Evaluation of the Role of Proton Pump Inhibitors on the Postoperative Course Following Pancreaticoduodenectomy

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Study Drug(s): Proton pump inhibitor
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Protocol Revision History

Initial Approval Version	**06 January 2022**
Amendment #1	**13 September 2022**
Amendment #2	**04 May 2023**
Amendment #2.1	**12 June 2023**
Amendment #2.2	**21 July 2023**
Amendment #3	**25 September 2023**

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

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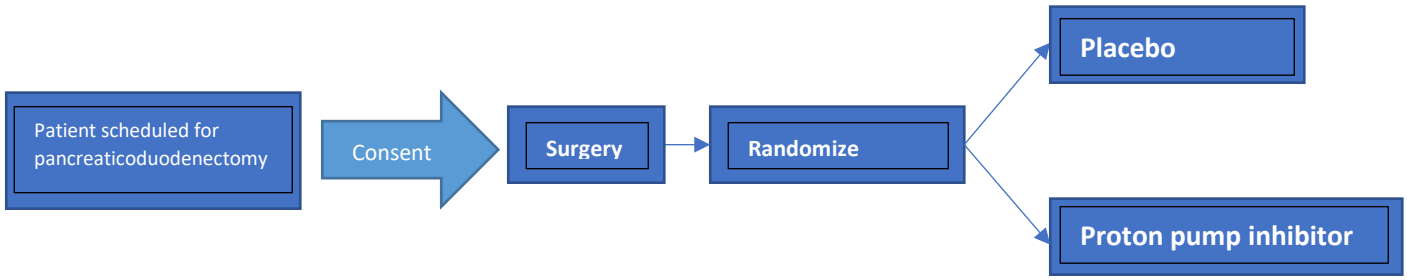
PROTOCOL SUMMARY

Title:	Evaluation of the Role of Proton Pump Inhibitors on the Postoperative Course Following Pancreaticoduodenectomy
Study Description:	This is a randomized placebo-controlled study of patients who will undergo pancreaticoduodenectomy at Washington University in St. Louis/Barnes-Jewish Hospital. The study aims to determine the impact of administration of Proton Pump Inhibitors (PPIs) on the postoperative course in these patients. Postoperative administration of PPI and no intervention are both considered standard of care approaches.
Objectives:	Primary Objective: Determine the effect of PPIs on the incidence of delayed gastric emptying within 90 days in patients after pancreaticoduodenectomy. Secondary Objectives: • Determine the effect of PPIs on the incidence of overall postoperative complications in the patients after pancreaticoduodenectomy. • Determine the marginal ulcer-free survival (MUFS) within 90 days after surgery in the patients undergoing pancreaticoduodenectomy.
Endpoints:	Primary Endpoint: Incidence of delayed gastric emptying using the ISGPS criteria and MAGS grading. Secondary Endpoints: • Incidence of surgical complication defined by the Modified Accordion Grading System. • MUFS.
Study Population:	Two hundred forty patients who will undergo standard of care pancreaticoduodenectomy and receive at least one dose of study treatment (PPI/placebo) at Washington University/Barnes-Jewish Hospital
Phase:	II
Description of Sites / Facilities Enrolling:	This study will take place at Washington University School of Medicine and associated hospitals/clinics.
Description of Study Intervention:	Immediately post-op, patients will be randomly assigned to one of the two standard of care approaches ("PPI" or "placebo") on a 1:1 basis in a blinded fashion. Patients will be initiated on pantoprazole or a visually equivalent placebo once daily from Postoperative Day 1 and continued for 10 doses or until the day of discharge (whichever is earlier).
Study Duration:	39 months
Participant Duration:	90 days

SCHEMA


Patient scheduled for pancreaticoduodenectomy
Consent
Surgery
Randomize
Placebo
Proton pump inhibitor

SCHEDULE OF ASSESSMENTS

Measure	Baseline[2]	Pre-op Visit[3]	Day of Surgery	Post-op Visit[4]	90 Days Post-Op
Confirmation of surgical plan	X				
Patient consent		X[5]			
Medical history		X			
Randomization			X[6]		
Demographics captured from EMR[1]		X			
Drug/placebo administration			X[7]		
Notes from surgery related hospitalization captured from EMR				X	
Information on surgical complications captured from EMR/HPB Whipple Database					X
Adverse event assessment		Continuous through 30 days after last day of PPI/placebo			X[8]

