UNIVERSITÄTS
KLINIKUM
HEIDELBERG

Name of Sponsor/Company: Universitätsklinikum Heidelberg		**Sponsor-Code of Study:** PROSPER	*(For National Authority Use only)*
Name of (Finished) Product: Todolac, Dociton		**Name of Active Ingredient:** Etodolac, Propranolol	
EudraCT-No.: 2018-000415-25	**CA Vorlage-No.:** 4042875	**IEC Antrags-No.:** AFmo-385/2018	

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

SYNOPSIS

Title of Study:

PANCREATIC **R**ESECTION WITH PERIOPERATIVE **O**FF-LABEL **S**TUDY OF **P**ROPRANOLOL AND **E**TODOLAC – A PHASE II **R**ANDOMIZED TRIAL (PROSPER)

Date of Approval / Vote:
BfArM: 28.08.2018 **Ethics Committee:** 10.08.2018

Amendments: Amendment 1 August 2019, Amendment 2 Dezember 2019, Amendment 3 Oktober 2020
Date of Approval / Vote:
BfArM: 1) 28.08.2019; 2) 19.12.2019; 3.) 16.11.2020 **Ethics Committee**: 1) 11.09.2019; 2) 17.12.2019; 3) 22.12.2020

Investigators:
Principle Investigator: PD Dr. med. Phillip Knebel
Deputy Investigator: Prof. Dr. med. Pascal Probst

Study Centre(s): University Hospital Heidelberg, Department of General, Visceral and Transplantation Surgery

Publication (reference):
in preparation

Study period: **(date of first enrolment)** **(date of last completed)**	FPI: 23.01.2019 LPO: 03.06.2020	**Phase of development:**	II

Objectives:
To assess safety, feasibility and to generate first efficacy data for the perioperative use of propranolol and etodolac in patients with resectable cancer of the pancreatic head scheduled for elective pancreatoduodenectomy.

Methodology:
Randomized, two-arm, double-blind, placebo-controlled, single-centre trial

Number of Volunteers (planned and analysed):
100 planned**,** 26 were randomized, 20 were analysed

Diagnosis and main criteria for inclusion: Non-metastatic, resectable pancreatic cancer
Principal inclusion criteria:
• Planned for elective pancreatoduodenectomy
• Eligible for perioperative therapy with propranolol / etodolac

Test product (IMP being tested), trade name, MA holder, MA number, dose and mode of administration, batch number(s):
IMP number PR1: Dociton, mibe GmbH Arzneimittel, 6328947.02.00, 1320 mg milligram(s) and oral use, PRO/201841
IMP number PR2: Todolac, Norpharma A/S, Frydenlundsvej, 17449, 20 g gram(s) and oral use, ETO/201841

Name of Sponsor/Company: Universitätsklinikum Heidelberg		Sponsor-Code of Study: PROSPER	*(For National Authority Use only)*
EudraCT-No.: 2018-000415-25	**CA Vorlage-No.:** 4042875	**IEC Antrags-No.:** AFmo-385/2018	

Reference therapy (IMP used a comparator), trade name, MA holder, MA number dose and mode of administration:
Placebo: PL1 placebo for PR1; PL2 placebo for PR2
PL1: capsule hard, oral use, Füllstoff nach DAC Mannitol/Aerosil, Universitätsklinikum Heidelberg-Apotheke
MA number: DE_BW_01_MIA_2016_0005/DE_BW_01_Uniklinik_Hd_Apotheke
PL2: tablet, oral use, Füllstoffe sind: Cellulose und Lactose, Aenova Group, Haupt Pharma Wülfing GmbH
MA number: DE_NI_02_MIA_2015_0036/41401/H-42

Duration of treatment:
Propranolol & Etodolac medication as well as placebo tablets were taken continuously for a total of 25 days starting from 10 days prior to surgery until 14 days postoperative.
Follow-up was 3 months for safety endpoints and 24 months for survival endpoints.

Criteria for evaluation: (efficacy, safety)
The main objective of the trial was the **assessment of safety** for the perioperative use of propranolol and etodolac in patients with resectable cancer of the pancreatic head planned for elective pancreatoduodenectomy.
The secondary objectives of the trial were to assess feasibility and to **generate first efficacy data** for the perioperative use of propranolol and etodolac in patients with resectable cancer of the pancreatic head planned for elective pancreatoduodenectomy.

Statistical methods:
The main safety, efficacy and main feasibility variables are analysed with generalized linear models or Cox regression models. Parameter estimates from these models are reported with 95 per cent profile likelihood based confidence intervals. All other variables are tabulated by treatment group using number of missing and non-missing values, the quartiles, mean and standard deviation.

Summary – Conclusions:

Efficacy Results:
The trial was prematurely closed due to feasibility reasons in terms of slow recruitment despite several adjustments of the trial design. A total of 26 patients were randomized to perioperative treatment with propranolol + etodolac (n=14) or placebo (n=12). Six of them, five in the verum group and one in the placebo group, never started intake of trial medication. Thus, 20 patients received trial medication at least once and were included in the analysis. One patient in the placebo group terminated trial participation before surgery. The adherence to etodolac was lower in the treatment group with 78% (±29%) in the placebo group and 50% (±20%) in the verum group. This did not result in a statistically significant difference with an estimated odds ratio of 3.42 (95%-CI 0.93 – 12.49; p=0.06). Similarly, the adherence to propranolol was 69% (±37%) in the placebo group and 47% (±28%) in the verum group, which did also not lead to a statistically significant difference with an estimated odds ratio of 2.42 (95%-CI 0.60 – 9.70; p=0.20).
Median overall survival was not reached (95%-CI 1.68 – not reached) in the verum group and 15.8 months (95%-CI 5.26 – not reached) in the placebo group. Median disease-free survival was 16.36 months (95%-CI 1.18 – not reached) in the verum group compared to 11.25 (95%-CI 2.2 – 17.25) in the placebo group. The rate of local recurrence was 22.2% in the verum group compared to 18.2% in the placebo group. In contrast, the rate of distant recurrence was 11.1% in the verum group compared to 54.5% in the placebo group.

Safety Results:
There was no SAR and a total of 20 SAE, 14 in the placebo group and 6 in the verum group, within 3 months postoperatively. In the placebo group 9 of the 11 patients (81.8%) suffered from at least one SAE compared to 5 of the 9 patients (55.6%) in the verum group. There was one fatal serious adverse event, which occurred in the verum group in terms of a postoperative upper gastrointestinal bleeding on postoperative day 36. Since this patient stopped intake of trial medication upon the patient's own request on postoperative day 10, a relation to study medication was judged as improbable. There were no substantial differences in postoperative morbidity and mortality.

Conclusion:
Although there were no safety concerns, the perioperative combination therapy with propranolol and etodolac was not feasible within the current trial setting.

Date of report: 13.12.2022

Name of Sponsor/Company: Universitätsklinikum Heidelberg		Sponsor-Code of Study: PROSPER	*(For National Authority Use only)*
EudraCT-No.: 2018-000415-25	**CA Vorlage-No.:** 4042875	**IEC Antrags-No.:** AFmo-385/2018	

Principal Investigator Signature:

Study Title:

Study Author(s):

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

Affiliation: