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Name of Sponsor/Company: Universitätsklinikum Heidelberg		**Sponsor-Code of Study:** PREBOT-II	*(For National Authority Use only)*
Name of (Finished) Product:		**Name of Active Ingredient:**	
EudraCT-No.: 2020-006001-35	**CA Vorlage-No.:**	**IEC Antrags-No.:**	

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

SYNOPSIS

Title of Study:
Randomized controlled trial of PREoperative injection of BOTulinum toxin into the sphincter of Oddi to reduce bile leakage after hepatic resection
PREBOT-II

Date of Approval / Vote:
BfArM: 27.10.2021 **Ethics Committee: 02.09.2021**

Amendments:

Date of Approval / Vote:
BfArM: 06.04.2023 **Ethics Committee: 15.03.2023**

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Publication (reference):
The trial protocol was published:
Protocol of a randomised controlled phase II clinical trial investigating PREoperative endoscopic injection of BOTulinum toxin into the sphincter of Oddi to reduce bile leakage after hepatic resection: the PREBOT-II trial
BMJ Open 2023 Sep 20;13(9): e065727. doi: 10.1136/bmjopen-2022-065727

Study period: **(date of first enrolment)** **(date of last completed)**	First patient in: 27.04.2022 Last visit last patient: 14.01.2025	**Phase of development:**	Phase-II-trial

Objectives:
The main purpose of this trial was to evaluate the safety and feasibility of a preoperative endoscopic injection of BTX into the sphincter of Oddi within 3-10 days before hepatic resection to reduce bile leakage and to gain preliminary efficacy data which could serve as a basis for a subsequent confirmatory trial.
The primary endpoint was the occurrence of a postoperative bile leakage within 30 days after hepatic resection. The primary endpoint was determined by evaluation of the clinical situation of the patient together with patient's bile values in abdominal drain outputs during study visits 4 to 6, i.e. on postoperative day (POD) 3, day of discharge and on POD 30 in an outpatient setting.
The secondary objectives were to evaluate clinically relevant postinterventional and postoperative complications as well as quality of life (QoL), (reinterventions/-operations, mortality), durations of intensive care unit (ICU)/intermediate care unit (IMC) stay and total hospital stay, and readmissions within three months after index surgery.

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 BOTOX® injection into the sphincter of Oddi 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):
Plan: To be assessed for eligibility (n = 140), to be allocated to trial (n = 70), to be analysed (n = 60)

In fact: The trial has recruited 19 of 70 patients in 30 months. Further patients were not available for this trial. 16 patients were analysed. 3 patients did not undergo hepatic resection and were not included in the analysis (as defined in the study protocol).

Diagnosis and main criteria for inclusion:

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Indication: Patients undergoing hepatic resection for various underlying diseases, e.g. hepatocellular carcinoma, intrahepatic cholangiocarcinoma, liver metastases, and liver cysts (ICD-10-GM-2019: C22.-, C78.-, D13.4, D37.6; OPS-2020: 5-501.0 bis 5-503.0; MedDRA-code: LLT: 10077348)
Inclusion Criteria:
– Patients scheduled for elective, primary hepatic resection with no planned biliary reconstruction
– 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 enrollment)
– 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 (Botox®)
In the intervention group, patients undergo preoperative endoscopy which includes the injection of a single deposit of 100 units of BTX (BOTOX® by Allergan®, acquisitioned recently by abbvie, reconstituted in 1 mL of isotonic saline), in the intraduodenal sphincter of Oddi segment. Hepatic resection is scheduled within 3-10 days after BTX-injection.

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)
In Germany, more than 24,000 patients are scheduled annually for hepatic resection which is the treatment of choice for various hepatobiliary diseases. Despite improvements in surgical techniques and perioperative management, bile leakage remains a major cause of postoperative morbidity and mortality. The improvement of drainage of bile towards the duodenum by botulinum toxin mediated relaxation of the sphincter of Oddi seems promising in the prevention of bile leakage after hepatic resection, as it will decrease intraductal pressure and thus lower back-pressure of bile at the resection margin of the liver, resulting in a reduced risk of the development of bile leakage.
BOTOX® is currently authorized for injection for intramuscular, intradetrusor and intradermal use in the treatment of specific forms of, inter alia, bladder dysfunction, specific forms of spasticity, specific forms of hyperhidrosis, and for the prophylaxis of specific forms of chronic migraine. Local BOTOX® injection has been used off-label in the treatment of diseases of the gastrointestinal tract owing to overactive smooth muscles and sphincters such as crycopharyngeal dysphagia, achalasia, gastroparesis, sphincter of Oddi dysfunction and anal fissure with convincing results in terms of safety and efficacy.