1. Patient characteristics will include gender, age, weight, BMI, surgery indication, staging, etc.
2. ≤ 30 days prior to surgery
3. ≤ 30 days prior to surgery at routine pre-surgery clinic visit
4. 2 (±1) weeks after surgery at routine post-surgery clinic visit
5. Consent may occur at the pre-op visit or on the day of surgery
6. Randomization will occur immediately post-op only for patients who successfully undergo pancreaticoduodenectomy
7. PPI/placebo will be given taken once daily for 10 days or until day of discharge (whichever is earlier)
8. Follow through 90 days for post op surgical complications

1.0 BACKGROUND

Proton Pump Inhibitors (PPIs) are widely recommended for common upper gastrointestinal acid-related disorders such as gastroesophageal reflux disease, peptic ulcer disease, *Helicobacter Pylori* Infection, and functional dyspepsia (1, 2). They are also frequently used in critically ill patients to avoid the development of stress ulcers and related upper gastrointestinal bleeding (3, 4). Studies estimate that between 53% and 69% of all PPI prescriptions are for inappropriate indications such as nonspecific abdominal symptoms without acid-related features; co-prescription with aspirin, NSAIDs, or corticosteroids in asymptomatic patients; and repeat prescription for a prior problem that has already resolved (5-7).

Moreover, PPIs are frequently initiated in the inpatient setting in non-ICU patients who are at very low risk of developing stress ulcers. In many cases, they are continued beyond discharge in primary care (8, 9). However, their strong efficacy has resulted in their overutilization in both outpatient and inpatient care, which can cause serious adverse events, including cardiovascular disease, pneumonia, osteoporotic fractures, acute kidney injury, chronic kidney disease, and dementia (4, 10-13). PPIs are also associated with an excess of mortality from cardiovascular disease and chronic kidney disease. These adverse effects highlight the need for judicious use of PPIs, which can be achieved by avoiding prescription of these agents for undocumented and unsubstantiated diagnoses, discouraging prolonged therapy, and adhering to step-down therapy per guidelines (14-17). In addition, PPI use in the inpatient setting should be limited to documented upper gastrointestinal tract indications and stress ulcer prophylaxis in the ICU population, and these medications should be discontinued before discharge unless indicated (17).

According to a meta-analysis performed by Butler et al., PPIs are frequently used in patients undergoing pancreaticoduodenectomy, with 86% of surgeons prescribing them after pancreatic resection. Forty-six percent of surgeons continue their patients on these medications for life, while 25% give the prescriptions for 30 days postoperatively (18). The main indication for their use is to reduce the occurrence of postoperative marginal ulcers, a morbid complication of pancreaticoduodenectomy with a reported average incidence of 2.0% after pylorus-preserving pancreaticoduodenectomy and 2.6% after classic pancreaticoduodenectomy (18). However, the onset of marginal ulcers is often delayed, with the median time for development of marginal ulceration after pancreaticoduodenectomy being 15.5 months (18, 19).

PPIs have been effective in decreasing the incidence of postoperative marginal ulcers. The development of marginal ulcers is driven by two mechanisms:

1. Local inflammation, ischemic changes at the anastomotic site, foreign bodies (sutures, staples), which is the primary mechanism in the immediate postoperative period, and
2. The direct effect of gastric acid on jejunal mucosa which is the primary mechanism in later periods (19).

Increased gastric acid production, low gastric pH, and prolonged duration of low pH are associated with marginal ulcers (20). However, the recommendations regarding the timing and duration of their use after pancreaticoduodenectomy remain unclear and need to be defined.

In our recently completed retrospective chart review **(IRB ID: 201711053),** we evaluated the

impact of gastric acid inhibitors (PPIs and H2Receptor antagonists) on postoperative outcomes following pancreatic resection i.e., pancreaticoduodenectomy, distal pancreatectomy, and completion pancreatectomy. H2Receptor antagonists are associated with postoperative delirium and, therefore, are not frequently used (21). In our study cohort, 66.5% of patients were administered gastric acid inhibitors postoperatively, with the majority of these patients (76.4%) receiving PPIs. Comparative analysis of postoperative complications in patients who received acid suppression and those who did not showed a significantly higher incidence of all complications (73.8 % vs 56.4%) (p=0.003), delayed gastric emptying (20.9% vs 6.4%) (p=0.002), postoperative hemorrhage (23% vs 8.5%) (p=0.003), failure to thrive (4.3% vs 0%) (p=0.042), and all infectious complications (23.5% vs 11.7%) (p=0.018) in the acid suppression group. Multivariate logistic regression analysis demonstrated a significant association between the use of gastric acid inhibitors and the incidence of all postoperative complications (Odds Ratio=2.176), including delayed gastric emptying (Odds Ratio=3.7148) in the patients undergoing pancreatic resection. Our analysis also showed a significant association between the use of these agents and postoperative complications (Odds Ratio=2.469) and delayed gastric emptying (Odds Ratio=2.355) in patients that underwent pancreaticoduodenectomy.

