenectomies, as POPFs in these patients have a more severe clinical impact regarding morbidity and mortality. A comparative trial is necessary to verify the effectiveness of the device.

Reference	Type of sealant	Patients enrolled	B and C POPF combined/ CR-POPF	
			Control	Intervention
Single arm trials				
Hüttner et al. (2018) [19]	2-octyl cyanoacrylate (surgical glue)	15	--	33.3%
Minh Luu et al. (2021) [20]	Vivostat®	41	--	27%
D Bubis et al. (2022) [5]	Hemopatch®	52	--	25%
Randomized controlled trials				
Montorsi et al. (2012) [21]	Tachosil®	275	14%	8%
Carter et al. (2013) [22]	Fibrin glue and Lig. falciforme patch	109	16.3%	16.6%
Sa Cunha et al. (2015) [15]	Tachosil®	270	24.3%	30.6%
Park et al. (2016) [23]	Tachosil®	101	28.3%	22.9%
Jang et al. (2017) [24]	Polyglycolic Acid Mesh	97	28.3%	11.4%
Mungroop et al. (2021) [17]	Tachosil®	247	24%	20%

Figure 3 Characteristics of prospective trials investigating POPF after additional application of a sealant device to the pancreatic remnant

The mortality rate after DP was 2.5% and the incidence of Clavien Dindo ≥ grade III complications of any cause at follow-up day 30 was 9.8%. Serious adverse events occurred in 20% of patients within the 30 days follow-up (for details see supplemental table 3). The incidence of complications (Clavien Dindo ≥ grade III) as serious adverse events is comparable to other published cohorts.[4,5,17] Readmissions, even if related to other comorbidities, were also considered as serious adverse events. As sealant patches detached due to simultaneous administration of intraperitoneal chemotherapeutic drugs (HIPEC), it has been identified as a contraindication within this study and it will be included within the risk management. Importantly, analysis of the safety endpoints revealed that there was no allergic reaction or localized infection due to the patch. SAE's were mainly explained by clinically relevant POPF or hospitalization due to the underlying disease (e.g. side effects of chemotherapy) and not attributed to patch application. The described SAE's were comparable to SAE's we normally see after distal pancreatectomies. A safety stop per protocol after the first ten patients, requested by the regulatory authorities, revealed no objections. Furthermore, evaluation of the safety endpoints and analysis by the data safety monitoring board demonstrated that the sealant patch is safe. There was no suspicion for a causal relationship regarding patch application and the occurrence of serious adverse events.

CR-POPF remains the most significant cause of postoperative morbidity and mortality after pancreatic resections. It is associated with short- and long-term consequences, especially in oncological patients. Strategies to reduce CR-POPF and the severity of CR-POPF are sorely needed. Several studies have investigated different attempts such as reinforced staplers, fibrin sealants and autologous patches; however, none of these strategies succeeded in reducing CR-POPF significantly.[9,17,18] Several trials and meta-analyses have evaluated the role of sealants, such as fibrin sealants as well as bovine-collagen based sealants, however none of the available products showed a robust reduction in CR-POPF(5,17). The results of the SHIELDS trial are promising, with ACTISEAL® as the first patch dedicated for the control of leakage after HPB surgery.

There are limitations to this study which merit consideration. First, pure laparoscopic approaches were excluded, as preclinical testing focused on the manual application. Especially in distal pancreatectomies the majority of patients is resected within a laparoscopic approach whenever suitable. However, ACTISEAL has been tested in animal studies in a laparoscopic setting and application of the sealant was feasible and easy without additional modifications. Upcoming trials will integrate the use of ACTISEAL as well in a laparoscopic or robotic setting. Second, the sample size of our cohort was - in accordance with the ethical committee and the regular authorities - small, as the study was designed as a safety and performance study, thereby limiting the statistical significance. As our patient cohort originates from centers with quite different caseloads as well as expertise in pancreatic surgery, our cohort reflects a real-life scenario in pancreatic surgery. However, due to this variability, selection bias might have occurred. A larger cohort could demonstrate stronger effects regarding the shift of CR-POPF towards pancreatic fistulas with lower clinical impact. Lastly, drain placement was not obligatory and remained the decision of the participating centers. Thereby, the incidence of biochemical leakage might be underrepresented and there is still an ongoing discussion, whether drain placement itself influences the incidence of POPF.[19]

In conclusion, application of ACTISEAL® to the pancreatic transection plane after DP was safe and feasible. Interestingly, application of ACTISEAL® resulted in low incidence of CR-POPF compared to literature and importantly in a shift towards less severe pancreatic fistulas. Based on the present findings, we recommend the use of ACTISEAL® in a randomized controlled trial in patients with DP to assess whether it can reduce the rate of CR-POPF as well as associated morbidity and mortality.

Conclusion

Our results show that the new sealant patch is safe to use and indicate that the new sealant patch may have a potential in reducing the rate of CR-POPF which now needs to be confirmed in a randomized trial. This is the first clinical report about this potentially effective sealing patch in HPB surgery.

Conflict of interest

Financial support as well as the sealant patches were provided by Polyganics BV. In addition, Maximilian Bockhorn, Asmus Heumann and Jakob R. Izbicki received consulting fees from Polyganics BV.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2024.03.002.