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Name of Sponsor/Company: Universitätsklinikum Heidelberg		**Sponsor-Code of Study:** PREBOTPilot	*(For National Authority Use only)*
Name of (Finished) Product:		**Name of Active Ingredient:**	
EudraCT-No.: 019-002461-35	**CA Vorlage-No.:**	**IEC Antrags-No.:**	

☒ **End of Trial Report** ☐ **Annual Safety Report**

SYNOPSIS

Title of Study:
Monocenter, randomized, controlled, open-label, phase-II clinical trial of PREoperative endoscopic injection of BOTulinum toxin in the sphincter of Oddi to reduce postoperative pancreatic fistula after distal pancreatectomy (PREBOTPilot)

Date of Approval / Vote:
BfArM: 07.01.2020 **Ethics Committee: 07.10.2019**

Amendments:

Date of Approval / Vote:
BfArM: 18.08.2022, 01.03.2023 **Ethics Committee: 16.08.2022, 14.03.2023**

Investigators:
Principle Investigator:
Prof. Dr. T. Hackert (until January 31st, 2023) and Dr. Claudia Mack (since February 1st, 2023), University Hospital Heidelberg, Department of General, Visceral, and Transplantation Surgery, Im Neuenheimer Feld 420, 69120 Heidelberg
Deputy Investigator:
Prof. Dr. Peter Sauer, University Hospital Heidelberg, Department of Internal Medicine IV, Im Neuenheimer Feld 410, 69120 Heidelberg

Study Centre(s):
University Hospital Heidelberg, Department of General, Visceral and Transplantation Surgery, Im Neuenheimer Feld 420, 69120 Heidelberg

Publication (reference):
The study protocol was published:
Klaiber U, Sauer P, Martin E, et al. „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 PREBOTPilot trial." BMJ Open 2020;10
A publication of the results is in progress.

Study period: **(date of first enrolment)** **(date of last completed)**	06.03.2020 26.06.2023	**Phase of development:**	Phase II study

Objectives:
Primary efficacy endpoint (combined primary endpoint): Occurrence of clinically relevant postoperative pancreatic fistula (POPF grades B/C) according to the International Study Group of Pancreatic Surgery (ISGPS) and/or death due to any cause within 30 days after distal pancreatectomy
Secondary endpoints: Occurrence of POPF within 3 months, severity of POPF, postinterventional pancreatitis, postoperative morbidity (delayed gastric emptying, intraabdominal fluid collection/abscess, postpancreatectomy hemorrhage, perioperative sepsis, lymphatic fistula etc.), reinterventions/-operations, mortality, quality of life, intensive/intermediate care unit stay, total hospital stay, readmission to hospital
Assessment of feasibility: Proportion of patients undergoing both successful botulinum toxin injection in the sphincter of

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Oddi and distal pancreatectomy in the experimental intervention group.
Assessment of safety: Patients will be closely monitored for the occurrence of adverse events (AE) and serious adverse events (SAE).

Methodology:
Consecutively screened and eligible patients were included in the trial after given informed consent. In order to achieve comparable intervention groups, patients were assigned 1:1 to intervention or control group by applying a central online randomization system. As soon as the individual patient was allocated to intervention or control group, the upcoming procedures were scheduled. In the intervention group, one preoperative esophagogastroduodenoscopy with sphincter BOTOX® injection was scheduled within 3-10 days before surgery in an outpatient setting, followed by the operative procedure and a 3-month follow-up phase. In the control group, esophagogastroduodenoscopy was not performed and surgery could be performed from the day after enrollment. Apart from one single preoperative esophagogastroduodenoscopy with sphincter BOTOX® injection, patients in intervention and control groups were treated equally. During the postoperative visits, postoperative complications were documented, in particular the endpoints.

Number of Volunteers (planned and analysed):
120 patients were supposed to be assessed for eligibility, 60 patients were supposed to be allocated to the trial, 50 patients were supposed to be analysed; by the end of the trial 50 patients were allocated to the trial of which 41 were analysed. 4 patients were inoperable due to liver metastasis or peritoneal carcinomatosis, 3 patients received other resection than distal pancreatectomy due to the extent of the tumour and 2 didn't undergo surgical procedure due to patients' wishes.

Diagnosis and main criteria for inclusion:
Indication: Elective distal pancreatectomy (DP) (open or minimally invasive technique) for any underlying disease
Inclusion criteria: Patients scheduled for elective, primary DP (open or minimally invasive technique), male or female patients ≥18 years of age, ability of patient to understand character and individual consequences of the clinical trial, written informed consent (available before enrolment), for women with childbearing potential, presence of negative urine or blood pregnancy test, and adequate contraception until 14 days after trial intervention

Test product (IMP being tested), trade name, MA holder, MA number, dose and mode of administration, batch number(s):
Clostridium botulinum toxin type A/onabotulinumtoxinA, BOTOX®, Allergan Pharmaceuticals, 100 units of BOTOX® reconstituted with 1 mL of sterile, preservative-free 0.9% sodium chloride, One single preoperative injection of 100 units of BOTOX® into the sphincter of Oddi during esophagogastro-duodenoscopy

Reference therapy (IMP used a comparator), trade name, MA holder, MA number dose and mode of administration:
None