Our results highlight the need for promoting pharmacovigilance when it comes to prescribing gastric acid inhibitors after pancreatectomies. Utilizing PPIs in the immediate postoperative period as prophylaxis against marginal ulcers that generally occur months after surgery at the cost of an increase in postoperative complications such as delayed gastric emptying is not in the patient's best interest, and therefore, should be avoided. The purpose of this study is to prospectively determine the effects of administering PPIs following pancreaticoduodenectomy on postoperative outcomes. The findings of this study will help in avoiding the widespread use of PPIs during the immediate postoperative period following pancreatic surgery.

2.0 OBJECTIVES

This is a randomized placebo-controlled study of patients who will undergo pancreaticoduodenectomy at Washington University in St. Louis/Barnes-Jewish Hospital. The study aims to determine the impact of administration of PPIs on the postoperative course in these patients.

Objectives	**Endpoints**	**Justification for Endpoints**
Primary		
Determine the effect of PPIs on the incidence of delayed gastric emptying within 90 days in patients after pancreaticoduodenectomy.	Incidence of delayed gastric emptying using the ISGPS criteria and MAGS grading.	International criteria for diagnosis and grading of the delayed gastric emptying. Incidence in the two groups will indicate the effect of PPI.

Secondary		
• Determine the effect of PPIs on the incidence of overall postoperative complications in the patients after pancreaticoduodenectomy. • Determine the marginal ulcer-free survival (MUFS) within 90 days in the patients undergoing pancreaticoduodenectomy.	• Incidence of surgical complication defined by MAGS Grading Criteria • MUFS	Complications graded by MAGS. Grade 1-6 will be tabulated across the two groups to evaluate any differences from PPI use. Treatment/Diagnosis of marginal ulcers.

3.0 ELIGIBILITY CRITERIA

1. All consecutive patients who will undergo pancreaticoduodenectomy with gastric/biliary reconstruction performed as definitive management for a benign or malignant disease at Washington University/Barnes-Jewish Hospital.

2. At least 18 years of age.

3. Ability to understand and willingness to sign an IRB approved written informed consent document.

3.1 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4.0 REGISTRATION PROCEDURES

Patients must not start any protocol intervention prior to registration through the Siteman Cancer Center.

The following steps must be taken before registering patients to this study:

1. Confirmation of patient eligibility
2. Registration of patient in the Siteman Cancer Center database
3. Assignment of unique patient number (UPN)

4.1 Confirmation of Patient Eligibility

Confirm patient eligibility by collecting the information listed below

1. The registering MD's name

2. Patient's race, sex, and DOB
3. Three letters (or two letters and a dash) for the patient's initials
4. Copy of signed consent form
5. Completed eligibility checklist, signed and dated by a member of the study team
6. Copy of appropriate source documentation confirming patient eligibility

4.2 Patient Registration in the Siteman Cancer Center OnCore Database

All patients must be registered through the Siteman Cancer Center OnCore database.

4.3 Assignment of UPN

Each patient will be identified with a unique patient number (UPN) for this study. All data will be recorded with this identification number on the appropriate CRFs.

4.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomized to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (if applicable).

4.5 Measures to Minimize Bias: Randomization and Blinding

Randomization will occur in the research pharmacy using a computer-generated randomization sequence. Consenting patients will be randomly assigned to receive pantoprazole or an identical appearing placebo in a 1:1 ratio. Medications will be prepared by the pharmacy and delivered to the treating nurse. The research team and the study participants will be blinded to treatment assignment.

Post-operative oral doses will be dispensed in identical capsules; active capsules will contain an over-encapsulated pantoprazole 40 mg delayed-release tablet with lactose monohydrate backfill and placebo capsules will contain lactose monohydrate to give equal weight and feel.

The research pharmacy will maintain documentation of medication procurement and preparation, as well as randomization, dispensing, and accountability logs. All medications and blinding supplies will be stored in a secure location within the research pharmacy and maintained under controlled environmental conditions.

5.0 STUDY PROCEDURES

We have set our criteria to review any pancreaticoduodenectomies with gastric/biliary reconstruction performed as definitive management for a benign or malignant disease in the Department of Surgery at Washington University/ Barnes Jewish Hospital.

