Phase 1/2 Trial of Indomethacin in Chronic Pancreatitis (The PAIR Trial)

Protocol Number: < Number>

National Clinical Trial (NCT) Identified Number: <NCT04207060>

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale

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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.]

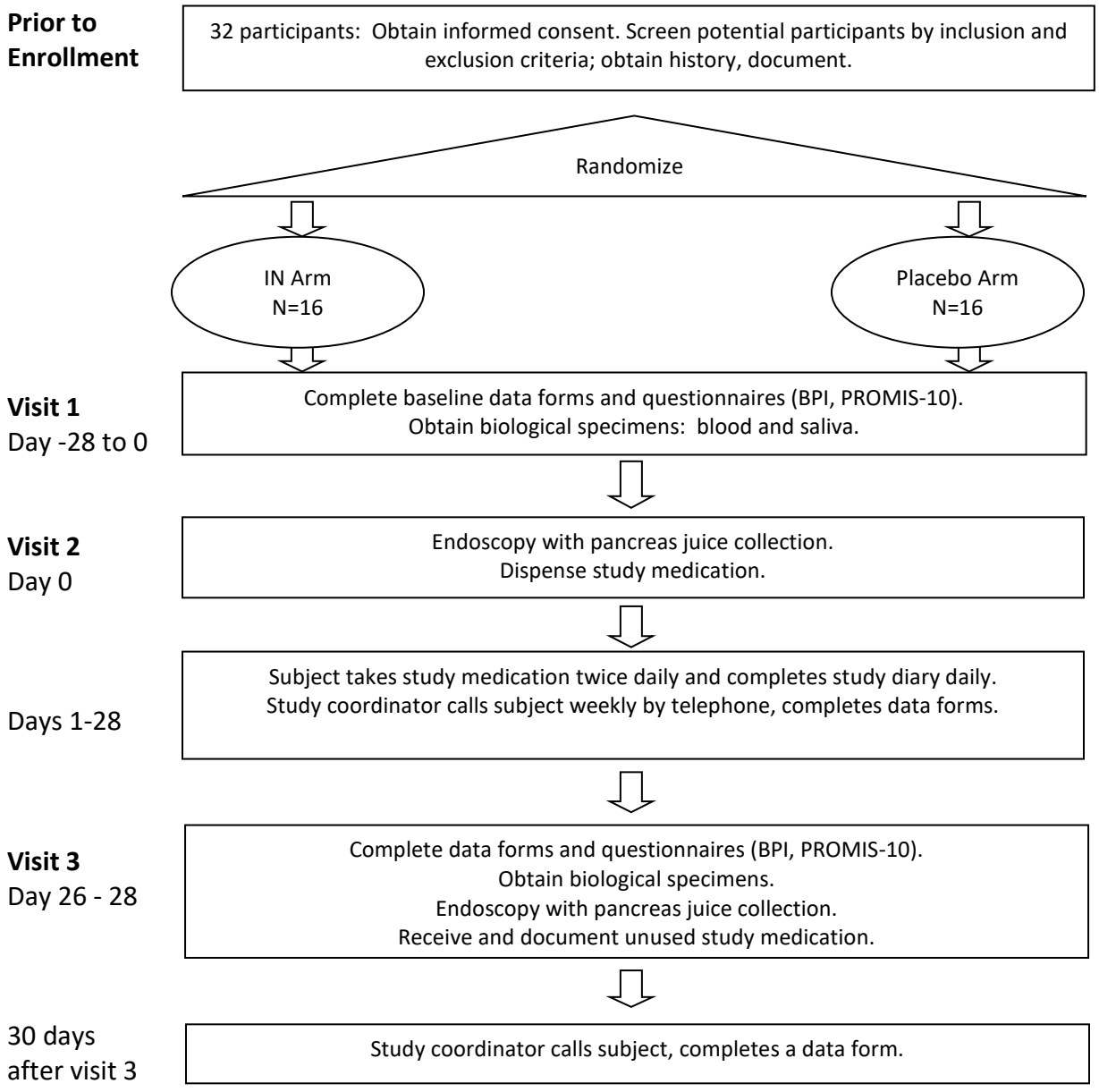
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Phase 1/2 Trial of Indomethacin in Chronic Pancreatitis (The PAIR Trial)
Study Description:	Chronic pancreatitis (CP) is a disabling disease that causes chronic pain, diabetes and malnutrition, and for which there is no effective, disease-modifying medical therapy. Preliminary studies suggest that widely available anti-inflammatory drugs such as indomethacin, which decrease prostaglandin E2 (PGE_2) production, could be repurposed to lessen the severity of CP. In this prospective, randomized, placebo-controlled study, indomethacin or placebo will be given to patients with CP, and pancreas juice PGE_2 levels will be measured, in order to determine whether standard doses of indomethacin effectively suppress pancreatic PGE_2 production and would be suitable for large scale, multicenter trials, with the goal of improving pain and quality of life in patients with this chronic illness.
Objectives:	Primary Objective: to assess the physiologic effect of orally administered indomethacin (IN) on pancreatic juice PGE_2 concentrations in patients with chronic pancreatitis (CP). Secondary Objectives: A) To correlate drug-induced changes in pancreatic juice PGE_2 levels with changes in salivary and blood PGE_2 levels, blood IN levels, and changes in patient-reported pain outcome (PRO) and quality of life (QOL), and B) to establish a basis for subsequent multicenter clinical trials of chronic COX-2 inhibition in CP.

