Clinical Trial Protocol

TransNiDeG - The Effect of Transcutaneous Nicotine Administration on the Development of Delayed Gastric Emptying following Pancreatodudoenectomy - a randomized, placebo-controlled, double-blind, multicenter trial

EU trial No.:	2023-503349-71-00
Protocol Code Number:	CHI-202002
Version:	2.0
Date:	28-JUN-2023
Trial Short Title:	TransNiDeG
Sponsor (name and address):	Rheinische Friedrich-Wilhelm-University of Bonn, represented by the Faculty of Medicine of the University of Bonn, represented by the Dean of the Medical Faculty, Venusberg-Campus 1, D-53127 Bonn
Sponsor Delegated Person (name and function):	PD Dr. Tim Glowka, consultant surgeon Department of Surgery, University Hospital Bonn

Document History

Version Number	Date of Issue	Summary of Changes
1.0	08-MAR-2023	First version
2.0	28-JUN-2023	As a result of a Request for Information during the CTIS assessment process the following changes were implemented: • clarification that labelling of IMPs will be performed by a pharmacy • clarification of AE/SAE documentation, reporting of SAEs after end of trial, and explanation of expedited SAE reporting in Sections 12.4, 12.5 and 12.5.1 • addition of exclusion criterion no. 13 to prohibit intake of inhibitors or strong inducers of CYP2A6 • check for concomitant medication every study visit in Section 2 and amending prohibited drugs in Section 11.1.4 • addition of Section 14.2.3 with results from a retrospective trial with response rates from smokers/non-smokers • addition of a justification for the inclusion of a placebo in the new Section 5.4 • formal corrections, typos

Protocol Approval Signatures

Sponsor/ Sponsor Delegated Person (SDP) and Coordinating Investigator:

PD Dr. med. Tim Glowka (SDP)	Signature	Date

Responsible Biometrician:

Dr. Robert Németh	Signature	Date

Investigator Agreement Page

Please provide institution´s / clinic´s stamp here

By my signature below, I confirm that I have read, understood and agree to adhere to all conditions, instructions and restrictions as specified in this Clinical Trial Protocol.

I will discuss the Clinical Trial Protocol in detail with my colleagues and ensure that they are comprehensively informed about the trial compound/preparation and the execution of the clinical trial.

I confirm that I and my colleagues will conduct this clinical trial in compliance with the protocol, the Declaration of Helsinki, the Regulation (EU) No 536/2014 and with the principles of good clinical practice, and that I will abide by the national laws and regulations.

Furthermore I and my colleagues commit ourselves not to commence subject enrollment before the authorization of the authorities, the acceptance by the relevant and responsible Ethics Committee and the legally valid conclusion of contract by the authorized representation of my institution concerning this clinical trial.

I recognize that any changes in the protocol must be approved by the Sponsor/Sponsor Delegated Person (SDP), the competent authority(ies), the Ethics Committee before implementation except when necessary to eliminate hazards to the subjects or when changes involve only logistical or administrative aspects of the clinical trial.

Under my supervision I will allocate copies of this Clinical Trial Protocol and possible updates as well as access to all information regarding the carrying out of this clinical trial at the disposal of my investigating team; in particular I will promptly forward all information from the Sponsor/Sponsor Delegated Person (SDP) in relation to pharmaceutical safety (SUSAR) to my investigating team.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without prior written consent of the Sponsor/Sponsor Delegated Person (SDP).

The investigational medicinal products will be used only for the purpose of the clinical trial.

(Deputy of) Principle investigator:

Name, first name (print)	Signature	Date

Table of Content

1 Synopsis

Clinical trial title	TransNiDeG - The Effect of Transcutaneous Nicotine Administration on the Development of Delayed Gastric Emptying following Pancreatoduodenectomy, a randomized, placebo-controlled, double-blind, multicenter trial
Trial short title	TransNiDeG
Trial Code	CHI-202002
EU trial No.	2023-053349-71-00
Phase of trial	Phase II, proof-of-concept trial
Investigational medicinal product, Dose and Mode of Application	Trade Name: Nicotinell 14mg/24-Stunden-Pflaster Substance: Nicotine Manufacturer: GlaxoSmithKline Dose: 14mg/24h Mode of application: transdermal patch Duration of treatment: 7 days
Comparative Drug, Dose and Mode of Application	Placebo patch Patchinga® Freestyle Libre 3 Manufacturer: Shanghai Ruiquan Medical Equipment Co., Ltd Dose: not applicable Mode of Application: patch Duration of Treatment: 7 days
Auxiliary medicinal product, Dose and Mode of Application	Not applicable
Indication	Male and female patients with benign and malignant lesions of the periampullary region (e.g. pancreatic carcinoma, distal bile duct carcinoma, duodenal carcinoma, ampullary carcinoma, cystic lesions, chronic pancreatitis) requiring pancreatoduodenectomy
Trial Design	Multi-center, prospective, randomized, double blind, placebo controlled

Objectives	Endpoints
Primary	
To assess the effect of transcutaneous administration of nicotine as compared to placebo on the development and severity of delayed gastric emptying (DGE) following pancreatoduodenectomy	Grade of delayed gastric emptying (none, grades A-C representing increasing severity) according to the consensus definition of the International Study Group of Pancreatic Surgery
Secondary	
To evaluate the safety, efficacy and tolerability of transcutaneous nicotine administration as compared to placebo in patients requiring pancreatoduodenectomy	<u>Assessment of tolerability:</u> • postoperative pancreatic fistula • postpancreatectomy hemorrhage • intraabdominal fluid collections • surgical site infections • re-intervention rate • re-operation rate • Clavien-Dindo classification • MTL30 score • quality-of-life questionnaires (QLQ-C30 and PAN26) • mortality • cardiovascular events ((non-fatal) myocardial infarction, (non-fatal) stroke, revascularization during admission) <u>Assessment of efficacy on DGE-development:</u> • requirement of naso-gastric tube (NGT) in the first 21 days after surgery • inability to tolerate solid oral food in the first 21 days after surgery • vomiting/gastric distension in the first 21 days after surgery • use of prokinetics in the first 21 days after surgery Additionally, the following parameters are used for grading (according to the International Study Group of Pancreatic Surgery • comorbidities • specific treatment • nutritional support • diagnostic evaluation • interventional treatment • prolongation of hospital stay • delay of potential adjuvant therapy

	Assessment of safety: Adverse Events and Serious Adverse Events
Subject Number	Four-hundred (400) subjects will be pre-assessed for eligibility, from whom 300 are expected to sign the informed consent and be eligible for surgery. A total number of 240 subjects will be randomized for IMP treatment (120 per treatment arm).
Inclusion Criteria	Subjects will only be included in the clinical trial if they meet all of the following criteria: General inclusion criteria: 1. Subjects aged ≥ 18 years 2. given written informed consent to participate in the trial Indication-specific inclusion criteria: 3. planned for pancreatoduodenectomy 4. smokers must be willing to stop smoking for the duration of the IMP application (i.e. from Day 1 to Day 7)
Exclusion Criteria	Subjects will not be included in the clinical trial if any of the following criteria applies: General Exclusion Criteria: 1. Subject without legal capacity who is unable to understand the nature, scope, significance and consequences of this clinical trial 2. Simultaneous participation in a clinical trial taking an investigational medicinal product, up to 30 days prior to last IMP intake in that clinical trial. Exclusion criteria regarding special restrictions for females: 3. Current or planned pregnancy or nursing women 4. Females of childbearing potential, who are not using and not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices) unless they are surgically sterilized / hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases Indication specific exclusion criteria: 5. distant organ metastases (which can be diagnosed after screening, e.g. during surgery; then no resection is performed according to guidelines) 6. former gastrectomy 7. liver fibrosis/cirrhosis

	8. Known history of hypersensitivity to nicotine or a component of the investigational drug 9. Systemic skin diseases (e.g. Lupus erythematodes) 10. Immediately after heart attack 11. Severe cardiac arrhythmia 12. Stroke that occurred shortly before 13. Concomitant medication with inhibitors or strong inducers of CYP2A6 (e.g. Trancylpromine, Desipramin, Ketoconazole, Valproic acid, Phenobarbital, Pilocarpine, Clotrimazole, Methoxsalen, Rifampicin)
Trial Procedures	Screening-Visit (Day -28 to Day -1) Visit 1 (Day 1, Surgery) Visit 1.2 – 1.7 (Post-operative Day 2 to Day 7) Visit 2 (Post-operative Day 14) Visit 3 (Post-operative Day 21 or discharge – whatever comes first) Visit 4 (Post-operative Day 30, follow Up)
Trial Specific Measurements	• Application of IMP-/Placebo-patch • Assessment of primary and secondary endpoints
Investigational trial sites	This is a multi-center trial with about six (6) investigational trial sites in Germany.
Statistical Rationale	The primary objective of the trial is to estimate the rates of DGE grades within the defined populations during a 21 days period after surgery after 7 days treatment either with nicotine or with placebo patch. These rates will be given together with their respective confidence intervals by treatment group. A comparison of the treatment groups will be performed by means of a proportional odds model (accounting for the stratification factors center and smoking status). The main outcome of this analysis will be an estimate of the odds ratio according to the explorative character of the trial. Additional sensitivity analyses will be performed to assess the robustness of the results: a dichotomized version of the DGE score will be investigated by means of a logistic regression model. In both models, the influence of additional covariates like sex, age, or other comorbidities will be investigated (for the purpose of the planning of later phase trials). Two analysis populations will be defined: intent-to-treat (ITT) and per-protocol (PP). The former includes all randomized patients whereas patients with relevant protocol deviations will be excluded from the latter. The main analysis will be performed within the ITT population.

	Safety parameters and secondary endpoints will be summarized by means of descriptive statistics or by absolute and relative frequencies according to the type of the variables by treatment.
Time Schedule	<u>Per Subject:</u> • 28 days for Screening + 30 days treatment phase = maximum 58 days in total <u>Trial duration:</u> • Recruiting Period: 24 months • Planned Start Date (FPFV/ FPI): August 2023 • Planned End Date (LPLV/ LPO): August 2025

2 Schedule

	Screening Visit	Treatment Phase		Follow up Phase		End of Trial
Time points (accepted deviation)	**Day -28 to Day -1**	**Day 1 (Surgery)**	**Day 2 to Day 7**	**Day 14 (+/- 1 Day)**	**Day 21 (+/-1 Day) or Discharge**	**Day 30 (+/- 2 Days)**
Visit No.	**0**	**1**	**1.2 to 1.7**	**2**	**3**	**4**
Informed Consent	√					
Demographics	√					
Medical History (including request for pregnancy in females of childbearing potential)	√					
Concomitant medication	√	√	√	√	√	√
In-/Exclusion Criteria	√	(√)[4]				
Application of IMP		√ (during or immedi-ately after surgery)	√			
Grading DGE[1]			√	√	√	
AEs and SAEs[2]		√	√	√	√	√
Checks for secondary Endpoints[3]		√	√	√	√	√
Histopathology					√	
Days of postoperative stay (i.e. from post-operative Day 1 until Discharge)					√	
MTL30						√

	Screening Visit	Treatment Phase		Follow up Phase		End of Trial
Time points (accepted deviation)	**Day -28 to Day -1**	**Day 1 (Surgery)**	**Day 2 to Day 7**	**Day 14 (+/- 1 Day)**	**Day 21 (+/-1 Day) or Discharge**	**Day 30 (+/- 2 Days)**
Visit No.	**0**	**1**	**1.2 to 1.7**	**2**	**3**	**4**
QLQ-C30						√
PAN26						√

[1] according to the definition of the International Study Group of Pancreatic Surgery. NGT requirement + solid food intake on every visit day indicated, all other parameters only on Visit 1.3, 1.7, 2 and 3.