Written consent will be obtained from the patients at their preoperative visit or at time of admission to BJH for pancreaticoduodenectomy. Patients may have their surgery postponed for up to 6 months and will be given the option to continue participation in the study. Subjects that decide to continue to participate will continue to be eligible for participation.

Immediately post-op, the patients will be randomly assigned to the "PPI" or "placebo" groups in a 1:1 ratio as described in Section 4.5. The patients will be initiated on pantoprazole or a visually equivalent placebo once daily from Postoperative Day 1 and continued for 10 doses or until the day of discharge (whichever is earlier). Other postoperative management will be performed as per institutional standard of care.

Any patient who appears to require administration of a PPI secondary to a postoperative indication, i.e. stress ulcer prophylaxis in ICU, gastrointestinal bleeding, will discontinue trial treatment and initiated on the indicated PPI. These participants will not be unblinded, nor will they be replaced.

The patients will be followed as per standard of care to record incidence of any postoperative complications, including marginal ulcers. There are no follow-up visits mandated by participation in this protocol. Patients' medical records will be reviewed to collect information about complications for 90 days post-op. The division's Whipple database will also be used to collect information regarding post-operative complications.

5.1 Definitions of Evaluability and Patient Replacement

Endpoint	**In order to be evaluable for this endpoint, a patient must have…**
Primary: Incidence of delayed gastric emptying using the ISGPS criteria and MAGS grading	Received at least one dose of study treatment (PPI/placebo)
Secondary: Incidence of surgical complication defined by MAGS grading criteria	
Secondary: Marginal ulcer-free survival	

Note: Patients who do not receive at least one dose of study treatment (PPI/placebo) are inevaluable for the primary endpoint and will be replaced. Patients who receive a PPI secondary to a postoperative indication will **not** be replaced.

5.2 Concomitant Therapy and Supportive Care Guidelines

Use of any investigational agent or device within 30 days before the first dose of study

drug and until last dose of study drug.

All other concomitant medications that are necessary for the health and well-being of the patient that are not specifically prohibited by the protocol are permitted.

5.3 Duration of Follow-up

Patients will be passively followed by review of the medical record for 90 days after surgery or until death, whichever occurs first.

6.0 REGULATORY AND REPORTING REQUIREMENTS

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below. Please refer to Appendix A for definitions and Appendix B for a grid of reporting timelines.

Adverse events will be tracked from start of treatment through 30 days after discontinuation of PPI/placebo. Adverse events that have been associated with PPI inhibitors include the following: allergic reaction; blurred vision; dry mouth; flushed, dry skin; fruit-like breath odor; increased hunger; increased thirst; increased urination; nausea; and stomach pain, sweating, trouble breathing, unexplained weight loss, vomiting All adverse events must be recorded on the toxicity tracking case report form (CRF) with the exception of:

- Baseline adverse events, which shall be recorded on the medical history CRF
- Adverse events that are considered surgical complications and are unrelated to treatment with PPI/placebo (followed for 90 days post op); these will be recorded on the Post-Operative Complications CRF and are not considered reportable per protocol but are collected for evaluation of the study endpoints

Refer to the data submission schedule in Section 8 for instructions on the collection of AEs in the EDC.

6.1 WU PI Reporting Requirements

6.1.1 Reporting to the Human Research Protection Office (HRPO) at Washington University

Reporting will be conducted in accordance with Washington University IRB Policies.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

6.1.2 Reporting to the Quality Assurance and Safety Monitoring Committee (QASMC) at Washington University

The PI (or designee) is required to notify the QASMC of any unanticipated problems involving risks to participants or others occurring at WU or any BJH or SLCH institution that has been reported to and acknowledged by HRPO. (Unanticipated problems reported to HRPO and withdrawn during the review process need not be reported to QASMC.)

QASMC must be notified within **10 days** of receipt of IRB acknowledgment via email to qasmc@wustl.edu. Submission to QASMC must include the myIRB form and any supporting documentation sent with the form.

7.0 PHARMACEUTICAL INFORMATION

7.1 Pantoprazole Sodium

7.1.1 Description

Pantoprazole is a proton pump inhibitor (PPI) indicated for the following:

- Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD)
- Maintenance of Healing of Erosive Esophagitis
- Pathological Hypersecretory Conditions Including Zollinger-Ellison (ZE) Syndrome

7.1.2 Clinical Pharmacology

Mechanism of Action
Pantoprazole is a PPI that suppresses the final step in gastric acid production by covalently binding to the (H, K)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H, K)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

Pharmacodynamics
Antisecretory Activity
Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) pantoprazole in healthy subjects. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once-a-day dosing for 7 days, the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies, pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was > 3 and > 4. Treatment with 40 mg of pantoprazole produced significantly greater increases in gastric pH than the 20 mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH.