Specific Aims:	1. To obtain steady-state pharmacologic data assessing the magnitude and variability of change in pancreas juice, blood, and saliva PGE_2 concentrations after administration of oral IN or placebo to CP patients for 28 days. 2. To correlate changes in pancreas juice PGE_2 concentrations with changes in PRO and QOL after 28 days of study drug administration.
Endpoints:	Primary Endpoint: Decrease in mean pancreatic juice PGE_2 concentration after indomethacin treatment, to no more than 66% of baseline, and statistically significant in comparison to placebo. Secondary Endpoints: Correlation of pancreatic juice, blood, and saliva PGE_2 levels; correlation of post-treatment decreases in pancreas juice PGE_2 concentrations with improvements in patient-reported outcomes (pain and quality of life).
Study Population:	32 persons with chronic pancreatitis of any gender, ≥18 years and ≤70 years of age, who are receiving care at Mayo Clinic Rochester or Ohio State University and are undergoing clinically indicated upper GI endoscopy (EGD) or endoscopic ultrasound (EUS).
Phase:	1/2
Description of Sites/Facilities Enrolling Participants:	Mayo Clinic Rochester and Ohio State University.
Description of Study Intervention:	Indomethacin 50 mg po BID vs placebo po BID for 28 days.
Study Duration:	2 years.
Participant Duration:	Up to 3 months.

1.2 SCHEMA


Prior to Enrollment
32 participants: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history, document.
Randomize
IN Arm N=16
Placebo Arm N=16
Visit 1
Day -28 to 0
Complete baseline data forms and questionnaires (BPI, PROMIS-10).
Obtain biological specimens: blood and saliva.
Visit 2
Day 0
Endoscopy with pancreas juice collection.
Dispense study medication.
Days 1-28
Subject takes study medication twice daily and completes study diary daily.
Study coordinator calls subject weekly by telephone, completes data forms.
Visit 3
Day 26 - 28
Complete data forms and questionnaires (BPI, PROMIS-10).
Obtain biological specimens.
Endoscopy with pancreas juice collection.
Receive and document unused study medication.
30 days after visit 3
Study coordinator calls subject, completes a data form.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedures	Screening Day -28 to 0	Study Visit 1 Day -28 to 0	Study Visit 2 Day 0	Phone Call A Day 7	Phone Call B Day 14	Phone Call C Day 21	Study Visit 3 Day 25 - 28	Phone Call D Day 56 - 58
Review inclusion/exclusion criteria	X							
Informed consent	X							
Demographics		X						
Medical history		X						
Medications (documented)		X					X	
BPI, PROMIS-10 completed		X					X	
List of NSAIDS to avoid given to participant		X						
Vital signs including height, weight		X						
Physical Exam documented		X						
Blood collection and processing, including serum creatinine if not already checked within 30 days		X					X	
Saliva collection and processing		X					X	
Pregnancy test [a]			X				X	
Randomization			X					
GI Endoscopy			X				X	
Pancreas juice collection and processing			X				X	
Dispense study medication			X					
Interim history form (telephone interview)				X	X	X		X
Daily medication and pain diary			X----------					----------X
Collect unused study medication and document							X	
Complete Case Report Forms (CRFs)	X	X	X	X	X	X	X	X

[a] Urine pregnancy test within 48 hours prior to GI endoscopy, in women of childbearing potential.

2 INTRODUCTION

2.1 STUDY RATIONALE

Chronic pancreatitis (CP) is a chronic fibro-inflammatory disease. There is no medical therapy that modifies the disease course of CP. Our **long-term goal is to identify effective disease-modifying therapeutic strategies for CP.** Chronic inhibition of pancreatic prostaglandin E_2 (PGE_2) production is one such promising strategy. Indomethacin (IN) is an inhibitor of COX-2 and suppresses systemic PGE_2 production, but the pharmacology of IN in human pancreas is unknown. This study will determine whether a standard clinical oral dose of IN, administered for 4 weeks, decreases PGE_2 concentrations in pancreatic juice, setting the stage for a subsequent large-scale clinical trial of IN in CP.

