

# BMJ Open Protocol of a randomised controlled phase II clinical trial investigating PREoperative endoscopic injection of BOTulinum toxin into the sphincter of Oddi to reduce postoperative pancreatic fistula after distal pancreatectomy: the PREBOT*Pilot* trial

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## ABSTRACT

**Introduction** Postoperative pancreatic fistula (POPF) is still the most frequently occurring and clinically relevant complication after distal pancreatectomy (DP). Preoperative endoscopic injection of botulinum toxin (BTX) into the sphincter of Oddi represents an innovative approach to prevent POPF. The aim of this project (PREBOT*Pilot*) is to generate the first randomised controlled trial data on the safety, feasibility and efficacy of preoperative endoscopic BTX injection into the sphincter of Oddi to prevent clinically relevant POPF following DP.

**Methods and analysis** PREBOT*Pilot* is an investigator-initiated, single-centre, randomised, controlled, open-label, phase II clinical trial with two parallel study groups and an exploratory study design. 60 patients scheduled for DP will be randomised to intervention and control group. In the intervention group, patients will undergo preoperative endoscopic injection of BTX into the sphincter of Oddi, whereas in the control group no preoperative endoscopy will be performed. The combined primary endpoint is the occurrence of clinically relevant POPF and/or death within 30 days after DP. The secondary endpoints comprise further postoperative outcome parameters and quality of life up to 3 months after DP as well as safety and feasibility of the procedure. Statistical analysis is based on the modified intention-to-treat population, excluding patients without status post DP. For safety analysis, rates of adverse events (AEs) and serious AEs will be calculated with 95% CIs for group comparisons.

**Ethics, funding and dissemination** PREBOT*Pilot* has been approved by the German Federal Institute for Drugs and Medical Devices (reference number 4043654) and the Ethics Committee of Heidelberg University (reference number AFmo-523/2019). This trial is supported by the German Federal Ministry of Education and Research (BMBF). The results of the trial will be presented at national and international conferences and published in a peer-reviewed journal.

## Strengths and limitations of this study

- This is the first randomised controlled trial to investigate the safety, feasibility and efficacy of preoperative endoscopic injection of botulinum toxin into the sphincter of Oddi to prevent postoperative pancreatic fistula after distal pancreatectomy.
- One of the strengths of this trial is the careful monitoring of adverse events and the comparison of the safety profile of this new and promising approach with a randomly assigned control group not receiving preoperative endoscopy.
- The results of this pilot trial will serve as a basis for planning a future confirmatory phase III clinical trial.
- One of the limitations of this trial is the open-label trial design, which is a potential source of performance and detection bias.

**Trial registration number** DRKS00020401.

## INTRODUCTION

### Rationale of the trial

Distal pancreatectomy (DP) is the standard surgical treatment for benign and malignant tumours of the pancreatic body and tail. It now has mortality rates below 5% when performed in specialised institutions.<sup>1,2</sup> However, postoperative morbidity may still be as high as 50%.<sup>3</sup> Of all the complications following DP, leakage from the pancreatic stump is the most frequent and is often associated with clinical symptoms and changes in patient management.<sup>4,5</sup> The incidence of clinically relevant postoperative pancreatic fistula



(POPF), that is, POPF grades B/C as defined by the International Study Group of Pancreatic Surgery (ISGPS),<sup>6</sup> still ranges up to 42% after DP.<sup>7</sup> Owing to the associated risk of severe sequelae such as intra-abdominal abscess and postpancreatectomy haemorrhage (PPH), clinically relevant POPF considerably impairs patients' postoperative outcome.<sup>8</sup> Furthermore, the need for postoperative diagnostics and specific treatments including radiological and surgical reinterventions for the management of POPF-related complications prolongs the hospital stay and increases healthcare costs.<sup>9</sup> The prevention of POPF is particularly important in patients undergoing pancreatic surgery combined with arterial resection due to the increased risk of life-threatening arterial bleeding.<sup>10</sup> Recent high-quality studies have provided level I evidence that none of the prevailing surgical techniques ensures secure closure of the pancreatic remnant.<sup>4 5 11 12</sup> Further research into the prevention of POPF is therefore mandatory, and the time has come to evaluate new approaches in the attempt to solve this hitherto intractable problem.