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of EE in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of Pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8-week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with Pantoprazole Sodium Delayed-Release Tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials. Following short-term treatment with Pantoprazole, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density, starting after the first year of use, which appeared to plateau after 4 years. In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by PPIs. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery.

Endocrine Effects

In a clinical pharmacology study, Pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T), thyroxine (T), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone. In a 1-year study of GERD patients treated with Pantoprazole 40 mg or 20 mg, there were no changes from baseline in overall levels of T, T, and TSH.

7.1.3 Pharmacokinetics and Drug Metabolism

Pantoprazole Sodium Delayed-Release Tablets are prepared as enteric-coated tablets so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral doses from 10 mg to 80 mg. Pantoprazole does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Following oral administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

In extensive metabolizers with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C) is 2.5 mcg/mL; the time to reach the peak concentration (t) is 2.5 h, and the mean total area under the plasma concentration versus time curve (AUC) is 4.8 mcg·h/mL (range 1.4 to 13.3 mcg·h/mL).

Absorption
After administration of a single or multiple oral 40 mg doses of Pantoprazole Sodium Delayed-Release Tablets, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and C was 2.5 mcg/mL. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids.

Administration of Pantoprazole Sodium Delayed-Release Tablets with food may delay its absorption up to 2 hours or longer; however, the C and the extent of pantoprazole absorption (AUC) are not altered. Thus, Pantoprazole Sodium Delayed-Release Tablets may be taken without regard to timing of meals.

Distribution
The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Elimination
Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Excretion
After a single oral dose of C-labeled pantoprazole to healthy, normal metabolizer subjects, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Specific Populations
Geriatric Patients
Only slight to moderate increases in the AUC (43%) and C (26%) of pantoprazole were found in elderly subjects (64 to 76 years of age) after repeated oral administration, compared with younger subjects.

7.1.4 Supplier

The study will use commercial supply.

7.1.5 Dosage Form and Preparation

Pantoprazole Sodium Delayed-Release Tablets, USP are supplied as 40 mg white to off-white, oval-shaped, coated tablet, debossed with "17" on one side and are available as follows: Unit dose packages of 80 (8 x 10) NDC 68084-813-09.

7.1.6 Storage and Stability

Store Pantoprazole Sodium Delayed-Release Tablets, USP at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F).

7.1.7 Administration

Pantoprazole will be given at a dose of 40 mg once daily for up to 10 days (POD 1 through POD 10), or until discharge, whichever is earlier.

7.2 Placebo

Placebo capsules contain pharmaceutical-grade lactose monohydrate NF, a naturally occurring disaccharide of galactose bound to glucose. Lactose monohydrate is a free-flowing, dry powder that is water soluble, inert, nontoxic, and chemically stable.

8.0 DATA SUBMISSION SCHEDULE

Case report forms with appropriate source documentation will be completed according to the schedule listed in this section.

Case Report Form	Submission Schedule
Original Consent Form	Prior to registration
On-Study Form Medical History Form	Prior to starting treatment
Surgery Form Randomization Form	Time of surgery
Treatment Form	End of treatment
Post-Operative Form	Day 30 Post-Op
Post-Operative Complication Form	Day 14 Post-Op Day 30 Post-Op Day 90 Post-Op
90-Day Follow-Up Form	Day 90 Post-Op
Adverse Event Form	End of treatment Day 14 Post-Op Day 30 Post-Op Day 90 Post-Op
Toxicity Form	Start of treatment through 30 days after discontinuation of PPI/placebo

8.1 Adverse Event Collection in the Case Report Forms

All adverse events that occur beginning with start of treatment (minus exceptions defined in Section 6.0) must be captured in the Post-Operative Complication Form. Baseline AEs should be captured on the Medical History Form.

9.0 DATA AND SAFETY MONITORING

In compliance with the Washington University Institutional Data and Safety Monitoring Plan, an independent Data and Safety Monitoring Board (DSMB) will be specifically convened for this trial to review toxicity data. A DSMB will consist of no fewer than 3 members including 2 clinical investigators and a biostatistician. DSMB members must be employed by Washington University, Barnes-Jewish Hospital, or St. Louis Children's Hospital. Like investigators, DSMB members are subject to the Washington University School of Medicine policies regarding standards of conduct. Individuals invited to serve on the DSMB will disclose any potential conflicts of interest to the trial principal investigator and/or appropriate university officials, in accordance with institution policies. Potential conflicts that develop during a trial or a member's tenure on a DSMB must also be disclosed.