[2] especially: surgical site infections, cardiovascular events, mortality

[3] Visit 1 only Lymphadenectomy, re-intervention, re-operation, nausea, cardiovascular events. Visit 1.2, 1.3, 1.5-1.7 no assessment. Visit 1.4, 2, 3, 4 only pancreatic fistula, postoperative hemorrhage, intra-abdominal fluid collections, re-laparotomy

[4] Exclusion Criterion No. 5 can only be answered during surgery

3 Abbreviations

AR	Adverse (Drug) Reaction
AE	Adverse Event
AMG	Arzneimittelgesetz
CA	Competent Authority
CI	Coordinating Investigator
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CTR	Clinical Trial Regulation
DGE	Delayed Gastric Emptying
EC	Ethics Committee
FPFV	First Patient First Visit
FPI	First Patient In
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
ISF	Trial site File
LPLV	Last Patient Last Visit
LPO	Last Patient Out
NGT	Naso-gastric tube
PD	Pancreatoduodenectomy
PI	Principal Investigator
SAR	Serious Adverse Reaction
SAE	Serious Adverse Event
SDP	Sponsor Delegated Person
SUSAR	Suspected Unexpected Serious Adverse Reaction
SZB	Study Center Bonn (Studienzentrum Bonn)
UAR	Unexpected Adverse Reaction

4 Trial Administration structure

Coordinating Investigator and Sponsor Delegated Person	**Priv.-Doz. Dr. med. Tim Rouwen Glowka** Department of Surgery University Hospital Bonn Venusberg-Campus 1 D-53127 Bonn Tel. No.: +49 228 287-15857 Email: tim.glowka@ukbonn.de
Sponsor	Medical Faculty of the University of Bonn, represented by the Dean Venusberg-Campus 1 D-53127 Bonn
Coordinating institution	**Clinical Study Core Unit, Study Center Bonn (SZB)** Institute for clinical chemistry and clinical pharmacology University Hospital Bonn Venusberg-Campus 1 53127 Bonn
Participating trial site(s)	6 German sites are planned
Statistician / Biometrician:	Dr. Robert Németh **Clinical Study Core Unit, Study Center Bonn (SZB)** Institute for Medical Biometry, Informatics and Epidemiology University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn Tel. No.: +49 – 228 287 15425 Fax No: +49 – 228 287 16093 Robert.Nemeth@ukbonn.de
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5 Introduction

The most frequent complication following pancreatoduodenectomy (PD) is delayed gastric emptying (DGE) with a reported incidence of 19%-57% [1]. A wide range of causative mechanisms has been proposed for DGE: the absence of hormonal stimulation due to the resection of the duodenum, ischemia of the stomach and duodenum following resection, denervation of the stomach and duodenum, post-operative pylorospasm, DGE secondary to other intraabdominal complications, pancreatic fibrosis, cholangitis, pancreatitis, alteration of the endocrinologic milieau or torsion/angulation of the reconstructed alimentary tract [2]. In fact, most studies concentrating on DGE accused technical aspects of the reconstruction to cause DGE, but none was able to ameliorate DGE. Neither ante- or retrocolic reconstruction route [3], pylorus resection and –preservation [4], nor single versus double loop reconstruction [5] does influence the frequency of DGE following PD. Often, DGE is self-limiting [2] and does not increase periprocedural mortality [6,7], but DGE is known to significantly increase hospital stay [8]. Recently DGE was described for the first time to negatively affect cancer specific survival [9]. So, strategies are needed for the treatment of delayed gastric emptying to increase the utilization of adjuvant chemotherapy with the goal of improved overall survival.

The aim of this clinical trial is to assess the effect of transcutaneous administered nicotine on the development and severity of delayed gastric emptying (DGE) following pancreatoduodenectomy (PD) as compared to placebo.

5.1 Background

Pancreatic ductal adenocarcinoma (PDAC) is a mortal disease with reported 5-year relative survival rates of 8% [10]. In addition, PDAC will represent the second leading cause of cancer related death in 2030 both in Europe and the United States [11,12]. Currently, the only curative therapy is surgical resection [13,14], but 5-year overall survival with surgery alone is low with 10.4% [15]. Several studies have demonstrated improved oncological survival in patients receiving adjuvant chemotherapy [15–17]. The current standard regimen for adjuvant therapy is modified FOLFIRINOX for patients with good performance status, achieving a 3-year overall survival of 63.4% [18]. Nevertheless, utilization of adjuvant chemotherapy is low, with 27,5% of patients receiving no chemo-therapy [19] and only 7% of patients following pancreatoduodenectomy (PD) receiving complete adjuvant chemotherapy [13]. This is important, as multiple studies have demonstrated, that perioperative chemotherapy significantly impacts overall survival [13,18]. Neoadjuvant chemotherapy is increasingly used as a strategy to improve the proportion of patients receiving perioperative chemotherapy, as most patients are in adequate condition prior to surgery to receive therapy [20]. With the potential disadvantage of delaying surgical therapy, neoadjuvant treatment has so far not been established as standard treatment and is currently only used in a locally advanced setting for downsizing [18,20,21].

Multiple factors can be the reasons for patients not beginning or completing adjuvant treatment. Age and early disease progression cannot be modified during treatment [22]. Postoperative complications represent about one third of the reasons for not undergoing adjuvant chemotherapy [22–24]. Pancreatic fistula, as the most feared major complication [25,26], cannot be affected by the way of reconstruction [27] nor do octreotide analogues improve outcome [28]. The most frequent complication following PD is delayed gastric emptying (DGE) with a reported incidence of 19%-57% [1].

5.2 Summary of findings from non-clinical studies and other relevant clinical trials

The action of nicotine on gastrointestinal motility is complex: in most species, nicotine causes contractions of stomach, jejunal and ileal musculature, and relaxation of colonic musculature and lower esophageal sphincter [29]. Especially the effect of nicotine on gastric motility remains controversial. In cats and dogs nicotine inhibits gastric contractions [30,31] with an opposite effect in rats [32]. In humans, the effect of nicotine is controversial. Cigarette smoke was shown to delay gastric emptying [33–35], while others groups reported an accelerated gastric emptying [36,37] or no effect on gastric empyting [38,39]. For understanding gastric emptying the effect of nicotine on the pylorus must be taken into account, as the innervation is different to the adjacent gastric and duodenal musculature [40]. Pylorus preservation was traditionally believed to worsen DGE following PD [41,42]. Cigarette smoke was described to decrease the pyloric pressure [43] and increase duodenogastric reflux [34,44]. This relaxing effect of nicotine on sphincter muscles was also described on the lower esophageal sphincter [45,46], indicating a uniform mode of action on sphincter muscles in the upper gastrointestinal tract. Presumably nicotine is the agent causing this relaxing effect on sphincter pressure [43], while the mechanism (directly or through chemical intermediaries [43] and the site of action (most likely the intramural ganglia)[47] are not fully understood. Eventually, nicotine exerts its effect through the cholinergic anti-inflammatory pathway. This pathway plays an important role in the development of postoperative ileus [48]. In a mouse model, nicotine agonists were able to treat postoperative gastric emptying, presumably mediated through the alpha7 nicotinic acetylcholine receptor [49,50]. No randomized controlled trial on nicotine action on gastric emptying to date has been conducted in a human postsurgical situs with its many implications on motility [2]. There is no accepted animal model for pancreatoduodenectomy, besides other than human examinations would make no sense due to the interspecies variability of nicotine action [30–32].

A recent retrospective study from the Department of Surgery, University Hospital Bonn [51], showed, that active smokers develop significantly less DGE compared to non- or former smokers (40% vs. 53%, P = 0,046). 295 patients recorded in the prospective pancreatic resection database were identified undergoing pancreatoduodenectomy between 2009 and 2019. Of these, 274 were retrospectively analyzed according to their smoking habits and the development of DGE. All other postoperative complications were evenly distributed. Non-smoking habit is one of the items defining the PrEDICT-DGE score, a scoring system identifying patients at risk for DGE development prior to PD [52].

5.3 Trial Rationale

At present, no prophylactic or therapeutic options exist for ameliorating delayed gastric emptying after pancreatoduodenectomy (studies with a beneficial effect of Erythromycin were all conducted prior to the ISGPS definition [1] and therefore lack transferability [2]). If transcutaneous nicotine administration has a significant effect, a safe, easy-to-apply and inexpensive method would be available to lower the incidence of the most frequent complication following pancreatic head resection.

With the TransNiDeG trial, a randomized, controlled, double-blinded two arm evaluation of the effect of transcutaneous administered nicotine on the development and severity of delayed gastric emptying following pancreatoduodenectomy compared to placebo will be conducted.

5.4 Justification for placebo

According to EU Directive 2001/81 clinical trials shall be done as “controlled clinical trials” if possible, randomized and as appropriate versus placebo and versus an established medicinal product of proven therapeutic value. Furthermore, as far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomization and blinding. The TransNiDeG clinical trial follows these requirements completely.

As described in the former Section, at present, no prophylactic or therapeutic options exist for ameliorating delayed gastric emptying after pancreatoduodenectomy (studies with a beneficial effect of Erythromycin were all conducted prior to the ISGPS definition [1] and therefore lack transferability [2]). Specifically, there is no evidence-based therapy ("with proven therapeutic value") against which the nicotine patch could be compared. Thus, a substance-free patch was chosen as placebo. Without this, a blinding as required in Directive 2001/83/EC would not be possible.

The ICH Guideline E10 states "When a new treatment is tested for a condition for which no effective treatment is known, there is usually no ethical problem with a study comparing the new treatment to placebo”. This point is considered in the TransNiDeG trial. With regard to an external control that is also conceivable (e.g. historical control), it is stated that "such trials are usually considered uncontrolled", so that according to Directive 2001/83/EC the TransNiDeG trial would then no longer be a controlled study.

6 Side effects and Risk Benefit Assessment

6.1 Benefit for study participants and patient population

With the application of a transdermal nicotine patch the respective patient population has the change to benefit from a lower incidence of DGE following PD. As a result, these patients may recover earlier, in connection with a perspective of a shorter hospital stay and improved quality of life, and, hopefully, will show an increased utilization of adjuvant treatment.

Patients receiving the placebo patch do not have an additional therapeutic benefit beyond the one conveyed by standard therapy regularly applied.

6.2 Risk for study participant

Of all substances in tobacco smoke, nicotine is the most likely prokinetic substance [39]. This substance can easily and safely be applied through a nicotine patch. This standard therapy for smoking withdrawal is extremely safe in terms of adverse and serious adverse events [53]. The most frequent adverse event was skin irritation in about 25% of the patients (while 13% of the placebo group experienced skin irritation) [54]. Gastrointestinal symptoms are rare, with only 5% of the patients developing nausea (placebo 4%) and another 4% developing constipation, diarrhoea or dyspepsia (placebo 4%)[54].

The dosing of 14mg/24h seems safe even in non-smokers with only transient nausea as the only symptom [55]. Even in the elderly, no serious adverse events were noted with nicotine patch administration [56]. Non-ischemic chest pain and palpitations were reported, but were extremely rare [53]. There is no evidence, that nicotine replacement therapy increases the risk of heart attacks [53]. In a postsurgical setting, transdermal nicotine was examined in non-smokers in several studies addressing postoperative pain. In none of these, serious adverse events occurred [57,58]. Nicotine application was safe in terms of anastomotic healing and surgical site infections [59,60]. Even in critically-ill non-smokers, transdermal nicotine application was safe in terms of side-effects and adverse events [61]. The safety of transdermal nicotine in non-smokers war confirmed in a recent review [62].

6.3 Risk Benefit Assessment

Considering the well-known and good safety profile of nicotine patches, which are marketed for nicotine cessation for a long time, the application of a transdermal nicotine patch 14mg/24h for a total duration of 7 days seems to be justifiable. No serious adverse events were reported even in postsurgical non-smokers which justifies the inclusion of also non-smokers in this clinical trial.

Since at present no prophylactic or therapeutic options exist for ameliorating DGE after PD and retrospective clinical data describe an improvement of DGE in active smokers following PD, there is a reasonable chance that application of a transdermal nicotine patch might have a positive effect. Thereby lowering the incidence of the most frequent complication following pancreatic head resection.

7 Trial Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess the effect of transcutaneous administration of nicotine as compared to placebo on the development and severity of delayed gastric emptying (DGE) following pancreatoduodenectomy	Grade of delayed gastric empyting (none, grades A-C representing increasing severity) according to the definition of the International study Group of Pancreatic Surgery.
Secondary	
To evaluate the safety, efficacy and tolerability of transcutaneous nicotine administration as compared to placebo in patients requiring pancreatoduodenectomy	<u>Assessment of tolerability:</u> • postoperative pancreatic fistula • postpancreatectomy hemorrhage • intraabdominal fluid collections • surgical site infections • re-intervention rate • re-operation rate • Clavien-Dindo classification • MTL30 score • quality-of-life questionnaires (QLQ-C30 and PAN26) • mortality • cardiovascular events ((non-fatal) myocardial infarction, (non-fatal) stroke, revascularization during admission) <u>Assessment of efficacy on DGE-development:</u> • requirement of naso-gastric tube (NGT) in the first 21 days after surgery • inability to tolerate solid oral food in the first 21 days after surgery • vomiting/gastric distension in the first 21 days after surgery • use of prokinetics in the first 21 days after surgery Additionally, the following parameters are used for grading (according to the International Study Group of Pancreatic Surgery • comorbidities • specific treatment • nutritional support • diagnostic evaluation • interventional treatment

Objectives	Endpoints
	• prolongation of hospital stay • delay of potential adjuvant therapy <u>Assessment of safety:</u> Adverse Events and Serious Adverse Events

8 Trial Design

8.1 Trial Design

This is a prospective, phase IIa, proof-of-concept, multi-center, placebo-controlled, randomized, double blind, parallel trial. 400 patients will be assessed for eligibility from whom 300 are planned for screening activities. 240 patients have to be randomized to have 120 patients in each treatment group for evaluation.