### Preliminary data

Besides the technical aspects of stump closure, POPF formation following DP is thought to be promoted by increased pressure on the resection margin, leading to leakage from ductal structures.<sup>13</sup> Studies investigating endoscopic stenting of the papilla of Vater with the aim of improving drainage of pancreatic fluid towards the duodenum, and thus lowering back pressure on the resection margin, have shown promising results, confirming the importance of pressure-induced leakage in the pathophysiology of POPF.<sup>14–16</sup> However, because of the risks associated with insertion of a prosthesis,<sup>17</sup> a stent-free approach to the prevention of POPF would be preferable. Endoscopic injection of botulinum toxin (BTX) into the sphincter of Oddi to reduce sphincter pressure is a long-established safe and effective treatment option in patients with sphincter of Oddi dysfunction.<sup>18 19</sup> In the setting of DP, two recent case series have reported pharmacologically induced sphincter relaxation by means of BTX as a new approach to the prevention of POPF. Hackert *et al*<sup>20</sup> showed that no clinically relevant POPF (grades B/C according to the ISGPS) occurred in a prospectively collected series of 24 patients undergoing preoperative injection of BTX into the sphincter of Oddi followed by DP, whereas 8 of 24 patients (33%) in a historical control group developed clinically relevant POPF (grades B/C). A subsequent retrospective case series by Volk and colleagues<sup>7</sup> could not reproduce the significant reduction of clinically relevant POPF in 19 patients undergoing preoperative BTX injection compared with a historical control group, but also found a reduced POPF rate in the intervention group (32% vs 42%). Apart from these two non-randomised studies, no further evidence on preoperative sphincter of Oddi BTX injection in the setting of DP has been reported.

The aim of the investigator-initiated, single-centre, randomised, controlled PREBOT*Pilot* trial is to generate

the first randomised controlled trial data on the safety, feasibility and efficacy of preoperative endoscopic BTX injection into the sphincter of Oddi to prevent clinically relevant POPF following DP.

### METHODS AND ANALYSIS

This clinical trial protocol is written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.<sup>21</sup> Adherence to these recommendations is documented in the SPIRIT checklist (see online supplementary additional file 1). PREBOT*Pilot* was registered at ClinicalTrialsRegister.eu (identifier 2019-002461-35) and the German Clinical Trials Register (DRKS00020401) before enrolment of the first patient.

### Trial design and trial-supporting facilities

This is an investigator-initiated, single-centre, randomised, controlled, open-label, phase II clinical trial with two parallel trial groups and an exploratory study design. The sponsor of the PREBOT*Pilot* trial is the University Hospital of Heidelberg, Germany. The sponsor had no role in the design of this study and will not have any role during its execution, analysis of the data, interpretation of the findings or the decision to submit the results for publication. The principal investigator is the sponsor's representative. He conceived the PREBOT*Pilot* trial and will conduct it in close cooperation with the Coordination Centre for Clinical Trials (KKS) and the Institute of Medical Biometry and Informatics (IMBI), both in University of Heidelberg, Germany. The KKS is in charge of pharmacovigilance and monitoring, while the IMBI is responsible for data management and biostatistics. The site of this trial is the Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Germany.

### Trial population

The trial population consists of consecutive patients scheduled for primary elective DP to treat various underlying diseases. It is expected that a total number of about 120 patients will be screened for the inclusion and exclusion criteria. A detailed overview of the eligibility criteria is given in [table 1](#). The planned number of patients for randomisation is 60 (see [figure 1](#)).

### Recruitment and trial timeline

The trial preparation phase started in June 2019. The inclusion of the first patient was on 6 March 2020. The duration of the clinical trial for each individual patient will be 3 months. The flow chart in [figure 1](#) illustrates the structure of the PREBOT*Pilot* trial. After treatment of the first 12 patients (intervention group), recruitment will be interrupted for 30 days while an interim analysis for safety is performed.