PGE_2 is produced at sites of inflammation by the cyclooxygenase-2 enzyme (COX-2), which is overexpressed in the pancreas of humans with CP. PGE_2 is a potent mediator of pancreatic chronic inflammation and stellate cell activity. Pancreas juice (PJ) PGE_2 concentrations are elevated in patients with CP and suspected early or "minimal change" CP (MCCP) compared to normal volunteers. PJ can be collected during GI endoscopy and subsequently assayed for PGE2, providing a minimally invasive method of assessing pancreatic COX-2 activity. Rectally administered IN prevents acute post-ERCP pancreatitis, although the mechanism by which it prevents human acute pancreatitis is uninvestigated.

Chronic inhibition of pancreatic COX-2 is a promising therapeutic strategy for CP, but there are no data regarding the drug, dose, and route of administration required for steady-state inhibition of human pancreatic COX-2 activity.

2.2 BACKGROUND

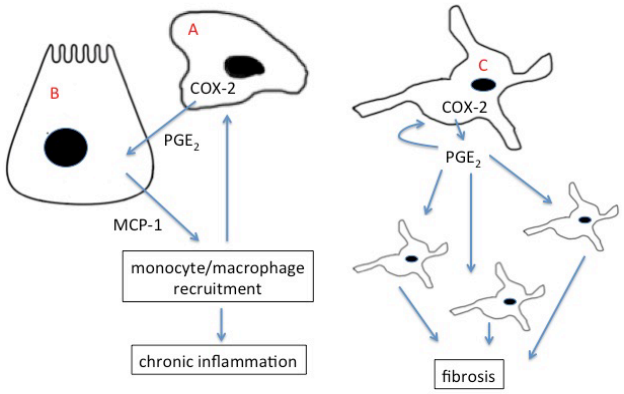
Significance

There is currently no medical therapy that alters the natural history of chronic pancreatitis (CP). CP is a chronic disease marked by pancreatic inflammation, fibrosis, and acinar loss, with clinical manifestations including chronic pain, bouts of acute pancreatitis, and loss of pancreatic function. CP is typically diagnosed on the basis of changes in pancreatic morphology apparent on imaging studies, and/or by demonstration of loss of pancreatic exocrine function.[3] The prevalence of CP is approximately 50 per 100,000 persons, or about 150,000 to 200,000 Americans, with about 15,000 to 20,000 new cases diagnosed annually in the United States.[4] CP often affects young adults in the prime of life, and is associated with profound disability and impairment of quality of life due to chronic pain and complications of pancreatic insufficiency.[5]

COX-2 inhibition may modify symptoms and retard progression of CP. Induction of the cyclooxygenase 2 (COX-2) enzyme leads to production of thromboxanes and prostaglandins, including prostaglandin E2 (PGE_2), a potent mediator of inflammation. PGE_2 is a potent mediator of chronic inflammation and stellate cell activity in the pancreas, as shown in **Figure 1**. COX-2 activity is increased in human chronic pancreatitis tissue.[6, 7] In normal human pancreas COX-2 expression is limited to islets, but in both early-stage and advanced CP COX-2 is also expressed in human acinar and ductal cells.[6, 7] In rat models of pancreatitis propagation of pancreatic inflammation is COX-2 dependent, [1] and COX-2 inhibition lessens the severity of CCK-octapeptide-induced acute pancreatitis.[8] In WBN/Kob rats who spontaneously develop CP, administration of rofecoxib (a selective COX-2 inhibitor) resulted in lower tissue PGE_2 levels and inhibition of pancreatic inflammation and fibrosis,[9] however COX-2 knockout mice develop similar cerulean-induced chronic pancreatitis as wild-type mice.[10] Sulindac attenuates inflammation and fibrosis in a mouse model of chronic pancreatitis,[11] and a COX-2 inhibitor blocked response of

activated pancreatic stellate cells to proinflammatory cytokines in an in-vitro study.[12] The role of PGE_2 in pancreatic inflammation and fibrosis may vary both with the species and the mechanism of pancreatic injury.