Duration of treatment:
Maximum of 30 minutes

Criteria for evaluation: (efficacy, safety)
Numerous clinical trials have dealt with the problem of POPF. POPF generation following distal pancreatectomy (DP) is supposed to be promoted by an increase of pressure on the resection margin, leading to leakage from ductal structures. In patients with sphincter of Oddi dysfunction endoscopic injection of botulinum toxin (BTX) into the sphincter of Oddi to reduce sphincter pressure has been a safe and effective treatment option for years. In the setting of DP, a pharmacologically induced sphincter relaxation by BTX to prevent POPF represented a new approach, which has been reported in recent case series. The data from these case series show that the procedure appears to be technically feasible, tolerable and safe in patients before DP. Additionally, the results suggest that a single injection of BTX into the sphincter of Oddi before DP may potentially prevent clinically relevant POPF. On the recommendation of the Federal Office for Drugs and Medical Devices (BfArM), this randomized-controlled pilot study was initially carried out. The design of the study was coordinated with the BfArM as part of a so-called "Scientific Advice".

Statistical methods:
The analysis was primarily performed based on the mITT population, defined as all patients with status post DP. This is reasonable as patients undergoing procedures different from DP, e.g. total pancreatectomy or explorative laparotomy

alone, generally will not have any risk of POPF. Due to the nature of the trial as an exploratory study, no confirmatory statistical test was applied. The descriptive p-value of a Chi-square-test comparing the rate of the primary endpoint between the two treatment groups is reported, together with 95% confidence intervals for the risk difference.

Summary – Conclusions:

Efficacy Results:
After 50 patients had been included, a safety evaluation of the randomized patients was performed (including 41 patients, as described above). In the intervention group, the rate of POPF was within the complication rate described in the literature. In the control group, however, the POPF rate was unexpectedly low. In conclusion, the evaluation did not show any tendency that preoperative treatment using BTX injection into the sphincter of Oddi had a beneficial effect on the rate of POPF after DP. Because recruitment of 10 additional patients would not have changed the result, the members of the Data Safety Monitoring Board (DSMB) recommended termination of the recruitment at a meeting on September 12, 2023. Recruitment was then stopped. In the final analysis regarding the mITT set, in the intervention group POPF within 30 days occurred in 6 of 21 patients (28.6%), in the control group POPF within 30 days occurred in 3 of 20 patients (15.0%, difference in rates with 95% CI: 13.6% [-11.3%; 38.4%]). No patient in the mITT set died within 30 days after DP.

Safety Results:
Safety regarding the preoperative injection of botox (BTX) into the sphincter of Oddi was analysed. An adverse event (AE) occurred in 37 (90.2%), a serious adverse event (SAE) in 16 (39.0%) of 41 patients. In the intervention group (21 patients), 18 patients (85.7%) had an AE and 10 patients (47.6%) had an SAE. In the control group (20 patients), 19 patients (95.0%) had an AE and 6 (30.0%) had an SAE. The severity of AEs and SAEs is shown in table 2 of the appendix. Three severe AEs (4.9%) and one severe SAE (2.4%) were recorded. None of the AEs or SAEs were related to the application of BTX. Major results of the safety analysis are shown in the appendix.

Conclusion:
Preoperative injection of 100 units of BOTOX® into the sphincter of Oddi is safe and feasible, but no tendency is shown, that the intervention had a beneficial effect on the rate of postoperative pancreatic fistulas after distal pancreatectomy.

Date of report: 16.12.2024

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Principal Investigator Signature:
Dr. Claudia Mack

Study Title:
Monocenter, randomized, controlled, open-label, phase-II clinical trial of PREoperative endoscopic injection of BOTulinum toxin in the sphincter of Oddi to reduce postoperative pancreatic fistula after distal pancreatectomy (PREBOTPilot Study)

Study Author(s):
Dr. Claudia Mack, Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Heidelberg, Germany

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

_____	_____	_____
Date	Name	Signature

Tables: Including patients of the mITT set

Table 1: Showing adverse and serious adverse events in all cohorts:

	BOTOX (N=21)	Control (N=20)	Total (N=41)
Any AE			
- no	3 (14.3%)	1 (5.0%)	4 (9.8%)
- yes	18 (85.7%)	19 (95.0%)	37 (90.2%)
Any SAE			
- no	11 (52.4%)	14 (70.0%)	25 (61.0%)
- yes	10 (47.6%)	6 (30.0%)	16 (39.0%)

Table 2: Showing severity of adverse and serious adverse events in all cohorts

	BOTOX (N=21)		Control (N=20)		Total (N=41)	
	# AE	# patients with AE	# AE	# patients with AE	# AE	# patients with AE
Severity						
- mild	22	12 (57.1%)	25	16 (80.0%)	47	28 (68.3%)
- moderate	34	13 (61.9%)	17	12 (60.0%)	51	25 (61.0%)
- severe	2	1 (4.8%)	1	1 (5.0%)	3	2 (4.9%)
	# SAE	# patients with SAE	# SAE	# patients with SAE	# SAE	# patients with SAE
Severity						
- mild	1	1 (4.8%)	3	2 (10.0%)	4	3 (7.3%)
- moderate	10	9 (42.9%)	4	4 (20.0%)	14	13 (31.7%)
- severe	0	0 (0.0%)	1	1 (5.0%)	1	1 (2.4%)

Table 3: Showing the relationship of the adverse and serious adverse events to botox and surgery

	BOTOX (N=21)			
	# AE	# patients with AE	# SAE	# patients with SAE
Relationship to Botox				
- no	57	18 (85.7%)	11	10 (47.6%)
- missing	1	1 (4.8%)		