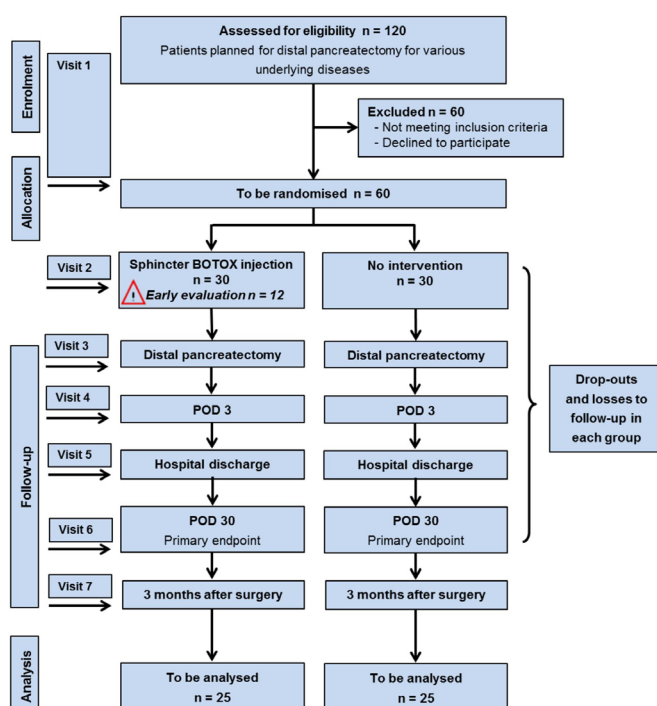
### Feasibility of recruitment

The time taken to recruit 29 patients out of the 76 patients screened for eligibility within the previous series

**Table 1** Inclusion and exclusion criteria

| Inclusion criteria   | Exclusion criteria   |
|--|--|
| Patient scheduled for primary elective distal pancreatectomy (open or laparoscopic technique)                                  | Serious cardiovascular disease (eg, myocardial infarction in the last 12 months, congestive heart failure NYHA III/IV, unstable angina pectoris)   |
| Patient ≥18 years of age   | Renal insufficiency, that is, creatinine clearance <30 mL/min  |
| Ability of patient to understand nature and individual consequences of clinical trial  | Liver cirrhosis (of any Child-Pugh grade)  |
| Written informed consent   | ASA score >III   |
| For women of childbearing potential, negative pregnancy test and adequate contraception until 14 days after trial intervention | Hypersensitivity to any BTX preparation or to any of the components in the formulation   |
|  | Neuromuscular disorder, for example, amyotrophic lateral sclerosis or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome), or any other neurological disorder with associated increased risk for the patient undergoing BTX injection |
|  | Any condition in which duodenoscopy and/or the trial intervention is not possible, for example, for anatomical reasons, or obsolete, for example, in patients with acute pancreatitis  |
|  | History of BTX administration and either positive or missing test for neutralising antibodies to BTX   |
|  | Comprehension or language problems   |
|  | Inability to comply with study and/or follow-up procedures   |
|  | Pregnancy or lactation   |
|  | Concurrent participation in another interventional clinical trial  |
|  | Any condition that could result in undue risk for the patient and/or influence outcome measures (in the opinion of the investigator)   |

ASA, American Society of Anesthesiologists; BTX, botulinum toxin; NYHA, New York Heart Association.



**Figure 1** Trial flow chart. POD, postoperative day.

by Hackert *et al* was 12 months.<sup>20</sup> Nowadays, our centre carries out at least 120 DP per year. Based on our experience in the recruitment of patients eligible for preoperative sphincter of Oddi BTX injection,<sup>20</sup> recruitment will be optimised in this phase II trial. We estimate that recruitment of 60 patients over a period of 12 months is feasible.

### Randomisation

In order to achieve comparable intervention groups, patients will be assigned 1:1 to intervention or control group by applying a central online randomisation system ([www.randomizer.at](http://www.randomizer.at)) shortly after enrolment. As soon as the individual participant is allocated to one of the two study groups, the upcoming procedures (ie, preoperative endoscopy for patients in the intervention group and surgery for patients in both groups) will be scheduled. Only authorised trial personnel will perform randomisation with their login data.