Figure 1: COX-2 and PGE2 in chronic pancreatitis



COX-2 in monocytes (A) produces PGE2, which stimulates acinar cells (B) to release monocyte chemoattractant protein-1 (MCP-1), recruiting additional monocytes and macrophages into the pancreas and propogating chronic pancreatic inflammation.[1] In addition, stromal PGE2 stimulates human pancreatic stellate cell (C) activation via the EP4 receptor, inducing stellate cell COX-2 activity, PGE2 release, and stellate cell propogation, activation, collagen production, and pancreatic fibrosis.[2]

Although current treatment guidelines advocate short-term NSAID administration as first-line therapy for pancreatic pain,[13] the possibility that chronic daily NSAID administration might alter the course of human CP is uninvestigated. A single 100 mg dose of rectal IN prevents post-ERCP pancreatitis in humans,[14] and prophylactic rectal IN is commonly administered for this indication. However the pancreatic mechanism of action of rectal IN for prevention of post-ERCP pancreatitis has not been investigated in humans. No pharmacological data are available regarding COX-2 inhibition by nonsteroidal anti-inflammatory drugs (NSAIDS) or aspirin (ASA) in human pancreas.

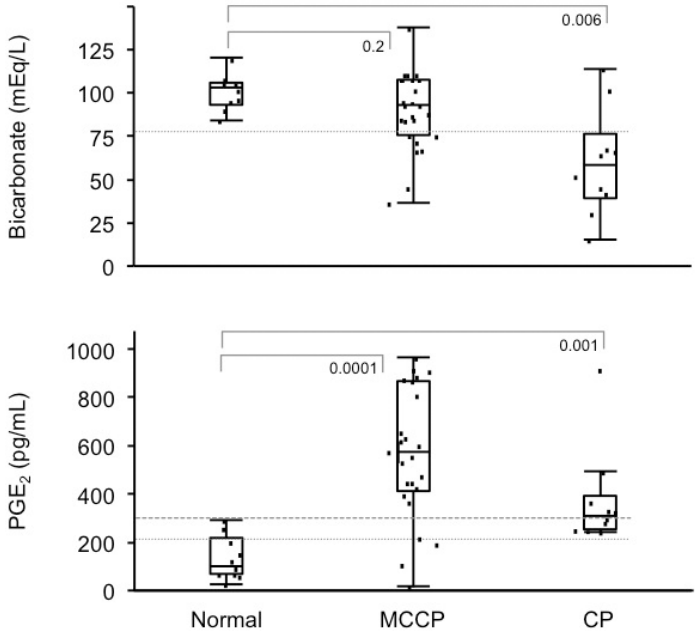
Although rectal indomethacin decreases the incidence of post-ERCP pancreatitis,[14] oral administration may be more appropriate for long-term treatment. For prevention of post-ERCP pancreatitis, rectal NSAID administration appears to be more effective than oral administration,[15] however rectal IN administration results in earlier but lower peak plasma concentrations with evidence of incomplete absorption when compared to oral administration.[15] Blood IN undergoes biliary recycling, resulting in high portal venous drug levels.[15] While the early peak plasma concentration may in part account for the superior prophylactic efficacy of single-dose rectal IN when compared to oral administration, long-term rectal administration is unlikely to offer significant pharmacokinetic benefits when compared to oral administration, and compliance will likely be better with oral medication. Daily NSAID dosing is required to maintain suppression of COX-2, and transient rebound above baseline may occur when treatment is stopped.[16]

Pancreatic COX-2 activity can be assessed by measuring PGE_2 in pancreas juice collected during routine upper endoscopy. Patients with known or suspected CP may undergo an endoscopic pancreatic function test (ePFT). During ePFT secretin is administered intravenously, causing secretion of pancreatic juice (PJ) into the duodenum. The secreted PJ is suctioned from the duodenum via an endoscope and collected in timed aliquots, which are assayed for bicarbonate concentration (a measure of pancreatic exocrine function). PJ aliquots collected during ePFT can be assayed for PGE_2, providing an assessment of pancreatic COX-2 activity. We will also assay saliva and blood PGE_2 levels to generate pilot data regarding their correlation

with PJ PGE_2 levels; if correlation is high it may be possible to use these non-invasive biospecimens as surrogates for pancreatic juice in future studies.

Preliminary Data: We measured pancreas juice (PJ) PGE_2 levels in patients with CP (n=10), minimal change CP (MCCP) (n=25), and normal volunteers (n=10).[17] There were statistically significant elevations of PJ PGE_2 in both MCCP and CP compared to normal volunteers (**Figure 2**). PJ PGE_2 (at a cutoff of 300 pg/ml) had a diagnostic accuracy of 92% for MCCP, compared to 62% for PJ bicarbonate concentration (at a cutoff of 80 mEq/L). These findings suggest that PJ PGE_2 levels may serve as a biomarker for pancreatic inflammation.

Figure 2: PJ PGE_2 activity in patients and controls



Rationale for study drug dosage: There is no published data on the effect of IN on human pancreatic COX-2 activity. Usual clinical doses of oral indomethacin are 25-50 mg BID to TID. This study's dose of oral IN was chosen based on standard clinical dosing, published literature showing that similar blood levels are achieved with oral vs rectal administration, and the fact that steady-state administration of IN 50 mg BID orally should result in higher blood and tissue drug levels than 100 mg administered rectally once. Common side effects of IN such as dyspepsia are often dose related. Five doses of drug are required to achieve pharmacological steady state.