The trial was the first GCP-conform study to gain the evidence on the safety and feasibility of preoperative injection of BTX in the sphincter of Oddi to prevent bile leakage following hepatic resection. It is a multicenter, randomized, controlled, open-label, phase-II, clinical trial with two parallel study groups. The primary efficacy endpoint is the occurrence of postoperative bile leakage within 30 days after hepatic resection according to the definition of the International Study Group of Liver Surgery (ISGLS).

Statistical methods:
The analysis was performed in the modified intention-to-treat population, which comprises all patients who underwent hepatic resection. Due to the exploratory nature of the trial and the very small sample size, a purely descriptive analysis was performed. For the primary endpoint (postoperative bile leakage within 30 days after surgery) and all binary endpoints, absolute and relative frequencies per treatment group were calculated.

Summary – Conclusions:

Efficacy Results:
No events in the primary endpoint occurred in both groups. Also in the secondary endpoints “bile leakage within 3 months after surgery”, “death due to any cause within 3 months after surgery”, “postinterventional pancreatitis”, “perioperative

sepsis", "post-hepatectomy liver failure", "post-hepatectomy hemorrhage" and "burst abdomen" no events were recorded. For "intraabdominal fluid collection / abscess" one event (12.5%) occurred in the botox as well as in the control group. One wound infection was observed in the botox group, no such event in the control group. One pulmonary infection occurred in the control group, no such event in the botox group. One acute kidney injury was recorded in the botox group, no such event in the control group. No reinterventions, no reoperations and no readmissions occurred. One patient in the botox group had an ICU/IMC stay for 2 days.

Safety Results:

In the botox group 3 patients (37.5%) experienced an AE and 1 patient (12.5%) experienced an SAE. In the control group, 4 patients (50%) had an AE and 2 (25%) had an SAE.

All recorded AEs and SAEs are shown in the listings below. "Onset" refers to the AE onset in days after sugery. The duration is also given in days. "Ongoing" states whether the AE was still ongoing at the end of study of the patient. In some cases, only month and year was given for the onset, in these cases a range is given. Note that none of the AEs and SAEs is related to botox.

Listing of adverse events:

ID	Group	Description	Intensity	Onset	Duration	Ongoing	Outcome
1	Botox	acute kidney injury	mild	3	3	no	recovered / resolved
1	Botox	pain thorathic + lumbar spine	mild	13	11	no	recovered / resolved
2	Botox	acute pyelonephritis	moderate	6	27	no	recovered / resolved
2	Botox	skin rash	mild	-9	2	no	recovered / resolved
3	Botox	intraabdominal fluid collection	mild	14	2	no	recovered / resolved
4	Control	wound dehiscence	mild	[45; 74]	.	yes	recovering / resolving
5	Control	pleural effusion	mild	12	19	no	recovered / resolved
5	Control	fluid collection with suspected superinfection in liver resection area	moderate	7	7	no	recovered / resolved
5	Control	lumbar disc hernitation	mild	[50; 80]	.	yes	recovering / resolving
6	Control	Bronchitis	moderate	8	35	no	recovered / resolved

Listing of serious adverse events:

ID	Group	Description	Intensity	Onset	Duration	Ongoing	Outcome
3	Botox	wound infection (infected subcutanous hematoma)	mild	13	17	no	recovered / resolved
3	Control	suicidality	moderate	14	22	no	recovering / resolving
5	Control	fluid collection with suspected superinfection in liver resection area	moderate	7	7	no	recovered / resolved

Conclusion:

Due to the small number of patients, no conclusion could be drawn.

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Date of report: 14.11.25

Principal Investigator Signature:

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Biometrics
Mag. Lukas Baumann

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	Dr. Claudia Mack	Signature

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