### Interventions

**Trial intervention (intervention group):**

esophagogastroduodenoscopy with sphincter of Oddi BTX injection  
In the intervention group, participants will undergo esophagogastroduodenoscopy with injection of BTX into

the sphincter of Oddi between 3 and 10 days before DP in an outpatient setting at the Interdisciplinary Centre of Endoscopy, University of Heidelberg, Germany. The study medication BOTOX (Allergan Pharmaceuticals, Dublin, Ireland) is stored and reconstituted according to the summary of product characteristics (SmPC). As established by Wehrmann *et al*<sup>19</sup> and recently developed by Hackert and coworkers,<sup>20</sup> the procedure will be carried out as follows: after positioning the endoscope in front of the papilla of Vater, 1 mL of the properly reconstituted BTX solution (100 units of BOTOX/1 mL) is injected into the intraduodenal sphincter of Oddi segment along the general direction of a virtual pancreatic sphincterotomy. For administration of the medication, the needle is inserted into the upper margin of the papillary orifice at the 1 o'clock position and 1 mL of the solution is injected as a single deposit. After sphincter of Oddi BTX injection, the procedure is terminated and patients are closely monitored according to the centre's standard safety measures for patients undergoing upper gastrointestinal endoscopy.

#### Control group

Patients in the control group will not undergo preoperative endoscopy because 'placebo endoscopy' is not justified in this phase II clinical trial. As there are no effective and generally accepted means of preventing POPF, patients in the control group will be treated according to the standard procedures. Thus, clinical equipoise is given.

#### Risk of bias

The open-label trial design is a potential source of performance and detection bias. However, since the primary endpoint can be assessed objectively, it is not likely to be biased by a non-blinded study design.<sup>21</sup> In addition, the patients concerned would be exposed to the possible (although low) risks of placebo esophagogastroduodenoscopy which therefore is not justified. To reduce performance bias, procedures will be standardised and the trial personnel will be informed and trained at the site initiation visit. Adherence to the protocol will be controlled by regularly monitoring procedures (see below).

#### Surgical intervention: exploratory laparoscopy/laparotomy and DP

In both study groups, patients will undergo exploratory laparoscopy or laparotomy depending on the preferences of the individual patient and the surgeon. After confirming technical resectability and the absence of liver or peritoneal tumour spread, DP will be performed by linear stapler or scalpel with suture closure of the cut margin. Additional resections will be carried out if necessary in the opinion of the surgeon, depending on the individual patient's intraoperative findings. No additional covering of the pancreatic remnant of any kind, for example, ligamentum teres hepatis patch, mesh implantation or the use of fibrin glue, will be permitted. The intraoperative placement of drains will be optional.

Perioperative administration of octreotide will be allowed, but will have to be documented in the electronic case report form (eCRF).

#### Outcome parameters

##### Primary outcome parameter

The primary endpoint is occurrence of clinically relevant POPF and/or death due to any cause within 30 days after DP. Clinically relevant POPF is defined as a grade B or C fistula according to the recently updated ISGPS definition.<sup>6</sup> Former grade A fistula, now called biochemical leaks will not be accounted for the primary endpoint. The rationale for the combination of POPF and death is the prevention of underestimated POPF rates due to undetectable fistulas in postoperative deaths. This combined primary endpoint has already been applied successfully in the multicentre DISPACT (efficacy of stapler versus hand-sewn closure after distal pancreatectomy) trial.<sup>22</sup>

##### Secondary outcome parameters

The secondary endpoints comprise overall pancreatic fistula rate and severity (ie, biochemical leaks, POPF grades B and C according to the ISGPS definition<sup>6</sup>), the occurrence of postinterventional pancreatitis, perioperative sepsis, delayed gastric emptying and PPH according to the ISGPS definitions,<sup>23–24</sup> intra-abdominal fluid collection/abscess, lymphatic fistula, wound infection, burst abdomen, reinterventions/reoperations, 3-month mortality, quality of life (assessed using the validated questionnaire of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and its extension EORTC QLQ-PAN26), the durations of intensive/intermediate care unit stay and total hospital stay, and readmission to hospital for management of postoperative complications.

##### Assessment of feasibility

Feasibility will be measured by calculating the proportion of patients with both successful BTX injection into the sphincter of Oddi and successful DP in the experimental intervention group.

##### Schedule of trial procedures

An overview of the scheduled study procedures is presented in [table 2](#). There will be seven study visits from screening to the last follow-up at 3 months after surgery, whereby visit 2 (endoscopy) will be exclusive to the intervention group. Preoperative endoscopy with sphincter BTX injection will be the only trial-related intervention for patients participating in this trial and will be performed only in the patients of the intervention group. All the other procedures, including assessment of laboratory parameters, belong to the standard perioperative and postoperative procedures performed in patients undergoing DP. In patients with childbearing potential, a pregnancy test will be performed during the routine preoperative laboratory examinations.



**Table 2** Study visits of the PREBOT*Pilot* trial

| Visit                           | 1<br>Enrolment and<br>randomisation | 2<br>Endoscopy<br>Intervention<br>group | 3<br>Operation | 4     | 5                | 6      | 7                          |
|---------------------------------|-------------------------------------|---|----------------|-------|------------------|--------|----------------------------|
| Day relative to index operation |                                     | Day -10 to day -3                       | Day 0          | POD 3 | Day of discharge | POD 30 | Three months after surgery |
| Visit window                    | ±0                                  | ±0                                      | ±0             | ±0    | -2               | ±3     | ±7                         |
| Inclusion/exclusion criteria    | X                                   |   |                |       |                  |        |                            |
| Informed consent                | X                                   |   |                |       |                  |        |                            |
| Baseline/demographic data       | X                                   |   |                |       |                  |        |                            |
| Prior/concomitant diseases      | X                                   |   |                |       |                  |        |                            |
| Prior/concomitant medication    | X                                   | X                                       | X              | X     | X                | X      | X                          |
| Randomisation                   | X                                   |   |                |       |                  |        |                            |
| Endoscopic intervention         |                                     | X                                       |                |       |                  |        |                            |
| Operative procedure             |                                     |   | X              |       |                  |        |                            |
| Laboratory parameters*          |                                     | X                                       | X              |       |                  |        |                            |
| Pregnancy test†                 | X                                   |   |                |       |                  |        |                            |
| Drainage amylase                |                                     |   |                | (X)   | (X)              | (X)    | (X)                        |
| Primary endpoint                |                                     |   |                | X     | X                | X      |                            |
| Secondary endpoints             |                                     |   |                | X     | X                | X      | X                          |
| AE/SAE                          | X                                   | X                                       | X              | X     | X                | X      | X                          |
| Quality of life                 | X                                   |   |                |       |                  | X      | X                          |

\*Standard peri-interventional/perioperative procedures.

†Females of childbearing potential only.

AE, adverse event; POD, postoperative day; SAE, serious adverse event.

### Safety and pharmacovigilance

For safety evaluation, patients will be monitored closely for the occurrence of adverse events (AEs) and serious AEs (SAEs). An SAE is defined as any AE occurring during the observation period that results in death, is life-threatening, requires or prolongs hospitalisation, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is otherwise medically relevant and/or requires intervention to prevent any of these outcomes. An SAE that is ‘suspected’, that is, possibly related to the study medication, and ‘unexpected’, that is, its nature and/or severity is not consistent with the applicable SmPC, will be classified as suspected unexpected serious adverse reaction (SUSAR). All SAEs will have to be reported by the investigator to the responsible safety officer at KKS Heidelberg immediately after the SAE becomes known (but not later than 24 hours). The reported SAE will be subject to a second independent assessment to evaluate causality, expectedness and to judge whether the benefit/risk assessment for the trial changes as a result of the SAE. All SUSAR occurring after administration of the study medication will be subject to expedited reporting by the responsible safety officer

at KKS Heidelberg. Following treatment of the first 12 patients (intervention group), recruitment will be interrupted for 30 days while an interim analysis for safety is performed. The results of this interim analysis will be discussed with the data safety monitoring board (DSMB) and the study coordinators.

### Statistical methods

#### Sample size calculation

Given that this is a phase II exploratory trial, no formal sample size calculation will be performed. To date, valid data from a phase II clinical trial performed according to the German Drug Law are lacking. Hackert *et al*<sup>20</sup> reported the rate of clinically relevant POPF and/or death as 0% in the intervention group, compared with 33% in the control group. Volk *et al*<sup>7</sup> found a rate of clinically relevant POPF and/or death of 32% in the intervention group, compared with 42% in the control group, which is quite high. In DISPACT,<sup>11</sup> a large multicentre randomised trial investigating two different surgical techniques for the resection and closure of the pancreatic stump, the clinically relevant POPF rate was 20% and mortality was 1% in both study groups up to and including