NIH-sponsored CPDPC Consortium: This protocol leverages resources of the NIH-funded, U01 Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC) Consortium. An overriding objective of CPDPC is "to encourage translational research focusing upon elucidating the pathogenesis that will provide a basis for understanding the natural history and developing means of diagnosis, treatment and clinical management of chronic pancreatitis". Mayo Clinic Rochester (Santhi Vege – PI) and Ohio State University (Darwin Conwell – co-PI) are members of the CPDPC, which funds principal investigator and study staff time at these institutions, providing a unique collaborative infrastructure for the proposed trial.

Impact of Study Findings: This trial will provide physiologic and pharmacologic rationale, and pilot patient-reported outcomes data, key to the design of subsequent studies of longer-term, daily IN administration to patients with CP. Such studies cannot be properly designed or funded without the data the current protocol will provide. Identification of a disease-modifying medical treatment for CP will be a major clinical advance impacting the health of persons everywhere who suffer from this disabling chronic illness.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

2.4 POTENTIAL RISKS

Endoscopy, EUS, and ePFT: Upper GI endoscopy (EGD) and endoscopic ultrasound (EUS) are routine clinical diagnostic procedures that are typically performed under conscious sedation or monitored anesthesia care. Diagnostic EGD and EUS have a low (< 1%) risk of risk of complications, including reactions to medications given for sedation, bleeding, infection, pancreatitis, perforation, or urgent surgery for complications. All study participants will be undergoing a baseline clinically indicated EGD or EUS exam as well as a subsequent research EGD exam, with endoscopic pancreatic function tests (ePFTs) during both exams.

ePFT is performed during EGD and EUS and involves administration of intravenous secretin. ePFT lengthens the duration of an endoscopic exam because pancreas juice is collected from the duodenum via the endoscope for 45 minutes after secretin administration. There is no evidence that performance of ePFT increases the overall risks of EGD or EUS.

Side effects of intravenous secretin administration occur in < 1% and include diaphoresis, hypotension, nausea, abdominal pain, vomiting, mild pancreatitis, upset stomach, diarrhea, flushing, and a warm sensation in the abdomen. Acute pancreatitis was observed after intravenous secretin administration during MRI in 2/10,000 patients (0.02%).[21] Contraindications to secretin administration include known hypersensitivity to secretin. Secretin is commonly administered to patients with a history of prior acute pancreatitis or chronic pancreatitis, and there is no evidence that risks are increased in these patient populations. The secretin administered in this study is a recombinant protein identical to human secretin, thus risks of allergic reactions are very low.

Indomethacin (IN) is a nonsteroidal anti-inflammatory drug (NSAID), and many drugs in this class are available over-the-counter. IN was chosen for use in this protocol because rectally administered IN is known to have a beneficial anti-inflammatory effect in human pancreas for prevention of post-ERCP pancreatitis. Like other NSAIDs, IN has a low risk of complications, including allergic reactions, gastrointestinal ulceration, GI bleeding, and a small increased risk of vascular events such as stroke or myocardial infarction. Patients with a history of allergy to NSAIDS, current or past gastroduodenal ulceration, or past history of stroke, myocardial infarction, or coronary artery disease are excluded from participation in this study.

Alternative approaches and treatments: The study protocol utilizes the least invasive, least risky method of assessing human pancreatic COX-2 activity at baseline and after drug treatment.

There are no effective medical therapies for CP that alter the natural history of the disease. Study participants will be patients with CP who will be receiving concurrent care for their condition as clinically appropriate and as determined by their treating physician.

Women who are pregnant or nursing: Risks of endoscopy and sedation may be increased in women who are pregnant or nursing, and they are excluded from participation in this study.

Women of child-bearing potential will undergo a urine pregnancy test within 48 hours of their research EGD exam. In addition, at the time of enrollment (as detailed in the ICF) they must agree to one of the following birth control methods:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

They must use birth control for the entire study and for at least 5 days after their last dose of study drug.

Psychological, legal and financial risks: Study questionnaires will collect confidential information, including medical history, medications used, pain ratings, and quality of life information. Public release of this information might have adverse consequences for study participants. All study data will therefore be stored in secure paper files or de-identified, password-protected electronic databases.