The trial design flowchart is presented in figure 1:

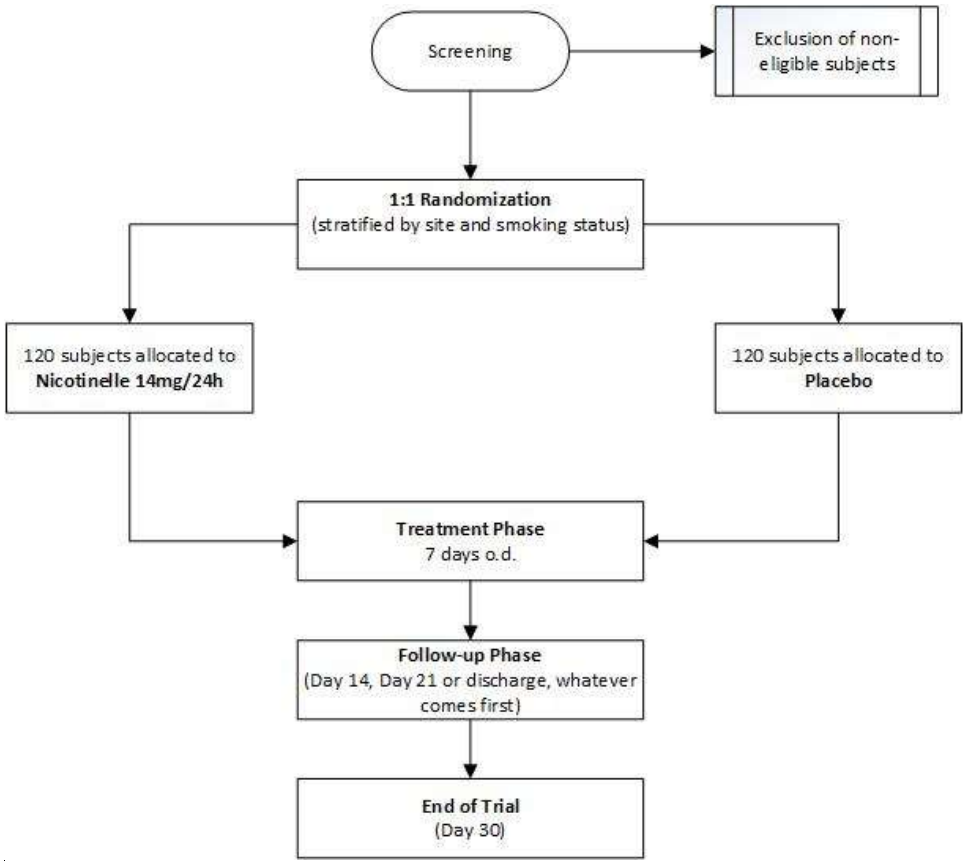

Figure 1: Trial Design

8.2 Treatment Groups

Treatment A: Nicotinell 14mg/24h patch

Treatment B: Placebo patch

Treatment A or Treatment B will be applied for 7 consecutive days (Day 1 to Day 7) once daily.

Patients will be treated with either Treatment A or Treatment B according to the randomization list.

8.3 Trial sites

The trial will be conducted in approximately six (6) sites in Germany which must meet the structural and personnel requirements for performing the planned regular trial-related investigations.

If necessary, additional qualified sites may be included in the performance of the trial.

8.4 Number of subjects

It is assumed that 400 patients will be pre-screened for general study eligibility. It is planned to enroll a total a number of 300 patients in this trial who have signed the informed consent for trial participation and are planned for surgery. Out of these, 240 patients are considered to be suitable for inclusion, i.e. allocation to the trial treatment.

120 patients will be randomized in treatment A,
120 patients will be randomized in treatment B.

There have to be at least 110 evaluable patients per treatment arm for statistical analysis.

Subject-Number
All screened subjects will be identified by a unique subject number with the first two digits representing the site and the following three digits representing the subject number in chronological order, i.e. the first subject of the first site = 01-001.

Randomization Number
Furthermore, a randomnumber will be allocated to every subject receiving treatment A or B:

[Site no.] – [RA/NR[1]] – [chronological number]

Example for the first subject at the site Bonn who is a non-smoker: 01-NR-001

[1] RA= Raucher (smoker)
NR = Nicht-Raucher (non-smoker)

8.5 Time Schedule

Trial duration per patient:

- 28 days for Screening + 30 days treatment phase = maximum of 58 days in total

Trial duration:

- Recruiting Period: 24 months
- Planned Start Date (FPFV/ FPI): August 2023
- Planned End Date (LPLV/ LPO): August 2025

8.6 Patient Involvement

The German self-help group “Arbeitskreis der Pankreatektomierten (AdP)” was involved in planning of the clinical trial and will serve as a part of the Data Safety Monitoring Board (DSMB) during conduct of the trial. As the AdP acts as close partner to nearly every center of excellence in pancreatic surgery, they will help disseminate the results of the study.

9 Trial Population and Selection Criteria

This trial can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

9.1 Gender and Age Distribution

No gender and age ratio has been stipulated in this trial as the results of preclinical and clinical studies or medical literature and did not indicate any difference in the effect of the trial treatment in terms of efficacy and safety.

9.2 Inclusion Criteria

Subjects will only be included in the study if they meet all of the following criteria:

General inclusion criteria:

1. subject aged ≥ 18 years
2. given written informed consent to participate in the trial

Indication-specific inclusion criteria:

3. planned for pancreatoduodenectomy
4. smokers must be willing to stop smoking for the duration of the IMP application (i.e. from Day 1 to Day 7)

9.3 Exclusion Criteria

Subjects will not be included in the study if any of the following criteria applies:

General Exclusion Criteria:

1. Subject without legal capacity who is unable to understand the nature, scope, significance and consequences of this clinical trial
2. Simultaneous participation in a clinical trial taking an investigational medicinal product, up to 30 days prior to last IMP intake in that clinical trial.

Exclusion criteria regarding special restrictions for females:

3. Current or planned pregnancy or nursing women
4. Females of childbearing potential, who are not using and not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices) unless they are surgically sterilized / hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases

Indication specific exclusion criteria:

5. distant organ metastases (which can be diagnosed after screening, e.g. during surgery; then no resection is performed according to guidelines)
6. former gastrectomy
7. liver fibrosis/cirrhosis
8. Known history of hypersensitivity to nicotine or a compound of the investigational drug
9. Systemic skin diseases
10. Immediately after heart attack
11. Severe cardiac arrhythmia
12. Stroke that occurred shortly before
13. Concomitant medication with inhibitors or strong inducers of CYP2A6 (e.g. Trancylpromine, Desipramin, Ketoconazole, Valproic acid, Phenobarbital, Pilocarpine, Clotrimazole, Methoxsalen, Rifampicin)

9.4 Contraception Requirements

Female subjects of childbearing potential must not become pregnant and so must be sexually inactive by abstinence or use contraceptive methods with a failure rate of < 1% per year when used consistently and correctly. Therefore, these women will be asked for their pregnancy status at screening and have to agree to 1 of the following:

Complete abstinence from heterosexual intercourse from 2 weeks prior to administration of the 1st dose of IMP until 1 day after the last dose of IMP. (Sexual inactivity by abstinence must be consistent with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception).

OR

Consistent and correct use of 1 of the following acceptable methods of birth control for 1 month prior to the start of the IMP, during the clinical trial, and 1 day after the last dose of IMP:

Consistent and correct use of one of the following acceptable methods of birth control for 1 month prior to the start of the study agent, during the study, and 6 months after the last dose of study agent:

- Oral contraceptive, either combined or progestogen alone
- Injectable progestogen
- Implants of levonorgestrel or etonogestrel
- Estrogenic vaginal ring
- Percutaneous contraceptive patches
- Intrauterine device (IUD) or intrauterine system (IUS) with <1% failure rate as stated in the product label
- Male partner sterilization (vasectomy with documentation of azoospermia) prior to the female subject's entry into the study, and this male is the sole partner for that subject. For this definition, “documented” refers to the outcome of the investigator's/designee’s medical examination of the subject or review of the subject's medical history for study eligibility, as obtained via a verbal interview with the subject or from the subject’s medical records

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The investigator is responsible for ensuring subjects to understand how to properly use these methods of contraception.

Women of non-childbearing potential who do not require contraception during the trial are defined as:

- Postmenopausal (defined as no menses for 12 months without an alternative medical cause)
- Permanently sterile (hysterectomy, bilateral salpingectomy, bilateral tubal occlusion / ligation procedures, and bilateral oophorectomy).

9.5 Subject Information and Recruitment Procedure

If a subject appears to be eligible for the trial, the investigator will inform the subject about the trial and ask the subject or in case of subjects without legal capacity the legal representative/authorised agent for his/her written consent.

It is a requirement that written consent is obtained prior to any trial-specific procedures. The investigator will then record the details of the eligible subjects on trial specific lists provided.

9.5.1 Subject Identification

Patients with periampuallary pathologies are either admitted by the general practioner or resident gastroenterologist or transferred from the internal departments of the study centers. Indication for surgery is determined in an interdisciplinary tumor board by default.

All patients with periampullary pathologies requiring surgery are screened for existing studies at the CIO ABCD centers by default.

9.5.2 Recruitment resources

The numbers of regularly admitted patients are sufficient to fulfill the number of included patients as described above. Additionally, generally accessible websites (local comprehensive cancer center, department of surgery, department of gastroenterology, department of oncology; e.g. https://www.ciobonn.de/forschung/klinische-studien/cio-studienregister) present the open recruiting studies for all entities. In addition, TransNiDeG trial will be presented on national congresses (Annual congress of the German Society for Surgery, Visceral medicine (annual congress of gastroenterologists and gastrointestinal surgeons), German Pancreas club).

9.5.3 Informed Consent Procedure

According to Art. 29 CTR and § 40b of the German Medicinal Products Act (“Arzneimittelgesetz (AMG)”) every participating clinical trial subject will be informed of nature, objectives, benefits, implications, importance, treatment methods, risks, consequences and inconveniences of the trial by the local investigator. Details of indemnity and insurance are also stated.

The local investigator is responsible for obtaining written informed consent from a subject before any protocol-specific screening procedures will be performed or any investigational products will be administered. The written informed consent document has to be prepared and provided in the language(s) of the potential subject population.

It is also the responsibility of the investigator for asking the subject if he/she agrees to have her the primary care physician informed of his/her participation in the clinical trial. If the subject agrees to such notification, the investigator shall inform the primary care physician of the subject’s participation by sending a message letter.

Subjects must understand that it is their own free will to participate and that they can withdraw consent at any time without giving reasons and without penalty or loss of benefits to which the subject is entitled. Also, subjects must understand that they will experience no disadvantage as a result of this decision and that no alternative therapy will be withheld by the investigator.

The subject will be given ample of time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the subject. On the other hand by personally signing the consent form subjects give their consent to the evaluation, recording and usage of their personal data according to § 40b Abs. 6 AMG.

The written consent form will be personally dated and signed by the subject and the by investigator conducting the informed consent discussion. The completed informed consent forms will be filed in the Trial site File (Investigator Site File – ISF) at each site.

The acquisition of informed consent and the subject’s agreement or refusal of the notification of the primary care physician should be documented in the subject’s medical record.

A copy of the signed and dated informed consent form will be given to the subject and a copy will be held in the subject’s medical notes. The existence of written informed consent will have to be confirmed before any trial-specific test/treatment has been performed.

In the case of substantial amendments, e.g. any new data providing information on the safety profile of any of the investigational medicinal product and leading to significant changes in the risk-benefit ratio, the subject must be informed with an appropriately revised subject information and the consent of the subject has to be obtained again.

Changed trial procedures can only be carried out if they have been approved authorized by the competent authority and the responsible Ethics Committee, and if the subject has been appropriately informed and has given his/her written consent, if applicable.

9.6 Randomization

The department of biometry of the SZB will generate a randomization algorithm according to their SOPs. The randomization procedures will be carried out stratified by site and smoking status (smoker vs non-smoker) via permuted blocks within each stratum. Allocation to treatments will be done in a 1:1 ratio:

Treatment group A (Verum): 120 subjects
Treatment group B (Placebo): 120 subjects

The unblinded randomization list with the allocation of randomization numbers to treatments is kept confidential with department of biometry of the SZB. The derived site-specific randomization list is forwarded only to un-blinded study personnel of the study site (refer to 10.8 and 10.12).

The allocation of a subject (Subject-ID) to a treatment is done by the randomization number as provided on the randomization list. After screening, the assignment of the randomization number to a Subject ID happens in consecutive order (i.e. “first-come-first-serve” approach).

Subjects who meet all eligibility criteria will be treated starting on Visit 1 (Day 1, during or immediately after surgery) either with Verum (Treatment A) or with Placebo (Treatment B).

Details are described in an IMP Manual.

9.7 Time of inclusion into clinical study

A patient is enrolled into the clinical trial after having signed the informed consent.

A patient is included in the clinical trial after having received a randomization number.

10 Investigational Medicinal Product (IMP)

10.1 General

Study drug includes both Investigational [Medicinal] Product (IP/ IMP) and Non-investigational [Medicinal] Product (Non-IP/Non-IMP) and can consist of the following:

- All products, active or placebo, being tested or used as a comparator in a clinical trial
- Study required premedication, and
- Other drugs administered as part of the study that are critical to claims of efficacy (e.g., background therapy, rescue medications)
- Diagnostic agents: (such as glucose for glucose challenge) given as part of the protocol requirements must also be included in the dosing data collection

10.2 Specification of IMP and auxiliary Medicinal Products (AxIMP)

IMP 1: Nicotinell 14mg/24-Stunden-Pflaster

Product name	Nicotinell 14mg/24-Stunden-Pflaster
Name of manufacturer	GlaxoSmithKline Consumer Healthcare GmbH & Co.KG
Substance name (if applicable, give substance code)	Nicotine
Name and dose of active ingredient per unit	14mg/24h
Other ingredients	Refer to SmPC
Pharmaceutical form	Transdermal patch
Mode of administration	transdermal
Batch number	Not yet available
Storage conditions	Not above 25°C
Expiry date	Not yet available
Mode of action	transdermal
Interactions	No interactions with other drugs are known

IMP 2: Placebo

Product name	Patchinga Freestyle Libre 3
Name of manufacturer	Shanghai Ruiquan Medical Equipment Co., Ltd.
Substance name (if applicable, give substance code)	Not applicable
Name and dose of active ingredient per unit	None
Other ingredients	Not applicable
Pharmaceutical form	Patch
Mode of administration	topical
Batch number	Not yet available

Storage conditions	No special requirements
Expiry date	Not yet available
Mode of action	Not applicable
Interactions	Not applicable
If necessary; additional information concerning toxicology, preclinical results, pharmacodynamics, pharmacokinetics	

The batch number / expiry date for IMP will be provided with the batch records in the Trial Master File.

No auxiliary IMPs will be applied in this clinical trial.

10.3 Authorization Statement

The IMPs are products with a marketing authorization in Germany.

Nicotinell 14mg/24-Stunden-Pflaster will be used in accordance with the marketing authorization with the exception that also non-smokers will be applied.

The Placebo patch is manufactured in accordance with ISO 13485:2016 and fulfills all legal requirements as per MDR 745/2017.

10.4 Side Effects

A summary of the most important side effects and contraindications which are reported in the corresponding Summary of Product Characteristic(s) (Fachinformation) for Nicotinell 14mg/24-Stunden-Pflaster is presented below:

Nicotine can cause headaches, dizziness and nausea, increase in heart rate and temporary mild increases in blood pressure. However, when using Nicotinell 14 mg / 24-hour patch, the level of nicotine in the blood remains largely the same and there are no levels are reached as after smoking a cigarette. Therefore, such side effects are unlikely to occur during treatment with Nicotinell 14 mg / 24-hour patch are much less pronounced.

Very frequent (> 10%) side effects:

- Headache
- Cold- and flu-like symptoms

Frequent (1-10%) side effects:

- Dizziness
- Agitation
- Feeling of fear
- Nervousness
- Concentration disturbance
- Sleeplessness
- Tiredness
- Abnormal dreams

- Change in blood pressure
- Cough
- Nausea
- Stomach pain
- Gastrointestinal disorder
- Skin reaction at the application site (e.g. burning feeling, swelling, redness, itching). Most of these reactions were of mild nature and resolved within 48 hours. In severe cases redness and swelling continued for 1-3 weeks. Significant skin reactions occurred after 3-8 weeks after start of treatment.
- Muscle pain
- Movement disorders

Occasionally (0.1 – 1%) side effects:

- Sleepiness
- Emotional lability
- Irritability
- Depressive mood
- Confusion
- Memory disorder
- Paresthesia
- Taste disorder
- Visual disorder
- Palpitation
- Heat waves
- upper respiratory tract Infection
- vomiting
- obstipation
- diarrhea
- flatulence
- abnormal stool
- dry mouth
- gingivitis
- Stomach ulcer
- Increased sweating
- Acne
- Joint pain
- Muscle cramps
- Back pain
- Swallowing disorder
- Thyroid disorder
- Painful lymph nodes
- Cystitis
- Weakness
- Pain

- Malaise
- migraine

Rare side effects (0.01 – 0.1%):

- Tremor
- Pain in the chest
- Breathing difficulties
- Cardiac arrhythmia
- Skin reaction at the application site like skin (hyper-)pigmentation, vasculitis

10.5 Packaging and Labelling of IMP

The IMPs (both, Verum and Placebo patches) will be ordered and supplied either by the local pharmacies or by the local purchase department of the study sites.

Nicotinell patches will be supplied as packages containing 7 patches in their authorized packaging with no modifications. Pursuant to Directive EU 536/2014 Art. 67 No. 2, a trial-specific label will be placed on the outer packaging in order to ensure subject safety and reliability and robustness of clinical trial data.

Placebo patches will be supplied as packages containing 25 patches. Subject-individual sets with 7 patches each will be assembled by the unblinded members of the investigator´s team. These sets will be labelled with a trial-specific label, too.

Labelling will be done by the local pharmacy of the study site or by a pharmacy with a respective manufacturing authorization.

Details are described in the IMP manual.

10.6 Transport of IMP

Since IMP is ordered and supplied by local pharmacies, no transport is necessary.

10.7 Storage requirements of IMP

The IMP(s) must be stored under the following conditions:

IMP 1 (Nicotinell patch): below 25°C

IMP 2 (Placebo patch): no special storage requirements

The investigator will be responsible for ensuring the correct storage and sufficient stocks of the IMP(s) at the site. The investigator bears the responsibility for the proper storage in a secure location at the site, preferably in a lockable cabinet. **Access to the IMPs has to be restricted only to unblinded members of the investigator´s team.** It has to be paid special attention that **study personnel who is applying and covering the IMP is not involved in any other trial-specific procedures.**

Personnel who have access to the IMPs need to be listed (name and responsibilities) on the Authorization and Delegation Log in the trial specific Investigator Site File (ISF). The investigator has to ensure that the IMP is only used according to the protocol.

10.8 Dosage, Mode of Application and Dose Schedule of IMP

IMP patches will applied by unblinded members of the investigator´s team only.

Application on Day 1 will be done during or immediately after surgery. Application on Days 2 to 7 should be done preferably in the morning with an interval of approximately 24h (+/-6h) between treatments.

The dose of 14mg/24h for Nicotine patches was chosen as the medium dose for Nicotine patches being used for smoking cessation. This dose was proven safe even in non-smokers with only transient nausea as the only symptom [55] and in the elderly, where no serious adverse events were noted [63]. Also in critically-ill patients, a dosing of 14mg/24h was tolerated without relevant side-effects [61]. The dose was chosen to have most likely a significant effect without causing harm to the subjects.

According to the SmPC, the patch has to be placed either on the upper arm, upper hip or in the shoulder area. For standardization purposes in this study, the patches will be applied on the upper arm.

The patch should be placed on non-injured, clean and dry skin with as less hair as possible. The patch will be left on the application area for approximately 24 hours (+/-6h) after which the patch will be replaced by a new one. The application area has to be changed every day to avoid skin reactions. Therefore, it is preferred to change the arm for application every day.

After application of the Verum or Placebo patch, another patch has to be placed over the IMP patch to cover it for blinding purposes. This “blinding patch” has to cover the IMP patch totally. It has to be ensured that any manipulation of the “blinding patch” can be discovered.

Both patches (the IMP patch and the “blinding patch”) must not be taken off during the time of application e.g. for taking a shower. Although the IMP patch is not water-resistant, it can be left on the skin when showering carefully.

The application and blinding process is described in detail in the IMP Manual.

10.9 Handling of IMP at the Site and Drug Accountability

Every trial site maintains records to document receipt of the IMP, the stocks of IMP, the dispense and use by the individual subject, the reconciliation, and the return of unused investigational medicinal products and their disposal on appropriate forms (e.g. drug dispensing log, drug accountability log).

Verification of (blinded) IMP accountability will be part of on-site monitoring activity. It is the responsibility of the investigator or the monitor (whoever first discovers it) to inform the sponsor delegated person/ Coordinating Investigator in case of deficiency regarding e.g. storage or accountability of the IMP.

Copies of all forms completed at the trial site will be returned to the sponsor delegated person/Coordinating Investigator at the end of the trial upon request or will be collected by the monitor during the close out visit.

IMP must only be applied to subjects who have signed the informed consent and who have been included in the trial. The dispensing of IMP to subjects outside of this clinical trial is not permitted.

Further details about receipt, storage, handling, dispensing are given in the IMP-Manual.

10.10 Subject/ Treatment Compliance

The IMP will be applied by an unblinded authorized member of the investigator´s team. Prior to every IMP application, the unblinded study team member will check the blinding patch and the underlying IMP patch of the former day for manipulation and detachment. IMP application and any deviations will be documented.

Treatment compliance will be determined via verification of the drug accountability after database lock (i.e. unblinding) by the Study Monitor.

10.11 Return and Disposal of IMP

All unused IMP will be destroyed at the trial site by the responsible Study Monitor according to SZB SOP. In case of destruction, a destruction form has to be completed with the information about date and location of destruction, sort and amount of IMP.

10.12 Blinding and Emergency Codes

This trial is double-blinded. After randomization, neither the subjects nor the investigator or sponsor will be aware of the treatment allocation.

The procedure for blinding is described in Section 10.8., details of the application and blinding process are described in an IMP Manual. Emergency envelopes for every subject will be provided by the Study Core Unit (SZB).

10.13 Unblinding

Unblinding may be performed by the trial site using Emergency Codes which are provided to the trial site by the SZB as sealed Emergency Envelopes. These envelopes have to be stored at a location known and accessible to all study personnel. All study personnel have to be specifically trained. Integrity of envelopes is controlled by the Study Monitor.

The investigator should adhere to the randomization procedure of the clinical trial and ensure that the code is only broken according to the protocol.

As a matter of principle, unblinding is only performed after the closing of the database for the final analysis.

However, premature unblinding of a subject subject may be necessary in order not to jeopardise his/her safety (ICH-GCP 5.13.4):

- In emergency situations, if it is necessary for the subject subject's safety, i.e. if the further treatment depends on the knowledge of the investigational medicinal product.
- In the event of accidental administration of the investigational medicinal product to a person who is not a clinical trial subject.
- In the event of the death of a subject, if a causal relationship between the treatment with the investigational medicinal product and death is suspected.

- In the event of SAEs/SUSARs, under certain conditions (causal relationship with the investigational medicinal product).

In emergency situations or in the event of accidental administration of the investigational medicinal product, the decision whether unblinding is necessary lies with the investigator. If possible, the sponsor delegated person/Coordinating Investigator should be consulted first. Date and time of unblinding, name of the person who has broken the blind have to be documented on the respective emergency envelope. Any broken emergency envelope has to be filed in the Investigator Site File (ISF).

10.14 Prior and Concomitant Therapy/Medication

Any concomitant therapy and concomitant medication of a subject should be carried out during the clinical trial in consultation with the (principal) investigator. The concomitant medication is documented in the patient file and in the CRF.

10.14.1 Prohibitions

As a rule, a subject should abstain from smoking during the 7 days of treatment with the IMP. In case a subject deviates from this rule, this should be documented in the patient file and in the eCRF.

It will be discussed in the Data Review Meeting together with the Coordinating Investigator and Biometrician whether the subject will be excluded from the analysis or not.

10.14.2 Rescue Therapy

Not applicable.