postoperative day (POD) 30. As the *PREBOTPilot* trial will examine patients with the same underlying condition and focus on the same surgical procedure, data from *DISPACT* can be transferred to patients in the control group and—with regard to the assumed POPF rate—to patients in the experimental group as well. Regarding the death rate, endoscopic BTX injection is not expected to increase the risk. For patients in the experimental group, a reduction in risk is anticipated owing to the preoperative endoscopic intervention, which is thought to prevent POPF and thus POPF-associated mortality. Therefore, including 50 patients (25 per group) in the final analysis and assuming that the rate of clinically relevant POPF and/or death within 30 days after surgery will not exceed 20%–21% in either of the two groups, the maximal width of an approximate 95% CI for the rate difference will be 44% points, illustrating the precision that can be achieved with this trial. After randomisation, loss of about 15% of patients ( $n=5$  per group) is expected owing to intraoperative discovery of extended or unresectable disease (this represents our experience in Heidelberg University Hospital) or due to loss to follow-up after DP (expected to be close to zero). Therefore, the total number of patients to be randomised is  $2 \times (5+25)=60$ . Patients lost to follow-up will not be replaced.

#### Compliance/rate of loss to follow-up

In the previous series by Hackert *et al* on the same topic,<sup>20</sup> the participants' compliance rate was 100%. Based on our experience from this previous series,<sup>20</sup> patients are expected to be highly motivated to take part in the *PREBOTPilot* trial and to comply with study procedures very well. The primary endpoint will be assessed on POD 30 and the last follow-up visit will be scheduled not later than 3 months after surgery. Thus, the rate of loss to follow-up after DP is expected to be close to zero.

#### Statistical analyses

The primary endpoint of this study will be the occurrence of clinically relevant POPF and/or death within 30 days after surgery. Before database closure, the assignment of each patient to the modified intention to treat (mITT) population and the per-protocol (PP) population (patients with no major protocol violations) will be defined in the statistical analysis plan. The analysis will be based primarily on the mITT population, defined as all patients with status post DP. This is reasonable, as patients undergoing procedures other than DP, for example, total pancreatectomy or explorative laparotomy alone, generally will not have any risk for POPF development. Because the *PREBOTPilot* trial will be an exploratory study, no confirmatory statistical tests will be applied. The descriptive  $p$  value of a  $\chi^2$  test comparing the rate of the primary endpoint between the two treatment groups will be reported, together with 95% CIs for the risk difference. In this single-centre trial with closely monitored patients, we do not expect any missing values for the primary endpoint in the mITT population. Nevertheless, if such

a missing value occurs, the value will be imputed using multiple imputation. A fully conditional specification method will be applied with intervention, age and BMI as covariates. A sensitivity analysis of the primary endpoint will be conducted based on the set of patients without major protocol violations (PP population). All secondary outcomes will be evaluated descriptively as well, and descriptive  $p$  values for the corresponding group differences will be reported along with 95% CIs. As an interim and final safety analysis, the rates of AE and SAE in both groups with 95% CIs will be provided. All analyses will be conducted using SAS V.9.4 or higher version.

#### Data collection and data management

The investigator or a designated representative will enter all protocol-required information in the eCRF (see online supplementary additional file 2). The eCRF will be completed as soon as possible after the information is collected, preferably on the same day when a trial participant is seen for an examination, treatment or any other trial procedure. The reason for any missing data should be provided. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified in accordance with the source data. Completeness, validity and plausibility of data will be checked at the time of data entry (edit checks) and using validating programmes, which will generate queries. The investigator or the designated representatives will be obliged to deal with the queries. If no further corrections are to be made in the database, it will be closed and used for statistical analysis. All data management procedures will be carried out according to the current standard operating procedures (SOP) of the IMBI.

#### Ethics and dissemination

The clinical trial protocol, version 1.3 (25/09/2019) and informed consent procedures including the patient information and informed consent documents were approved by the independent ethics committee of the University of Heidelberg on 10 October 2019 (AFmo-523/2019). The trial was approved by the German Federal Institute for Drugs and Medical Devices (BfArM) on 16 December 2019 (reference number 4043654). Before the first patient is enrolled in the trial, all ethical and legal requirements will have to be met. All planned substantial changes (see §10, (1) of the German GCP Regulation) will be submitted to the independent ethics committee of the University of Heidelberg and the BfArM in writing as protocol amendments. They will be signed by the sponsor's representative and biometrician and approved by the ethics committee and the competent authority.