The DSM report for the DSMB will be prepared by the study team with assistance from the study statistician, will be reviewed by the DSMB, and will be submitted to the Washington University

Quality Assurance and Safety Monitoring Committee (QASMC). The DSMB must meet at least every six months beginning six months after accrual has opened (if at least one patient has been enrolled), no more than one month prior to the due date of the DSM report to QASMC. This report will include:

- HRPO protocol number, protocol title, Principal Investigator name, data coordinator name, regulatory coordinator name, and statistician
- Date of initial HRPO approval, date of most recent consent HRPO approval/revision, date of HRPO expiration, date of most recent QA audit, study status, and phase of study
- History of study including summary of substantive amendments; summary of accrual suspensions including start/stop dates and reason; and summary of protocol exceptions, error, or breach of confidentiality including start/stop dates and reason
- Study-wide target accrual and study-wide actual accrual
- Protocol activation date
- Average rate of accrual observed in year 1, year 2, and subsequent years
- Expected accrual end date and accrual by cohort
- Objectives of protocol with supporting data and list the number of participants who have met each objective
- Measures of efficacy
- Early stopping rules with supporting data and list the number of participants who have met the early stopping rules
- Summary of toxicities separated by cohorts
- Abstract submissions/publications
- Summary of any recent literature that may affect the safety or ethics of the study

Further DSMB responsibilities are described in the DSMB charter.

The study principal investigator and coordinator will monitor for serious toxicities on an ongoing basis. Once the principal investigator or Research Patient Coordinator becomes aware of an adverse event, the AE will be reported to the HRPO and QASMC according to institutional guidelines.

Refer to the Washington University Quality Assurance and Data Safety Monitoring Committee Policies and Procedures for full details on the responsibilities of the DSMB. This is located on the QASMC website at https://siteman.wustl.edu/research/clinical-research-resources/protocol-office-prmcqasmc/.

10.0 STATISTICAL CONSIDERATIONS

This is a randomized placebo-controlled study. Patients who will undergo pancreaticoduodenectomy at Washington University in St. Louis/Barnes-Jewish Hospital will be randomized on a 1:1 basis to receive either PPI or placebo.

10.1 Statistical Hypotheses

10.1.1 Primary Objective and Endpoint

The primary objective is to determine the effect of PPIs on the incidence of delayed gastric emptying within 90 days in patients after pancreaticoduodenectomy. The primary endpoint is the incidence of post-operative delayed gastric emptying using the ISGPS criteria and MAGS grading.

10.1.2 Secondary Objectives and Endpoints

1. Determine the effect of PPIs on the incidence of overall postoperative complications in the patients after pancreaticoduodenectomy.
2. Determine the marginal ulcer free survival (MUFS) within 90 days after surgery in the patients undergoing pancreaticoduodenectomy.

Secondary endpoints include: the incidence of surgical complication defined by the modified accordion grading system and MUFS.

10.2 Sample Size Determination

For primary endpoint, our preliminary study showed that the rates of delayed gastric emptying in the control the PPI groups are 7% and 21%, respectively. 110 patients per group achieve 80.4% power to detect a 14% difference between two groups using the two-sided Fisher's Exact test at the significance level of 5%.

For the endpoint of surgical complication, our preliminary study showed that the rates in the control the PPI groups are 56% and 74%, respectively. 120 patients per group achieve 80.0% power to detect a 18% difference between two groups using the two-sided Fisher's Exact test at the significance level of 5%.

The preliminary data show approximate 27% of randomized patients did not receive at least one dose of study treatment (PPI/placebo) and were replaced. We will randomize 330 patients in order to obtain 80% power for these two endpoints and account for possible 27% drop-out. We estimate that 12 patients per month would be eligible for the trial and the enrollment could be complete within 36 months.

10.3 Randomization

Three hundred thirty patients will be randomized on a 1:1 basis to receive either PPI or placebo. A computer-generated randomization scheme with a various block size will be used to assign patients. It is maintained centrally by the study statistician. Randomization will take place after surgery in REDCap.

10.4 Population for Analyses

10.4.1 Efficacy Analyses Set

The Intent-to-Treat (ITT) population will consist of all randomized patients.

10.4.2 Safety Analyses Set

The safety analysis set will consist of all patients who receive the assigned treatment.

10.5 Statistical Analyses

10.5.1 General Approach

Descriptive statistics will be calculated on all variables by treatment group. Frequencies will be computed for all binary/categorical variables, and continuous variables will be summarized using medians, quartiles, and ranges. Data from schedules may be pooled. Exploratory and post hoc analyses may be conducted at the discretion of the PI.