11 Trial Procedures

11.1 Methods of Assessment and Procedures

The following section will give an overview and adequate explanations to the examinations and procedures to be performed in this trial and will be determined according to the time schedule given in section 2. The results of these assessments and procedures have to be documented on source documents and transferred to the eCRF.

11.1.1 Informed Consent

Refer to 9.5.3

11.1.2 Demographics

For demographics, the following items will be recorded: age, sex, height, weight, BMI

11.1.3 Medical History

The following items will be recorded for medical history:

- Smoking history (PY in the lifetime)
- active smoker (yes/no)
- weight loss (>10% of body weight in the last six months)

- bile duct stent in situ (yes/no), diabetes mellitus (yes/no)
- neoadjuvant chemotherapy administered (yes/no)
- previous abdominal surgery (yes/no)
- updated Charlson Comorbidity Index (0 to 37)
- request for current pregnancy and nursing status (females of childbearing potential only)
- infection and allergies since the last 12 months

11.1.4 Concomitant Medication

The following inhibitors and strong inducers of CYP2A6 are prohibited as concomitant medication during the trial:

- Trancylpromine (e.g. Jatrosom®)

- Desipramin (e.g. Norpramin® Pertofrane®)

- Ketoconazole (e.g. Nizoral®, Terzolin®)

- Valproic acid (e.g. Convulex®, Orfiril®)

- Phenobarbital (e.g. Luminal®)

- Pilocarpine (e.g. Salagen®, Spersacarpin®)

- Clotrimazole (e.g. Canesten®)

- Methoxsalen (e.g. Meladinine®)

- Rifampicin (e.g. Eremfat®, Rifa®)

If the above named agents cannot be discontinued for the trial period, patients cannot be included in the study.

If patients already included into the study have to be treated with the above named drugs due to unforeseen circumstances, an individual estimation of the risk has to be performed by the physician in charge. Depending on the duration of the concomitant treatment, the respective patient should to be excluded from the study. This will be decided by the Investigator in consultation with the Sponsor.

The intake of concomitant medication will be documented in the patient´s record and in the e-CRF. However, once concomitant medication use is documented, changes (e.g. in dose or added therapies) may not need to be documented unless they contribute to the follow-up of any safety issue (ICH Guideline E19).

11.1.5 In-/Exclusion Criteria

In-/Exclusion criteria will be checked thoroughly after the Screening Visit. Only eligible subjects will be included into the trial by the investigator.

11.1.6 Grading DGE

The parameters are applied for grading delayed gastric emptying (DGE) according to the International Study Group of Pancreatic Surgery definition [1]:

Depending on these parameters, DGE is graded in four grades: none, grade A, grade B and grade C:

DGE grade	No DGE	Grade A	Grade B	Grade C
NGT requirement	< POD 4	POD 4-7	POD 8-14	> POD 14
NGT reinsertion	≤ POD 3	> POD 3	> POD 7	> POD 14
Unability to tolerate solid food on POD		7	14	21
Vomiting/gastric distension	-	±	+	+
Use of prokinetics	-	±	+	+
Nutritional support (pp enteral or parenteral)	No	Possibly yes	Yes	Yes
Prolongation of hospital stay	No	Possibly yes	Yes	Yes
POPF/intraabdominal abscess	No	No	Possibly yes	Possibly yes
Diagnostic evaluation for DGE (Endoscopy, CT)	No	No	Possibly yes	Yes
Interventional treatment (abcess drain, relap)	No	No	No	Yes
Delay of potential adjuvant therapy	No	No	No	Yes

*** NGT according to long-term respiration or vacuum therapy is not considered for DGE grading**

Table 1: DGE grading

DGE grading should be done considering the algorithm as above. However, the investigator may overrule this grading according to his own judgement in compliance with the International Study Group of Pancreatic Surgery definition [1].

NGT requirement and the ability of solid food intake will be assessed on every day as indicated in the study schedule. The other parameters as per Table 1 will be assessed only on Visit 1.3, 1.7, 2 and 3.

11.1.7 Checks for Endpoints

The following checks will be performed on the dates indicated in the study schedule:

- Occurrence of pancreatic fistula
- Occurrence of postoperative hemorrhage
- intraabdominal fluid collections
- re-intervention rate
- re-operation rate
- nausea
- occurrence of cardiovascular events
- re-laparotomy

- lymphadenectomy
- MTL-30 (Mortality, Transfer, Length of stay)

Furthermore, the days of hospital stay (calculated from the day of discharge) will be documented in the eCRF.

11.1.8 Questionnaires/Scores

The following questionnaires will be provided to the subjects on Day 30 (+/- 2 Days):

- EORTC QLQ-C30 (Quality of Life Questionnaire C30)
- EORTC QLQ-PAN26

The questionnaires are free of charge and will be provided by the Coordinating Investigator for the trial sites. This includes a reference to the evaluation methodology.

11.1.9 Histopathology

Histopathology as diagnosed during routine pathology workup.

11.1.10 AEs and SAEs

Refer to Section 12.

12 Safety Data Collection, Recording and Reporting

Safety data collection, documentation and reporting of adverse events will be performed according to the applicable laws and regulations (CTR, AMG, ICH Guideline E19).

Details regarding safety data documentation and reporting are specified in the Safety Management Plan (SMP) of this trial. The Investigator's Brochure for an unapproved investigational product or summary of product characteristics for an approved product will be used as reference documents referring to safety specifications.

The investigator will be provided with AE and SAE reporting forms by SZB and will receive training for AE/SAE definition, documentation and reporting. The AE/SAE documentation and reporting will be monitored on site.

12.1 Definitions

12.1.1 Adverse Event (AE)

Adverse event means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

A subject means an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control.

An investigational medicinal product (IMP) is a medicinal product, which is being tested or used as a reference, including as a placebo, in a clinical trial.

12.1.2 Adverse (Drug) Reaction (AR)

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase „responses to a medicinal product“ means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

12.1.3 Unexpected Adverse (Drug) Reaction (UAR)

An adverse reaction, in which the nature or severity of the event is not consistent with the applicable reference safety information (e.g., Investigator's Brochure for an unapproved investigational medicinal product or package insert/summary of product characteristics for an approved product)

12.1.4 Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

A serious adverse event or reaction is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity, or
- Results in a congenital anomaly or birth defect,
- Is another, according to medical assessment, clinically relevant event.

- 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it has been more severe
- In general, 'hospitalization' signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious
- In-patient stays without an underlying adverse event are not SAE (e.g.: elective in-patient treatment due to a pre-existing condition; inpatient admission for social reasons; admission to a rehabilitation clinic or hospice)
- The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

12.1.5 Suspected Unexpected Serious Adverse (Drug) Reaction (SUSAR)

A SUSAR is an adverse reaction, which is suspected, serious and unexpected because the nature, severity or outcome of this event is not consistent with the applicable reference safety information (e.g. Summary of Product Characteristics for an authorized product or Investigator's Brochures for an unauthorized investigational medicinal product).

12.2 Criteria to be evaluated by the investigator (1st assessment)

By including the patient in the clinical trial and first administration of IMP, all adverse events (AEs), including intercurrent diseases, must be documented in the patient file and subsequently in the CRF. Disease signs, symptoms and laboratory changes should, as far as possible, be combined **into one single diagnosis**. The documentation of the event shall include the following criteria: "type", "beginning and end" and "outcome of the event" (recovered, improved, unchanged, recovered with sequelae, worsened death, unknown). The event is then evaluated according to the following criteria:

12.2.1 Assessment of Intensity

An assessment of intensity grade will be made using the general categorical descriptors outlined in the WHO Toxicity Grading Scale (see Table below). The investigator should use clinical judgment in assessing the severity of events not directly experienced by the subject (e. g, laboratory abnormalities).

MILD	Does not interfere with subject's usual function, easily tolerated.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function, incapacitating with inability to work or carry out usual activity.

12.2.2 Assessment of Seriousness (AE vs. SAE)

Determination of the seriousness of the adverse event according to the definitions for a serious adverse event (SAE) given in section 12.1.

12.2.3 Assessment of Causality

Determination of the relationship of the adverse events to the medicinal product(s) being studied after having evaluated all accessible data according to the following classification:

Suspected relationship (related):

The temporal relationship between the event and the administration of the IMP makes a **causal relationship possible, probable, or definite,** or other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No suspected relationship (not related):

The temporal relationship between the event and the administration of the IMP makes a **causal relationship unlikely or impossible (i.e. not related),** or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

The evaluation should consider nature and pattern of the reaction, temporal relationship to study medication, the clinical status of the patient, the concomitant medication and other relevant parameters. When the final causality assessment is unknown and it is uncertain whether or not the investigational product caused the event, then the event should be handled as an SAE related (suspected) to the investigational product for reporting purposes. If the investigator believes that the SAE is not related to the investigational product but is potentially related to the conditions of the trial the relationship should be specified in the narrative section of the SAE report form.

12.3 Criteria to be evaluated by the Sponsor for SAEs (2nd assessment)

To take into account safety data available to the sponsor but not to the investigator at the time an SAE was detected, in addition to the initial assessment of a serious adverse event by the investigator, a second assessment of the event by the sponsor in terms of causality and probability of occurrence ("expectedness") and a continuous benefit-risk assessment are performed.

- **Causality**: If no information on causality is available from the investigator rapporteur, the sponsor should consult the investigator rapporteur and ask him to comment on this aspect. The sponsor should not downgrade the investigator's assessment of causality. If the sponsor disagrees with the investigator on the causal link, the report should include the opinion of both the investigator and the sponsor.
- **Expectedness:** Whether a serious adverse reaction is to be expected is assessed using the reference safety information (RSI). If the rapporteur investigator has provided information on whether an event is expected, the sponsor should take this into account.

12.4 Documentation and Reporting of AEs, Follow-up

Any AE defined in clinical trial protocol as relevant for the evaluation and analysis of the clinical trial has to be documented in the CRF on the respective Adverse Event Report Form. Documentation and evaluation of each AE occurring between:

- the visit with the first administration of IMP to the subject and
- the visit of discharge.

According to the CTR, only adverse events and unexpected clinical diagnostic findings that are identified in the protocol as critical to safety evaluations must be reported by the investigator to the sponsor.

All medical conditions prevalent prior to study enrolment and all Adverse Events (AE) that occur after first dosing until discharge will be collected throughout the study and documented in the subject's medical record using medical terminology and transferred to the CRF. If applicable, AEs and SAEs that relate to any later protocol-specified procedure will be recorded. Furthermore, the investigator should report any SAE that occurs after these time periods and after end of the clinical trial, if the SAE is believed to be related to the study drug. An SAE report should be completed for any event where doubt exists regarding its seriousness. To ensure comparability of the safety data of the two study arms any adverse event in patients of the control arm will also be recorded although no study drug will be administered. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology. All measures required for adverse event management must be recorded in the source document and reported according to sponsor`s instructions. The investigator evaluates all Adverse Events regarding severity, causality as well as seriousness.

12.5 Documentation and Reporting of SAEs

Every SAE will always be documented in the patient file and in the eCRF even if they are

- not severe
- meeting CTCAE grade 1 or 2
- not at least possibly related
- declared in the protocol as being exempt from reporting without undue delay, by the investigator to sponsor (refer to Section 12.5.1)
- primarily attributed to the underlying disease

Every SAE has to be reported immediately to the Sponsor Delegated Person/ Coordinating Investigator and SZB except those SAEs the protocol identifies as not requiring immediate reporting. However, **every SAE that is considered related to the IMP will always be reported to the Sponsor Delegated Person/ Coordinating Investigator without undue delay** According to the documentation of AEs any adverse event in patients of

the control arm meeting the criteria of an SAE will also be recorded although no study drug will be administered to ensure comparability of the safety data of the two study arms.

The documentation of the SAEs for a patient is carried out as described under 12.4, the reporting of SAEs for study patients is carried out within the following time periods:

- after the subject has been randomized and has received IMP for the first time
- up to 24h after the subject has received the last dose of IMP
- after these time periods until end of trial, when the SAE is believed to be related to the IMP
- after the end of trial when the investigator becomes aware of a SAE with a suspected causal relationship to the IMP

Any SAE occurred after application of study drug should be reported **immediately** after investigator awareness of the event to the sponsor (at the latest within 24 hours):

Study Coordinating Center of the SZB
Studienzentrale Studienzentrum Bonn (SZB)
FAX: +49 (0)228 287 9080110
E-Mail: safety-szb@ukbonn.de

Reporting should occur by fax on the **SAE report form** provided for this purpose. Symptoms, signs and laboratory changes should, as far as possible, be combined into one **single diagnosis**. The investigator is responsible for assessing the event (seriousness, intensity, causality). If necessary information is not fully available at this time, follow-up reports should be sent as soon as possible. Questions must be answered promptly. Further information and details how to report are described in the **Safety Management Plan**.