The results of this trial will be presented at national and international conferences and submitted for publication in a peer-reviewed journal.

#### Screening and informed consent

Eligible patients attending the outpatient clinic of the trial site will be informed about the clinical trial and will

be provided with the patient information and informed consent documents. Before admission to the clinical trial, each patient will have to consent to participate after explanation of the nature, scope and possible consequences of the clinical trial in a form understandable to him or her. The patient will have to give consent in writing. This informed consent to participate in the clinical trial may be withdrawn by the patient verbally in the presence of, or in written form directed to, the investigator or a member of the investigating team at any time during the trial. Withdrawal must not entail any disadvantage to the patient, nor may the patient be coerced or unduly influenced to continue his or her participation. Furthermore, the patient will not be obliged to disclose the reasons for withdrawal of consent.

### Quality control and quality assurance

#### Data protection

The data obtained in the course of the trial will be handled pursuant to local regulatory requirements (eg, the EU General Data Protection Regulation, ‘Datenschutzgrundverordnung’). During the clinical trial, patients will be identified solely by means of their individual identification code (ie, screening number, randomisation number). Trial findings stored on a computer will be treated in accordance with local data protection law and will be handled in strictest confidence. Organisational procedures will be implemented to prevent distribution of trial data to unauthorised persons. The relevant stipulations of local data legislation will be fulfilled in their entirety. Each patient will consent in writing to release the investigator from his/her professional discretion insofar as necessary to allow inspection of original data for monitoring purposes by health authorities and authorised persons (inspectors, monitors, auditors).

The investigator will maintain a patient identification list (screening numbers and corresponding patient names) to enable records to be identified. Patients who do not consent to circulation of their pseudonymised data will not be included in the trial.

#### Monitoring

Monitoring will be done remotely and by personal visits from a clinical monitor according to the SOPs of the KKS Heidelberg. During on-site visits, the monitor will review entries into the eCRF on the basis of source documents. Additionally, by means of remote monitoring and frequent communication (letters, telephone, fax), the monitor will ensure that the trial is conducted according to the protocol and regulatory requirements. Therefore, the investigator will have to allow the monitor to verify all essential documents and support the monitor at all times. Frequency and other details of monitoring will be defined in the monitoring manual.

#### DSMB and steering committee

To ensure the ethical conduct of the trial and protect the rights and welfare of patients, a DSMB has been set

up. The DSMB will communicate the state of the trial on a regular basis, at least once a year. After reviewing the data on study conduct, for example, recruitment and protocol adherence, and on safety issues the DSMB will make recommendations to the steering committee on the further conduct of the study, for example, modification, continuation or closure. The data necessary for the DSMB to fulfil its function will be provided on a regular basis, at least every 6 months, and when the results of early safety evaluation (ie, after treatment of 12 patients with the investigational drug) are available. The working procedures will be described in detail in a DSMB charter.

#### Patient involvement

To involve patients in the PREBOT*Pilot* trial, patients treated at our department as well as members of the ‘Arbeitskreis der Pankreatektomierten e.V.’, a patient’s self-support group, have been asked to take part in the planning and conduct of this trial. As a consequence, study endpoints were defined in accordance with the concerns of the patients, especially quality of life was considered as secondary endpoint and the primary endpoint ‘pancreatic fistula’ was turned into ‘clinically relevant pancreatic fistula’ (ie, POPF grades B and C) because POPF grade A has no relevance for patients. To further guarantee that patients’ interests are represented throughout the trial conduct, a patient advocate will be member of the steering committee. Furthermore, one patient representative will be co-author of the publication of the study protocol and the publication of the results of the study.

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**Contributors** TH and MWB conceived the trial. TH is the sponsor’s representative and principal investigator of this trial. TH and UK applied for funding and drafted the study protocol. PS established the trial intervention. TH and UK drafted this manuscript. TB conceived the statistical analysis plan. SL is responsible for monitoring and pharmacovigilance. EM, MKD, PK, PP and CT provided essential scientific input. All authors read and approved the final manuscript.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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