10.5.2 Analysis of the Primary Endpoint

The primary outcome is the incidence of post-operative delayed gastric emptying using the ISGPS criteria and MAGS grading, coded as yes and no. The rate per group, odds ratio (OR) and the associated 95% confidence intervals (CIs) will be calculated assuming a binomial distribution. The logistic regression model will considered to investigate the effect of PPIs accounting for the interested variables on the incidence of post-operative delayed gastric emptying. The interested variables include age, gender, body mass index, comorbidities, preoperative proton pump inhibitor usage, and surgical reconstruction method. The relationships between these variables and the endpoint may exist.

10.5.3 Analysis of Secondary Endpoint(s)

Secondary endpoints include the incidence of surgical complication and marginal ulcer free survival. Surgical complication is defined by the Modified Accordion Grading System, coded as yes and no. The similar statistical approach to the primary endpoint will be employed. Any clinical diagnosis is used to define a marginal ulcer within 90 days after surgery. MUFS is defined as the days from the date of randomization to diagnosis of a marginal ulcer. The patients without marginal ulcer are censored at the date of last follow-up. The Kaplan-Meier method will be used to calculate the probability of marginal ulcer free survival at specific time points, e.g. 30 days, 90 days after surgery. The 95% CIs will be also provided. Differences between groups will be determined by log-rank tests. Cox

proportional-hazards models will be used to evaluate the effect of PPIs accounting for the other interested variables.

10.5.4 Planned Interim Analysis

Not applicable.

10.5.5 Sub-Group Analyses

Not applicable.

10.5.6 Tabulation of Individual Participant Data

Individual patient data will be listed by group.

A tabulation of patient disposition, including the number screened, the number enrolled in each schedule, the number in each patient population for analysis, the number of protocol deviations, the number that discontinued treatment and reasons for treatment discontinuation, and the number that withdrew from study and reasons for withdrawal will be presented.

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APPENDIX A: Definitions for Adverse Event Reporting

A. Adverse Events (AEs)

As defined in 21 CFR 312.32:

Definition: any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services' Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP's website:
http://www.hhs.gov/ohrp/policy/advevntguid.html

B. Suspected Adverse Reaction (SAR)

As defined in 21 CFR 312.32:

Definition: any adverse event for which there is a reasonable possibility that the drug caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. "Suspected adverse reaction" implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

C. Life-Threatening Adverse Event / Life Threatening Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: any adverse drug event or suspected adverse reaction is considered "life-threatening" if, in the view of the investigator, its occurrence places the patient at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

D. Serious Adverse Event (SAE) or Serious Suspected Adverse Reaction

As defined in 21 CFR 312.32:

Definition: an adverse event or suspected adverse reaction is considered "serious" if, in the view of the investigator, it results in any of the following outcomes:

- Death
- A life-threatening adverse event

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Any other important medical event that does not fit the criteria above but, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

E. Protocol Exceptions

Definition: A planned change in the conduct of the research for one participant.

F. Deviation

Definition: Any alteration or modification to the IRB-approved research without prospective IRB approval. The term "research" encompasses all IRB-approved materials and documents including the detailed protocol, IRB application, consent form, recruitment materials, questionnaires/data collection forms, and any other information relating to the research study.

A minor or administrative deviation is one that does not have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

A major deviation is one that does have the potential to negatively impact the rights, safety, or welfare of participants or others or the scientific validity of the study.

APPENDIX B: Reporting Timelines

Expedited Reporting Timelines		
Event	**HRPO**	**QASMC**
Serious AND unexpected suspected adverse reaction		
Unexpected fatal or life-threatening suspected adverse reaction		
Unanticipated problem involving risk to participants or others	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	Report via email after IRB acknowledgment
Major deviation	Report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day.	
A series of minor deviations that are being reported as a continuing noncompliance	Report within 10 working days.	
Protocol exception	Approval must be obtained prior to implementing the change	
Clinically important increase in the rate of a serious suspected adverse reaction of that list in the protocol or IB		
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Breach of confidentiality	Within 10 working days.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Adverse event or SAE that does not require expedited reporting	If they do not meet the definition of an unanticipated problem involving risks to participants or others, report summary information at the time of continuing review	Adverse events will be reported in the toxicity table in the DSM report which is typically due every 6 months.