Protections Against Risk

Endoscopic procedures will be performed on clinical GI Endoscopy Units at the current standard of clinical care at Mayo Clinic Rochester and Ohio State University, including the use of monitored anesthesia care (MAC) or general anesthesia (GA) at the discretion of the attending gastroenterologist and anesthesiologist. Participants will receive pre-procedure evaluation, intra-procedural monitoring, and post-procedural recovery care identical to that provided to patients undergoing endoscopy in these units. Staff nurses, anesthetists, and GI endoscopists will be available to assess symptoms and adverse events and provide appropriate treatment during endoscopic procedures and their recovery period. Participants will be discharged from the endscopy unit when they meet the unit's standard discharge criteria.

Subjects with a history of gastroduodenal ulceration, GI bleeding, stroke, myocardial infarction, or currently active acute pancreatitis are excluded from participation. Subjects found to have active gastric or duodenal ulceration at the time of baseline endoscopy are also excluded. Women who are pregnant or nursing and persons older than 70 years of age, who are at higher risk for aspirin or NSAID-related adverse events, are also excluded from this study.

Women of child-bearing potential (i.e., women who are pre-menopausal and have not had a hysterectomy) must have a negative urine pregnancy test within 48 hours of initiating study drug treatment, and must agree to remain sexually abstinent or use birth control measures (as detailed above) for the duration of their study participation and for 5 days afterward.

Subjects will be contacted weekly by telephone by a study coordinator during their 4 weeks of study drug administration. The coordinator will ask about compliance with study medication, completion of the daily symptom and medication diary, and new or worsening symptoms or

health concerns. Subjects will be encouraged to report new symptoms or health problems to study staff, which will result in communication between a physician-investigator and the subject. Subjects will be able to report symptoms or ask questions at other times by telephone. A study physician will be available to respond to subjects by telephone at all times.

Study enrollment logs containing individually identifiable private information will be stored in secure non-public sites at each study site, as detailed above.

Incidental findings noted during study endoscopy will be described in the clinical endoscopy report generated after each endoscopy exam, which is placed in the patient's medical record. Subjects will be informed of incidental findings and encouraged to follow-up with their clinical care professional about any incidental findings.

2.4.1 KNOWN POTENTIAL BENEFITS

Subjects are unlikely to benefit from participation in this study. If indomethacin suppresses pancreatic PGE_2 production it may improve symptoms and delay progression of CP, but this would probably require long-term administration. On the basis of knowledge gained by this study there is substantial potential benefit to future patients with CP. The risks of study participation are low, and the potential benefit to future patients justifies the risks undertaken by subjects in this study.

2.4.2 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Potential risks and benefits, and adequacy of protection against risks, are described in the proceeding sections. There are currently no effective medical therapies for CP, and there is promising background and preliminary data to suggest that NSAIDs may be such a therapy, suggesting that there is significant potential for future benefit of CP patients. The overall risks to subjects are low, and are outweighed by the potential benefits.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Primary Objective: to assess the physiologic effect of orally administered indomethacin (IN) on pancreatic juice PGE_2 concentrations in patients with chronic pancreatitis (CP).	Primary Endpoint: Decrease in mean pancreatic juice PGE_2 concentration after indomethacin treatment, to no more than 66% of baseline, and statistically significant in comparison to placebo.	Physiologic endpoint that would justify future large-scale clinical trials of IN in CP with primary endpoints related to patient-reported outcomes.
Secondary/Exploratory		

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary Objectives: A) To correlate drug-induced changes in pancreatic juice PGE_2 levels with changes in salivary and blood PGE_2 levels, blood IN levels, and changes in patient-reported pain outcome (PRO) and quality of life (QOL).	Secondary Endpoints: Correlation of pancreatic juice, blood, and saliva PGE_2 levels; correlation of post-treatment decreases in pancreas juice PGE_2 concentrations with improvements in patient-reported outcomes (pain and quality of life); explore changes in cytokine, microbiome and pancreas function with IN administration	Provide further insight into the pancreatic effects of IN, determine whether measurement of PGE_2 in fluids collected noninvasively correlate with pancreatic juice PGE_2 concentrations, and provide pilot data regarding PRO and QOL outcomes useful for planning subsequent clinical trials.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a phase 1 / 2, randomized, placebo-controlled, double-blinded study of oral indomethacin 50 mg po BID vs. placebo po BID in patients with chronic pancreatitis. The study will be conducted at Mayo Clinic Rochester and Ohio State University.

The study **hypothesis** is:

1) That mean pancreatic juice PGE_2 concentration will decrease after indomethacin treatment to no more than 66% of baseline, and will be significantly lower than after placebo treatment.