12.5.1 Serious Adverse Events exempted from expedited reporting

According to the ICH Guideline E19[2] in certain situations selective safety reporting may be appropriate. This applies for example if the IMP has received a marketing authorization from a regulatory authority, the safety profile is well-known, the clinical pharmacology has been described and understood, post-authorization data is sufficiently available.

In this clinical trial the test-IMP has a marketing authorization for more than 30 years in Germany and a very well-know safety profile from a large number of post-authorization data [54]. The aim of this trial is to provide evidence of efficacy of nicotine treatment in patients suffering from DGE after PD.

Surgical resection is a pre-planned procedure and not considered as trial treatment. Therefore, complications from surgical resection (PD) from the date of surgery until the end of follow-up are not considered AEs/SAEs unless the complications are considered to be related to treatment with the IMP. Surgical complications will be documented in the eCRF and the patient file.

Furthermore, events that are probably related to the underlying disease are not considered as AE/SAE as long as the severity of the event is to be expected and not aggravated.

[2] ICH Guideline E19 on a selective approach to safety data collection in specific late-stage pre-approval or post-approval clinical trials (16-Mar-2023)

The underlying disease is a condition prior to inclusion in the clinical trial. Events that are probably related to the underlying disease are not considered as AE/SAE as long as the event and the severity of the event are to be expected and not aggravated.

The following events are most likely to occur after surgical resection or are most likely related to the underlying disease:

- Postoperative pancreatic fistula
- Relaparotomy
- Postoperative haemorrhage
- Insufficiency of the biliodigestive anastomosis
- Insufficiency of the GE (Gastroenterostomy)
- (Superficial) wound infections
- Intra-abdominal abscess
- Pleural effusion
- Pneumonia

In recent studies, nicotine application was extremely safe in terms of anastomotic healing and surgical site infections [59,60]

12.5.2 Reporting of events to authorities and ethics committees

AEs

The sponsor shall submit the documentation of AEs to the responsible competent authority upon request.

SUSARs

Regarding suspected unexpected serious adverse reactions (SUSARs) the sponsor has to inform the responsible ethics committee, the competent higher federal authority and the investigators participating in the clinical trial. The sponsor shall report electronically and without delay to the European Medicines Agency (EMA) via database Eudravigilance all relevant information about SUSARs to IMPs occurring in that clinical trial or occurring in any of the subjects of the clinical trial, and which are identified by or come to the attention of the sponsor after the end of the clinical trial.

The period for the reporting of SUSARs by the sponsor shall take account of the seriousness of the reaction:

- in the case of fatal or life-threatening SUSARs, as soon as possible and in any event not later than seven calendar days after the sponsor became aware of the reaction, followed by as complete a report as possible within 8 additional calendar days;
- in the case of non-fatal or non-lifethreatening SUSARs, not later than 15 calendar days after the sponsor became aware of the reaction.

Re-examination of the risk-benefit assessment

The sponsor shall rapidly inform the competent authority (CA) of any information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal

product administration or in the overall conduct of a clinical investigation represents such situations. This includes in particular:

- For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
- A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
- A major safety finding from a newly completed animal study (such as carcinogenicity).

Annual Safety Report (ASR)

Regarding investigational medicinal products other than placebo, the sponsor shall submit annually to the competent authority (CA) a report on the safety of each investigational medicinal product used in the clinical trial. The safety report is prepared in accordance with the ICH Guideline E2F "Development Safety Update Report - DSUR".

The data-lock point of the patient data included and analyzed in the report refers to the date of approval of the clinical trial by the competent authority. The sponsor will provide the report within 60 days of the data-lock point annually.

Arrangements to protect trial participants against imminent danger

Whenever the safety of subjects is compromised and the sponsor and investigator are taking measures to protect subjects from imminent danger, the sponsor has to inform the competent authority of such arrangements and their underlying circumstances, as soon as possible.

12.6 Pregnancy

Any pregnancy that occurs during trial participation must be reported to the Sponsor. To ensure subject safety, each pregnancy and pregnancy outcome must be reported to the Sponsor Delegated Person/Coordinating Investigator and the SZB. For this purpose, the investigator documents and reports the pregnancy and outcome on the registration forms provided for this purpose and remits this immediately (at the latest after 24 hours) to the Sponsor Delegated Person/Coordinating Investigator and the SZB.

The pregnant subject has to discontinue the treatment with the IMP permanently and has to be excluded from the trial.

The pregnancy itself is not classified as an AE or an SAE, but must be followed up to determine outcome (including premature termination) and status of mother and child. According to CTR, pregnancies shall be subject to the same obligation to report as adverse reactions. The investigator will request this information after the scheduled date of birth and provide it in writing to the (sponsor/sponsor's representative).

Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE.

Any SAE occurring in association with a pregnancy brought to the investigator’s attention after the subject has completed the trial and considered by the investigator as possibly related to the study treatment, must be reported.

If the outcome of the pregnancy corresponds to one of the following cases

- spontaneous or therapeutic abortion or voluntary abortion

- stillbirth
- the presence of birth defects, or
- congenital anomalies (also in miscarriages, stillbirths or premature death),

the investigator reports this case as SAE. In the case of stillbirth, the (presumed) causality is documented. Reporting should occur by fax on the **SAE report form** provided for this purpose..

12.7 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as a serious breach (see Section 18.5. for reporting details).

12.8 Unblinding

See Section 10.13.

13 Data Safety Monitoring Board (DSMB)

The Data Safety Monitoring Board (DSMB) is an independent committee which is monitoring the study progress of the safety of trial participants and the quality of the collected data and should make recommendations on the discontinuation, modification or continuation of the trial. The tasks of the DSMB in the trial are the following:

To review the safety data of this trial after 50% of the patients have been enrolled. The DSMB is charged with reviewing safety data in both arms of the trial. The DSMB will be empowered to stop the study for evidence of harm but not for evidence of lack of efficacy. The DSMB is also asked to offer perspective on any therapeutic or diagnostic testing advances that may occur during the course of the trial that may influence the outcome. If protocol modifications are warranted, close consultation among the DSMB, the SZB staff, and the study leadership will be required. Further details are provided in a separate DSMB charter

The Coordinating Investigator can ask the DSMB at any time to review any data from the trial and to decide whether to proceed with the trial without changes, to modify the trial or to stop the trial entirely. The data provided to the DSMB for review may also include so far unmonitored data.

The DMSB is free to suggest any modifications regarding the trial (e.g. stopping of the trial, modifications of the protocol).

The DSMB will include at least 3 members with experience in the conduct of study and individually expertise in the field of surgery and biometrics. Further details concerning members, function, reports and modalities of meetings are provided by the DSMB Charter of this trial.

14 Statistic and Analysis

Full details of all statistical analyses will be specified in a separate Statistical Analysis Plan (SAP), which will be finalized prior to locking and unblinding of the study database. The study database will be locked once the last patient has completed the trial or has been withdrawn. A summary of the proposed methods of analysis is provided below.

14.1 Trial Design

See also Section 8.1.

14.2 Target Variable/Endpoints

14.2.1 Primary Target Variable

The primary objective of this trial is to assess the effect of transcutaneous administration of nicotine as compared to placebo on the development and severity of delayed gastric emptying (DEG) following pancreatoduodenectomy.

Primary Endpoint:

Grade of delayed gastric empyting according to the definition of the International Study Group of Pancreatic Surgery (i.e. 0, A, B, C).

14.2.2 Secondary Target Variables

The secondary objective is to evaluate the safety and tolerability of transcutaneous nicotine administration as compared to placebo in patients requiring pancreatoduodenectomy.

Secondary Endpoints

Assessment of tolerability:

- postoperative pancreatic fistula
- postpancreatectomy hemorrhage
- intraabdominal fluid collections
- surgical site infections
- re-intervention rate
- re-operation rate
- Clavien-Dindo classification
- MTL30 score
- quality-of-life questionnaires (QLQ-C30 and PAN26)
- mortality
- cardiovascular events ((non-fatal) myocardial infarction, (non-fatal) stroke, revascularization during admission)

Assessment of efficacy on DGE-development:

- requirement of naso-gastric tube (NGT) in the first 21 days after surgery
- inability to tolerate solid oral food in the first 21 days after surgery
- vomiting/gastric distension in the first 21 days after surgery
- use of prokinetics in the first 21 days after surgery

Additionally, the following parameters are used for grading (according to the International Study Group of Pancreatic Surgery

- comorbidities
- specific treatment
- nutritional support
- diagnostic evaluation
- interventional treatment

- prolongation of hospital stay
- delay of potential adjuvant therapy

Assessment of safety:

Adverse Events and Serious Adverse Events

14.2.3 Sample Size Calculation

This is an exploratory Phase II trial, therefore the sample size calculation will not use the usual type I and II error levels. The calculation is based on the precision of the estimate of the odds ratio characterized by the half-width of the 90% confidence interval.

In a previous retrospective trial (see also [51]) the following rates were observed of the different DGE grades in the smoker/non-smoker groups and overall:

DGE grade	No DGE	Grade A	Grade B	Grade C
Smoker (N=88)	53 (60.2%)	18 (20.5%)	7 (8.0%)	10 (11.4%)
Non-smoker (N=186)	87 (46.8%)	54 (29.0%)	30 (16.1%)	15 (8.1%)
Overall (N=274)	140 (51.1%)	72 (26.3%)	37 (13.5%)	25 (9.1%)

The analysis of the data by means of a proportional odds model with smoking status as independent variable resulted in an estimate of -0.43 (-0.92; 0.06) (on the logarithmic log-scale) with a corresponding odds ratio was 0.65.

According to the character of the endpoint a proportional odds model is planned for the primary analysis. Therefore, a prior estimate for the overall rates of the different grades is needed. These overall rates will be assumed to be the same as in the mentioned retrospective trial (own data) p=(0.5, 0.25, 0.15, 0.1). The observed parameter estimate will be applied as the desired measure of effect size precision.

Using a sample size of N=220 subjects the precisions of the estimate of the odds ratio on the log scale (characterized by the width of the 90% confidence interval) will be less than 0.42 (the calculation was done using the function posamsize of the R package Hmisc).

Due to an anticipated drop-out rate of approximately 10% overall 240 subjects should enter the trial.

14.2.4 Definition of Populations Included in the Analysis

This clinical trial will be analysed according to the intention-to-treat (ITT) principle. This means that the subjects will be analysed in the treatment arms to which they were randomised, irrespective of the occurrence of any intercurrent events (e.g. whether they refused or discontinued the treatment or whether other protocol violations are revealed).

The per-protocol (PP) population is a subset of the ITT population and is defined as the group of subjects who had no major protocol violations, received a predefined minimum dose of the treatment and underwent the examinations required for the assessment of the endpoints at relevant, predefined times i.e. representing a hypothetical population without intercurrent events and adhering to the protocol. The analysis of the PP group will be performed for the purpose of a sensitivity analysis.

14.2.5 Methods of Analysis

Statistical analysis will be performed at the Institute of Medical Biometry, Informatics and Epidemiology (IMBIE) at the University of Bonn Medical Center.

To estimate the rates of DGE grades within the defined populations during a 21 days period after surgery after 7 days treatment either with a nicotine or with placebo patch.

These rates will be given together with their respective confidence intervals by treatment group. A comparison of the treatment groups will be performed by means of a proportional odds model (accounting for the stratification factors). The main outcome of this analysis will be an estimate of the odds ratio according to the explorative character of the trial.

Additional sensitivity analyses will be performed to assess the robustness of the results: a dichotomized version of the DGE score will be investigated by means of a logistic regression model.

In both models, the influence of additional covariates like sex, age, or other comorbidities will be investigated (for the purpose of the planning of later phase trials).

Two analysis populations will be defined: intent-to-treat (ITT) and per-protocol (PP). The former includes all randomized patients whereas patients with relevant protocol deviations will be excluded from the latter. The main analysis will be performed within the ITT population.

Safety parameters and secondary endpoints will be summarized by means of descriptive statistics or by absolute and relative frequencies according to the type of the variables by treatment.

14.2.6 Interim Analysis(es)

No interim analysis is planned.

14.2.7 Protocol Violations

Protocol violations are major deviations from the procedures outlined in this document including but not limited to:

- missed evaluations
- incorrect timing of evaluations
- relevant non-compliance with investigational medicinal product, if applicable
- the intake of medications not allowed
- smoking during the IMP treatment phase
- any non-adherence to the protocol that would have an impact to the subject's rights, safety or welfare and or reliability and robustness of study data

After a subject has been enrolled, it is the investigator's responsibility to make a reasonable effort to correct any protocol violations and to continue the subject's participation in the trial, if possible.