Routine Reporting Timelines		
Event	**HRPO**	**QASMC**
Minor deviation	Report summary information at the time of continuing review.	
Complaints	If the complaint reveals an unanticipated problem involving risks to participants or others OR noncompliance, report within 10 working days. If the event results in the death of a participant enrolled at WU/BJH/SLCH, report within 1 working day. Otherwise, report at the time of continuing review.	
Incarceration	If withdrawing the participant poses a safety issue, report within 10 working days. If withdrawing the participant does not represent a safety issue and the patient will be withdrawn, report at continuing review.	

APPENDIX C: ISGPS Criteria for Delayed Gastric Emptying

DGE grade	NGT required	Unable to tolerate solid oral intake by POD	Vomiting/gastric distension	Use of prokinetics
A	4–7 days or reinsertion > POD 3	7	±	±
B	8–14 days or reinsertion > POD 7	14	+	+
C	>14 days or reinsertion > POD 14	21	+	+

DGE, Delayed gastric emptying; *POD*, Postoperative day, *NGT*, Nasogastric tube.

APPENDIX D: Modified Accordion Grading System

TABLE 5. Accordion Severity Classification of Postoperative Complications: Expanded Classification

1. Mild complication
   Requires only minor invasive procedures that can be done at the bedside such as insertion of intravenous lines, urinary catheters, and nasogastric tubes, and drainage of wound infections. Physiotherapy and the following drugs are allowed-antiemetics, antipyretics, analgesics, diuretics, electrolytes, and physiotherapy.
2. Moderate complication
   Requires pharmacologic treatment with drugs other than such allowed for minor complications, for instance antibiotics. Blood transfusions and total parenteral nutrition are also included.
3. Severe: invasive procedure without general anesthesia
   Requires management by an endoscopic, interventional procedure or re-operation* without general anesthesia.
4. Severe: operation under general anesthesia
   Requires management by an operation under general anesthesia.
5. Severe: organ system failure†
6. Death
   Postoperative death.

*An example would be a wound reexploration under conscious sedation and/or local anesthetic.

†Such complications would normally be managed in an increased acuity setting but in some cases patients with complications of lower severity might also be admitted to an ICU.

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The Accordion Severity Grading System of Surgical Complications

Strasberg, Steven M.; Linehan, David C.; Hawkins, William G.
Annals of Surgery250(2):177-186, August 2009.
doi: 10.1097/SLA.0b013e3181afde41

Accordion Severity Classification of Postoperative Complications: Expanded Classification

APPENDIX E: Expected Post-Surgical Adverse Events

Gastrointestinal:

- Delayed gastric emptying
- Pancreatic fistula
- Intraabdominal abscess
- Clostridium difficile infection
- Leak (chyle, biliary, pancreatic, gastric, enteric)
- Anastomotic ulcer
- Bowel obstruction
- Bowel perforation
- Bowel ischemia
- Mesenteric ischemia
- Colitis
- Gastritis/esophagitis

Cardiovascular:

- Myocardial infarction
- Arrhythmia
- Cardiac arrest
- Congestive heart failure
- Hemorrhage
- Deep vein thrombosis
- Pulmonary embolism
- Ischemic stroke
- Hemorrhagic stroke
- Venous or arterial thrombosis
- Hypotension

Urinary:

- Urinary retention
- Urinary tract infection
- Acute kidney injury/failure

Respiratory:

- Pneumonia
- Subcutaneous emphysema

Neurological:

- Delirium/agitation

General:

- Surgical site infection
- Pancreas endocrine insufficiency
- Pancreas exocrine insufficiency
- Bacteremia/sepsis
- Failure to thrive
- Death

APPENDIX F: Study-Specific DSM Tables

Protocol Objectives and Subject Evaluability	
Objective	**# of patients evaluable for this endpoint to date**
Primary	
Determine the effect of PPIs on the incidence of delayed gastric emptying within 90 days in patients after pancreaticoduodenectomy.	
Secondary	
Determine the effect of PPIs on the incidence of overall postoperative complications in the patients after pancreaticoduodenectomy.	
Determine the marginal ulcer-free survival (MUFS) within 90 days in the patients undergoing pancreaticoduodenectomy.	

Interim Analysis and Early Stopping Rules
Does the study design include an interim toxicity analysis? No
Does the study design include an interim futility analysis? No
Are there early stopping rules that outline circumstances under which the study must be suspended or closed? No

Response and Survival							
UPN	**On tx date**	**# doses**	**Pt replaced? (y/n)**	**Delayed gastric emptying? (y/n)**	**Off tx reason**	**Vital status**	**If dead, cause**

Summary of Specimen Collections			
Type of specimen	**Time point**	**# of patients eligible for collection at this time point**	**% of patients who have reached this time point and had the specimen collected**
N/A (no research specimens collected on this study)			