Exploratory hypotheses are:

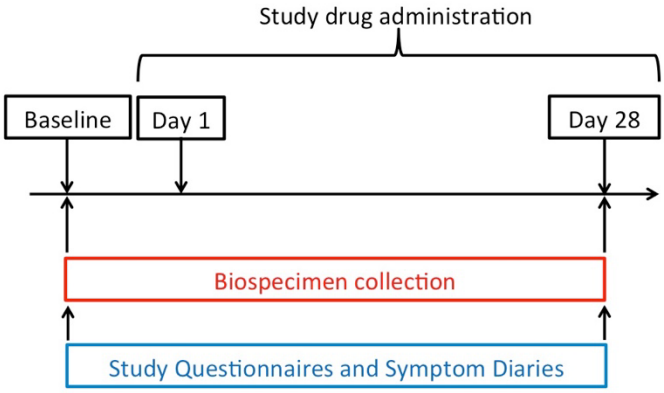
1) That peak blood IN levels at the conclusion of treatment will correlate with degree of change in pancreas juice (PJ) PGE_2 concentrations.
2) That baseline salivary and blood PGE_2 concentrations, and changes in these concentrations after treatment, will correlate with blood and saliva PJ PGE_2 concentrations.
3) That improvement in pain and quality of life of study participants will correlate with changes in PJ PGE_2 concentrations.

Overview: 32 participants with CP will be randomized to receive 28 days of IN 50 mg po BID or placebo (2 study arms). Blood, saliva, and pancreatic juice will be collected from each participant prior to study drug administration and again on the 28^{th} day of study drug administration. Participants will complete daily pain diaries as well as questionnaires assessing pain and quality of life at baseline and day 28. Primary outcome is a comparison of the mean change in PJ PGE_2 concentrations at 28 days in the IN vs. placebo groups. Secondary outcomes include changes in

pain and quality of life from baseline to 28 days in the IN vs. placebo groups, and their correlation with changes in PJ PGE_2 and blood IN concentrations, as well as correlation of PJ, saliva, and blood PGE_2 concentrations (to determine whether non-invasive measures correlate with PJ measures).

Methods: Up to 40 participants will be enrolled in order to accrue 32 participants who complete the study protocol. As shown in **Figure 3**, all study participants will undergo a biospecimen collection at baseline and day 28 including blood, saliva, and pancreatic juice (PJ). PJ will be collected during endoscopic pancreatic function tests (ePFT). Up to 4 weeks may elapse between the baseline biospecimen collection and day 1 of study drug administration. 16 participants will receive oral indomethacin 50 mg BID, and 16 will receive matched placebo BID. Participants will complete the Brief Pain Inventory (BPI) and PROMIS 10 quality of life instrument at baseline and day 28, and will also complete daily symptom and medication diaries.

Figure 3: Study Flowchart



Definitions: CP will be diagnosed per American Pancreatic Association criteria for definite CP. These include a compatible clinical picture with definite findings of CP (Cambridge 3-4 ductal changes, and/or calcifications) on cross-sectional imaging studies.

Study Interventions and Measures: The *endoscopic pancreatic function test (ePFT)* will be performed at baseline and on day 28. ePFT is a standardized test used in medical pancreatology clinical practice that involves administration of intravenous secretin (0.2 mcg/kg slowly over one minute) to stimulate pancreatic juice secretion, followed by aspiration of pancreatic juice from the duodenum via an endoscope. Some subjects will undergo a baseline ePFT as part of their routine clinical care; other subjects, who are having upper GI endoscopy or endoscopic ultrasound (EUS) performed as part of their clinical care, will undergo ePFT during endoscopy for research purposes. Fluid will be aspirated from the duodenum via an endoscope at baseline and from 0-10 and 10-20 minutes following secretin administration, and processed per CPDPC pancreas juice/fluid SOP. Participants will be instructed to take their study drug 2 hours prior to their follow-up research endoscopy with ePFT on day 28.

PJ bicarbonate and lipase concentrations will be measured on duodenal aspirates from each time point using a previously validated method. [18] *PGE_2 concentrations* will be measured in saliva, blood, and pancreatic juice from baseline and day 28 using a tandem mass spectroscopy assay developed and validated at Mayo Clinic Rochester. *Peak IN drug levels* will be measured in blood on day 28, providing an assessment of participant compliance with study drug administration.

The *Brief Pain Inventory (BPI)* and the *PROMIS-10* are validated scales that quantify pain and quality of life, respectively, and will be completed at baseline and day 28. A *medication and pain diary* will be completed daily by all subjects at baseline and during the 28-day treatment period,

including all narcotics and over-the-counter medications used. Oral opioid usage will be expressed in oral morphine equivalents for purposes of data analysis.