Protocol violations do not constitute a justification for withdrawal of a subject from the trial themselves.

Protocol violations will be reported to the sponsor/sponsor delegated person during the course of the trial in the monitoring reports and the clinical study report.

All protocol violations will be listed and the impact on the evaluation of the subjects concerned will be discussed prior to statistical analysis.

14.2.8 Handling of Drop-outs, Withdrawal, and Missing Data

- Subjects dropping out of the trial after enrolment and prior to randomization will be listed including the reason of drop-out.
- Subjects dropping out of the trial after randomization will be analysed using all available data.

During the failure time analysis subjects with premature termination will be censored at the time when they leave the trial. Missing values for the analysis of the secondary endpoints will be treated as such. A sensitivity analysis will be performed by applying likelihood based methods (like logistic regression or mixed linear models).

If the drop-out rate exceeds 10%, the coordinating investigator will decide after consultation of the statistician whether the drop-outs have to be replaced or not.

More details for the replacement of missing values will be defined in the statistical analysis plan. A check of a possible treatment effect on the frequency of missing values will be done.

15 Data Collection, Handling and Record Keeping

15.1 Data Management

Data management of the study will be carried out by the Clinical Study Core Unit, Study Center Bonn (SZB) of the University Hospital Bonn. The study data is recorded and stored in a suitable, validated CDMS (Clinical Data Management System). Details on data management (procedures, responsibilities, data corrections, if any, which may be made by Data Management staff themselves, etc.) will be described in a **data management plan** prior to the trial. During the trial, the performance of data management and any deviations from the data management plan will be documented in a data management report. Queries and edit checks will be specified in a **data validation plan**. Before any data entry is performed, the trial database will be validated and the technical specifications of the database will be documented in a variable-plan.

The study data is entered into the electronic Case Report Form (eCRF) directly at the site by trained staff. The eCRF-System “MARVIN” from xclinical will be used in this clinical trial. Access and user rights are defined by predetermined roles. A GCP-compliant audit trail is kept to track changes. In general, queries are programmed in the CDMS itself to be generated, and displayed to the study team member and answered in the system. The data management personnel systematically monitors the correctness and completeness of the data input. In addition, in case the monitoring requires more complex queries or checks, which cannot be programmed in the DSMS, external CDMS programs created with the SAS software can be used.

15.2 Data Coding

The following clinical data are to be recorded using a standardized coding system:

- The description of AEs with MedDRA

The versions of the coding systems to be used are defined in the Data Management Plan.

15.3 Documentation of Trial Data

15.3.1 Documentation of Trial Data in the Medical Record

The investigator will record the participation in the trial, the frequency of the trial visits, the relevant medical data, the concomitant treatment and the occurrence of adverse events in the medical record of each subject.

Data collected on the CRFs must match the source data. These may include but are not limited to the hospitals' medical files, laboratory and pharmacy records, diaries etc. A site-specific source data location list will be filed in every ISF.

In some cases, the CRF, or part of the CRF, may also serve as source document. In these cases, a document should be available at the investigator's site that clearly identifies those data that will be recorded directly in the CRF, and for which the CRF will stand as the source document.

15.3.2 Case Report Form (CRF)

The (principle) investigator has ultimate responsibility for the accuracy, authenticity, timely collection and reporting of all data entered in the CRFs. All data may only be entered into the CRF by authorized trial personnel as promptly as possible.

In this clinical trial the eCRF-System "MARVIN" from xclinical will be used. The eCRF-System is fully validated and fulfills the requirements of GCP for computerized systems.

All data collected during the trial will be documented electronically on the trial-specific eCRF pages by the responsible investigator, or an individual who is designated by the investigator, as timely as possible. Entry and corrections on eCRF pages are automatically documented via "audit trail" created by the program. The investigator signs completed data electronically in due time.

The Study Monitor is responsible to verify the eCRF at regular intervals throughout the trial to verify the adherence to the protocol, completeness, accuracy, and consistency of the data. Therefore, the Study Monitor should have access to subject medical records and other trial-related records needed to verify the entries on the eCRF.

The investigator agrees to cooperate with the Study Monitor to ensure that any problems detected in the course of the monitoring visits, including delays in completing eCRF are resolved.

A clinical data management review will be performed on subject data entered in the eCRF database.

A separate eCRF-Manual is available to support the data entry.

15.4 Investigator Site File

The trial site will be provided with a Clinical Trial Master File (Investigator Site File (ISF)) containing all sponsor-specific essential and trial specific documents. The monitor will regularly check the ISF for accuracy and completeness. The trial site file has to be stored locked and sure. After end of trial or early termination of the trial the ISF should be retained for 25 years at the site.

The ISF includes the subject identification list, where the investigator has to record the trial participation of each subject. This list allows identification of each subject and contains the subject number, the name, telephone number (if applicable), birth date and the date of inclusion of the subject into the trial, and will be reviewed by the monitor for completeness. After end of the trial the subject identification list remains with the

subject site, no copies will be provided to the sponsor nor monitor. In addition, trial participation of the subject should be recorded in the subject chart (trial drug, screening/randomization number, start and end date of the trial).

The investigator will maintain a list of appropriately qualified persons to whom he/she has delegated trial duties. This list will be filed with the ISF, too.

Furthermore, trial personnel responsible for documentation in the CRFs should be identifiable. Therefore, a signature list with the name, signature, initials/abbreviation and trial responsibilities of all persons who are allowed to make entries into the CRF will be filed in the ISF.

Trial documents provided by the sponsor/ Study Coordinating Center of the SZB are confidential and may not be made accessible to third parties not involved in the trial by the investigator or other staff members. All trial data are collected pseudonymously, where applicable.

15.5 Archiving

15.5.1 Sponsor

The sponsor must retain all essential documents inclusively the case report forms (Subject Master File) for the duration of at least 25 years after end or stop of trial. The sponsor must archive all trial related documents according to regulatory requirements.

15.5.2 Investigator

The investigator should maintain all subject documents as specified in Essential Documents for conduct of a clinical trial (see ICH-GCP, section 8) and as required by the applicable regulatory requirement(s) after completion of the clinical trial so that they will be available for audits and inspections by the authorities. The investigator will be responsible for the storage.

The following retention periods will apply after completion or stop of the clinical trial:

- all essential documents and trial related data must be retained securely for at least 25 years (CTR Art. 58),
- medical records of subjects and other source documents shall be archived in accordance with national law.

The investigator/institution should take arrangements to prevent accidental or premature destruction and illegitimate access to these documents.

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e. g. CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, drug accountability and adequate documentation of relevant correspondence (e. g. letters, meeting minutes, telephone calls reports).

The trial site will maintain a file of essential subject documentation (Trial site File). It is the responsibility of the site to retain copies of all completed CRFs for the subject and their trial file on site.

16 Definition of End of Trial

16.1 Regular End of the Trial

The regular end of trial is defined as **Data Base Lock**.

This allows an appropriate time window for preparation of a publication of study results in a scientific paper prior to publication of the summary of study results in the European Clinical Trial Database.

16.2 Termination of the Trial for Individual Subjects

If the clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the subject subjects and ensure appropriate therapy and follow-up for the subjects.
Where required by the applicable regulatory requirements, the competent authority(ies) and the ethics committee(s) will also be informed (this is usually done by the sponsor).

Details of the criteria for premature termination can be found below.

16.2.1 Termination by the Subject

Subjects may withdraw from the trial at any time at their own request without stating the reason(s) for withdrawal. They will experience no disadvantage as a result of this decision and no alternative therapy will be withheld by the investigator.

In this case the investigator is urged to ask the subject to return for an early termination visit and to document information as much as possible in the CRF.

16.2.2 Termination by the Investigator

Subjects may also be withdrawn at any time at the discretion of the investigator for safety, behavioral, or administrative reasons, e.g.:

- Occurrence of intolerable adverse events and which would constitute an unacceptable high risk for the subject
- Lack of efficacy
- Medically indicated e.g. because it is found that inclusion/ exclusion criteria were violated
- Continuation is unacceptable because risks outweigh the benefits
- Pregnancy
- Lack of compliance of the subject (e.g. taking prohibited medication)
- Significant protocol violations
- Logistical reasons (e.g. subject changes his/her doctor or hospital or moves to another location)

16.2.3 Procedures for Withdrawal of Subjects

Whenever a subject is withdrawn from the trial, the circumstances of the withdrawal or discontinuation have to be recorded in detail in the CRF and a complete final examination as scheduled for the termination visit should be conducted.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject.

In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal. The subject has to be requested to return all unused investigational product(s), if applicable, and followed-up regarding any unresolved adverse events.

16.3 Termination of the Entire Trial

The Sponsor Delegated Person/ Coordinating Investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of a treatment arm or the entire clinical trial.

The Sponsor Delegated Person/ Coordinating Investigator will be supported in this responsibility by a data monitoring safety board, if necessary.

The entire clinical trial must be terminated prematurely if:

- new information on the risk-to-benefit ratio of the IMPs or on the treatment methods used in the trial become available, making the use of the IMP unfavorable even in a controlled situation,
- the Sponsor Delegated Person/ Coordinating Investigator notices and agrees upon that patient recruitment is insufficient and that this cannot be expedited by appropriate measures,
- the Sponsor Delegated Person/ Coordinating Investigator notices that the conduction of the trial is not compliant with ICH-GCP and / or is not according to the protocol, the patient recruitment and / or the quality of the data is insufficient.

The reasons for such a decision should be documented in written form.

16.4 Termination of the Trial in Individual Sites

Both the investigator and the Sponsor Delegated Person/ Coordinating Investigator have the right to terminate the trial at one of the centers at any time for instances:

- Unforeseeable circumstances have arisen at the trial center concerned what preclude the continuation of the clinical trial.
- The investigator considers that the resources for continuation are no longer available.
- The investigator considers that the continuation of the trial is no longer ethically or medically justifiable.
- Subject recruitment is inadequate.
- Serious problems arise with regard to the quality of the collected data which cannot be resolved.
- Withdrawal of the opinion of the EC and/or regulatory authority.

Premature termination at one of the trial centers does not automatically mean a termination of already enrolled trail subjects. A separate decision on further treatment must be made for each subject, depending on the overall situation. So, it has to be clarified that:

- An adequate further treatment and follow-up of already enrolled subject subjects must be ensured.

- The documentation of already enrolled subject subjects will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the centre is closed. These queries must be answered properly by the centre.
- The competent authority(ies) and ethics committee(s) must be duly notified of the centre's closure, including reasons, within the specified period(s).
- The trial site concerned will be closed in stages by the Study Monitor when a decision has been made on the further treatment of the subjects concerned.

16.5 Further treatment after termination of the clinical trial

Not applicable.

17 Quality Management

During the clinical trial, quality control and quality assurance will be endured through monitoring and auditing. Furthermore, inspections by authorities may take place.

17.1 Risk Assessment

17.2 Monitoring

To ensure accurate, complete, consistent, and reliable data, the investigator's site(s) and trial procedures will be monitored by a representative of the sponsor (Study Monitor). The Study Monitor will visit the site:

- to evaluate the progress and recruitment of the trial,
- to review the source documents and CRFs for protocol compliance, accuracy and validation,
- to assess facilities and equipment,
- to check for protocol compliance,
- to assure the AE/SAE reporting,
- to verify proper handling and dispensing of the IMP(s), and other factors.

Frequency and scope of the monitoring visits will be defined in the **Monitoring Plan** for this trial, which also includes the extent of source data verification that is required.

The investigator agrees to cooperate with the Study Monitor to ensure that any problems detected in the course of these monitoring visits are addressed and resolved, and therefore ensures the accuracy and consistency of the trial with GCP and all applicable laws. The investigator allows the monitor to have access to all trial related original data and documents relevant for the monitoring of the trial.

17.3 Source Data Verification (SDV)

Source data verification will be performed in order to verify the accuracy and completeness of the entries on the case report form (CRF) by comparing them with the source data, and to ensure and increase the quality

of the data. All data, which are subject to SDV must have been entered in the medical record or, in the case of source documents, enclosed with the medical record. The investigators will afford the Study Monitor access to the medical records for the performance of SDV. The extent of SDV will follow a risk-based approach and will be laid down in the Monitoring Plan.

Source data as defined by ICH-GCP include data such as hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. Source data and corresponding source documents will be documented for each clinical trial site on a Source Data Identification List.

17.4 Audits and Inspections

In accordance with ICH GCP this trial may be selected for audit by representatives of the sponsor, for inspection by site responsible representatives of the local regulatory authority or competent authority.

The investigator and institution involved in the clinical trial permit clinical trial-related monitoring, audits and regulatory inspections, including provision of direct access to source data and documents and agree to support the sponsor to solve possible audit or inspection findings concerning the trial conduct at the respective site.

After every audit the auditee(s) will receive an audit confirmation by the auditor. This document has to be filed together with the trial documentation and has to be made available also to the authorities in case of an inspection.

At the end of the trial, a copy of the audit certificate(s) will be included in the final report.

18 Regulatory Aspects and Good Clinical Practice

The trial will be conducted in compliance with the protocol, the Regulation (EU) No 536/2014, Regulation (EU) 2016/679 (GDPR) and with the principles of good clinical practice (GCP).

18.1 Responsibilities of the Sponsor

According to CTR and German Medicinal Products Act (AMG §§ 40 – 42) the sponsor is responsible for obtaining approval from the competent authority and the responsible ethics committee before initiation of the trial.

18.2 Responsibilities of the Investigator

By signing this protocol the local investigator declares his/her commitment:

- to not enroll any person dependent on him/her or the sponsor in accordance with the principles of ICH-GCP
- to follow the applicable regulations for data privacy and security according to CTR and GDPR
- to inform the subjects of the transmission of their pseudonymized data according to documentation and transmission obligations (CTR Article 56) and to make sure that subjects unwilling to give consent to the processing of their data are not included into the trial

- to certify that he/she is familiar with the appropriate use of the IMP, as described in this protocol, the current Investigator´s Brochure and Summary of Product Information, if applicable
- to be qualified by education, training and experience to assume responsibility for the proper conduct of the subject
- to be thoroughly familiar with the appropriate use of the trial drug(s), as described in the protocol, the product information and other information sources provided by the sponsor
- to be aware of, and comply with GCP and the applicable regulatory requirements
- to maintain a list of appropriately qualified persons to whom the investigator has delegated significant subject related duties (if applicable).

18.3 Ethics Committee and Competent Authority

The clinical trial protocol and amendments have to be approved by the Competent Authority (CA), in addition to protocol and amendments the subject information and informed consent, and any other written information to be provided to the trial subjects have to be approved by the responsible ethics committee (“zuständige Ethikkommision”).

The Sponsor Delegated Person will authorize the Study Coordinating Center of the SZB with submitting respective documents to the responsible ethics commitee (EC) and to the NCA via the EU portal CTIS.

Any substantial amendments to the protocol or subsequent changes to the informed consent form as a result of changes to the protocol must also be submitted to the EC/NCA via CTIS. Records of the regulatory review, communication and opinion of all documents pertaining to this trial must be kept on file by the investigator and are subject to regulatory authority and / or sponsor inspection during or after completion of the trial.

The Study Coordinating Center of the SZB will provide a safety update of the trial to the EC(s)/NCA, including line listing, individual reports of SUSARs, if applicable, annually or more frequently if requested. Furthermore, SZB will perform applicable notifications in CTIS such as start of recruitment, start of trial.

At the end of the trial, the Study Coordinating Center of the SZB will notify the EC(s)/NCA via CTIS about the trial completion. A copy of all reports submitted to the EC will be provided to the sponsor.

18.4 Compliance with the Protocol

The investigator should conduct the clinical trial in compliance with this protocol. For this purpose, the document will be signed by the Sponsor Delegated Person/Coordinating Investigator and the Principal Investigator of each participating trial site. As a general rule, the investigator should not deviate from the protocol or make amendments to the protocol without the agreement of the sponsor/ competent authority/ethics committee (unless subject safety is at risk, see below).

Any deviations from the approved protocol should be documented and explained by the investigator or an individual who is designated by the investigator.

The investigator may deviate from the protocol or make an amendment to the protocol without prior approval of the ethics committee to eliminate immediate risks to the subject subjects. The deviation or amendment should subsequently be reported to the ethics committee, the sponsor or sponsor delegated person and, if necessary, the competent authority, giving reasons.

18.5 Serious Breach

Protocol violations that constitute a serious breach according to Art. 52 CTR will be reported to the competent authority and responsible ethics committee no later than 7 days after becoming aware of that breach.

Deviations from this clinical study protocol or CTR may constitute a serious breach if they are likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial (Art. 52 CTR). The sponsor shall notify the Member States concerned about a serious breach at the time of the breach through the EU portal without undue delay but not later than seven days of becoming aware of that breach.

Default definition and management of protocol violations are described in a Standard Operation Procedure of the SZB. The following deviations should in any case be considered a serious breach:

- fraud
- documented informed consent not available
- clinical trial conduct without available regulatory authorization
- systematic or significant mis-dosing
- lack of SUSAR reporting that results in trial participants being put at a significant degree of risk
- deviations that lead to removal of data from the trial analysis
- severe violation of data privacy rules

Serious breaches will be reported to the Sponsor Delegated Person/ Coordinating Investigator during the course of the trial via the monitoring reports and additionally via:

E-Mail: **Serious-breaches@ukbonn.de**

Telephone: **+49 (0)228-287 16849**

18.6 Notification of Modifications to the Protocol

The sponsor can make general amendments to the protocol after the clinical trial has started. These may be of an administrative nature (logistical/administrative amendments) or substantial.

Substantial Amendments are changes that likely affect and /or change:

- the safety of the persons concerned,
- the interpretation of the scientific trial documents or the scientific informational value of the trial results,
- the nature of management or conduct of the clinical trial (e.g. change of principal investigator, sponsor or sponsor's deputy),
- the pharmaceutical quality or safety of the investigational medicinal products
- the risk assessments concerning the health of persons who are not concerned, or the environment, in clinical trial with drugs consisting of or containing genetically modified organisms

require an new authorization of the NCA and a new favourable opinion by the responsible ethics committee.

The clinical trial may only be continued after authorization for the substantial modification has been obtained from the responsible ethics committee and the NCA.

If applicable, an updated Informed Consent Form has to be signed by all subjects enrolled in the trial who are affected by the amendment.

If administrative protocol changes (e.g. change of monitoring, telephone numbers) are necessary, the EC and NCA will be notified via CTIS only.

18.7 Notification of the end of the trial

According to Art. 37 CTR, the ECs and NCAs of all member states concerned will be notified via CTIS about the end of the clinical trial. The notification will be done by the SZB on behalf of the sponsor.

Within one year after the end of the complete trial a summary of the trial report will be provided to the NCA(s) and EC(s) via CTIS. This includes a summary that is understandable to laypersons and which fulfills the requirements of Annex V CTR.

18.8 Subject Insurance

Every subject participating in the trial is insured against any trial-related illness/injuries pursuant to the legal requirements which may occur during the trial, in Germany according to § 40a Nr.3 AMG.

Excluded from this, however, are injuries to health and deterioration of illnesses already in existence, which would have continued to exist even if the subject had not taken part in the clinical trial.

The investigator will inform the subject of the existence of the insurance, including the obligations arising from it. The subject subjects must be afford access to insurance documents and provided with a copy of the general conditions of insurance on request.

The insurance cover is jeopardized if the subject fails to immediately report to the investigator or responsible physician any injury to health which might have resulted from the participation in the clinical trial, or if she/he undergoes any other medical treatment (except for emergency treatment) without the investigator's knowledge before her/his participation in the clinical trial has officially ended.

In case of any health impairment the subject, subject's parents (if applicable), or legally authorized representative is obliged to notify the insurance and additionally the investigator as soon as possible. The investigator is obliged to make a report to the sponsor.

The subject insurance will be arranged by the Sponsor Delegated Person/Coordinating Investigator. The insurer will be:

Name of Insurer:	HDI Global SE
Insurance Number:	57 010323 03010/09022023102
Address:	Riethorst 2 30659 Hannover
Represented by:	Niederlassung Düsseldorf Am Schönenkamp 45, 40599 Düsseldorf
Insurance Broker:	Ecclesia mildenberger HOSPITAL GmbH Ecclesiastraße 1-4, 32758 Detmold

Phone:	+49 (0)5231 / 603-6239
Fax:	+49 (0)5231 / 603-606239

This insurance covers trial related injuries to health up to a maximum of 500.000 Euro per subject and 50 Mio Euros for the entire trial.

18.9 Data Protection and Subject Confidentality

The pertinent provisions of the country-specific legislation on data protection must be fully complied with.

The collection, transmission, archiving and evaluation of personal data in this clinical trial are performed according to local applicable laws (Data Protection Act, General Data Protection Regulation). Prior to trial participation each subject must be informed by the investigator about the purpose and extent of the collection and use of personal data, particularly medical data and must give written informed consent.

The subjects must be informed that:

a. Any subject related data in this trial are handled confidentially and will be captured in pseudonymized form (subject ID number for the trial – subject number-, year of birth) and will only be transmitted to
    i. the coordinating investigator/sponsor/sponsor delegated person/data monitoring safety board for scientific and adverse event evaluation
    ii. the competent authority (in Germany: BfArM), the responsible EC and the European Clinical Trial Information System (CTIS) for verifying the proper conduct of the trial and for assessment of trial results and adverse events

2. During monitoring, audits or inspections representatives of the sponsor (monitor, auditor) or of the local regulatory authority(ies) must have direct access to personal data. In this case, the investigator is released from confidential medical communication.

3. Consent to the collection and processing of personal data within the scope of this clinical trial can be revoked at any time. A subject is informed that he/she can terminate his/her participation in the clinical trial at any time - without giving reasons and without any of the following disadvantages. In the event of revocation of the declaration of consent, the data stored up to this point in time will continue to be used without mentioning names, insofar as this is necessary to determine the effects of the medicinal product under investigation and to ensure that the interests of the person concerned which are worthy of protection are not impaired, or to comply with the obligation to submit complete approval documents.

18.10 Data security breach

Data security breaches are handled as serious breaches (refer to 18.5).

18.11 Data Sharing Statement

Individual participant data will not be available (including data dictionaries).

The following documents will be made available: Study Protocol, Statistical Analysis Plan, Master-Informed Consent Form, Clinical Study Report.

The data will be shared beginning 6 months following publication and ending 36 months following article publication.

The data will be shared with anyone who wishes to access the data/ researchers who provide a methodologically sound proposal/ investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose.

Proposals should be directed to tim.glowka@ukbonn.de. To gain access, data requestors will need to sign a data access agreement. Proposals may be submitted up to 36 months following article publication

18.12 Financing of the Trial

The present trial is an investigator initiated subject (IIT). The trial is financially sponsored by the BMBF.

18.12.1 Trial Agreement / Investigator Compensation

According to ICH-GCP 4.9.6, a trial agreement on the conduct of the clinical trial and the compensation for conducting the subject will be signed between the sponsor (donor) of the clinical trial and the investigators including their heads of administration (donee). A compensation will be paid for each fully documented, completed case.

18.12.2 Reimbursement of Subjects

Subject will not be compensated.

19 Trial Reports

19.1 Interim Report

Not applicable.

19.2 Final Report

After completion of the statistical analysis by the responsible biostatistician, the final summary of study results will be prepared by the Sponsor Delegated Person/ Coordinating Investigator. This summary of study results will be signed jointly by the Sponsor Delegated Person and the biostatistician.

The Summary for Laypersons will be written by the responsible Project Manager of the SZB.

Except when required by law, no one will disclose a result of the clinical trial to third parties unless all parties involved have first agreed on the results of the analysis and their interpretation.

20 Publication Policy

The results of the trial will be published by the Coordinating Investigator under participation of all institutions taking part. The manuscript will be provided to every co-author before publication. The publication of partial results after the main publication is possible depending on the approval of the protocol committee.

To maintain the scientific integrity of the subject, data will not be released prior to the end of the subject, either for subject publication or oral presentation purposes, without the permission of the Coordinating Investigator or the protocol committee.

Data of the trial will be registered in a public data base (e. g. www.drks.de). The results of the trial shall be published. Publication or lecture of data needs a previous annotation and approval of the Coordinating Investigator. All subject related data need to be published in a pseudonymous form.

The right of publication rests primarily with the sponsor, the coordinating investigator and the other investigators involved. All data collected in connection with the clinical trial will be treated in confidence by the sponsor/coordinating investigator and all others involved in the trial, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the sponsor (Dean of the Medical Faculty, Bonn), the coordinating investigator and the other investigators. This is indispensable for a full exchange of information between the above-named parties, which will ensure that the opinions of all parties involved have been heard before publication. The agreement, which does not include any veto right or right of censorship for any of the parties involved, may not be refused without good reason.

Specific regulations concerning the publication policy in the applicable contracts will precede this trial protocol in any case.

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