Randomization, Allocation and Blinding

Randomization: Subjects will be assigned to receive IN or placebo according to a computer generated randomization list composed of randomized blocks of sizes of 2 or 4. Two separate sets of blocks will be created, one for subjects with alcoholic CP and the other for those with other causes of CP. Within each block, equal number of subjects will be assigned to IN and placebo. Separate sets of randomization blocks will be provided for Mayo and Ohio State. The randomization lists will be computer generated by the study statistician (Dr Li), and kept in a secure computer file and paper study binder in the Mayo and Ohio State Research Pharmacies. No investigators or study personnel other than Dr Li will have knowledge of the randomization list. Dr Li will not participate in any aspect of subject recruitment, subject allocation, conduct of the study, or data ascertainment, but will perform data analysis.

Subject allocation will be known only to the staff of the Mayo and Ohio State Research Pharmacies, who will assign subjects to IN or placebo according to their randomization list provided by Dr. Li. Allocation will be performed by matching the subject's study number with the randomization list. Allocation will not be revealed to subjects, investigators, other study personnel, or clinicians caring for subjects until all subjects have completed the clinical trial or for medical emergency. Because subjects, investigators, and study personnel will be blinded, they will not be able to determine subject allocation before or during data ascertainment.

In case a subject is allocated to receive study medication, but is withdrawn from the study before completing the protocol, study medication will be returned to the Research Pharmacy for disposal, and the following subject will be assigned the same allocation. All investigators will remain blinded to the allocation of the withdrawn subjects and their replacements.

Blinding: Study medication will be labelled "indomethacin 50 mg or placebo capsule" with the subject's name, hospital or clinic number, study IRB number, and subject number. Placebo and IN capsules will be identical in appearance. The investigators, study coordinator, and clinical caregivers will remain blinded to subject allocation throughout the data ascertainment and data entry phase of the study.

The success of blinding will be evaluated by asking the investigator, the study coordinator, and the subject the following question during their final study visit: "Which treatment group is this subject/were you assigned to: placebo, active drug, or unsure?"

Statistical Analysis and Sample Size

For Specific Aim 1, the primary analysis will be a linear random intercept model that incorporates PJ PGE_2 data from both baseline and day 28 from all randomized patients. Transformation will be used as appropriate to reduce the skewness of data and satisfy modeling assumption. The model includes randomized groups, time, and their interactions as fixed effect covariates, from which the mean change in PJ PGE_2 will be estimated for each randomized group. Effects of additional covariates, such as sex and sites, will be explored. The intra-subject correlation will be

estimated from the variances of the random intercepts and residuals. Other outcome variables, such as other biomarkers and questionnaire data, can be analyzed in a similar way. The estimates about the variability of data and intrasubject correlations will be useful for designing a subsequent larger study.

For Specific Aim 2, we will use multivariate analysis of variance model (MANOVA) with repeated measures. The multivariate outcomes include patient-related outcomes (BPI and PROMIS-10 scores) and PJ PGE_2 concentrations at baseline and day 28. Fixed effect covariates include randomized groups, time, and their interactions. Additional secondary analyses include descriptive analysis and statistical comparison of PJ PGE_2 concentrations at baseline and after secretin administration between the various study groups, and correlations between baseline PJ PGE_2 levels, clinical features, and changes in plasma and saliva PGE_2 levels. Changes in daily pain ratings and narcotic use (in morphine equivalents) will be analyzed in comparison to changes in PJ PGE_2 concentrations. Any dropout before Day 28 will be documented and descriptively summarized. Sensitivity analysis on dropout will be conducted in an exploratory manner according to standard missing data analysis procedure for longitudinal data.[19] As a pilot study, we will collect and descriptively analyze data on feasibility, patient compliance and satisfaction, and attrition, in order to inform the possible future study.

We propose a sample size of 16 patients per treatment arm. Since this is a pilot study, this sample size is largely limited by budgetary restraint. However, this sample size is adequate for studying the primary hypothesis with a two-sample two-sided t-test on the mean PGE_2 level at day 28 between the randomized groups. We expect to show that the treatment group has significantly lower mean PGE_2 than the placebo group. In our previous publication on PJ PGE_2,[20] we reported that median PJ PGE_2 level in 10 CP patients was 307 pg/ml with IQR of 249-362 pg/ml and standard deviation of 84 pg/ml. The boxplot of that data suggests that normality is a reasonable distributional assumption for the PGE_2 data. That study also found that mean PJ PGE_2 in a healthy control group was 104 pg/ml, about one third of the mean level of the CP group. If we conservatively assume that the control group in the proposed trial has 50% decrease in mean, with a Type I error of 0.05, the power of the t-test is 0.998. If we use an even more conservative mean for the control group, with 1/3 reduction in mean PGE_2, the power is 0.94. If we additionally assume that there is some data loss (due to consent withdrawal, dropout, or specimen mishandling) so that the sample size per treatment group is 12 instead of 16, the statistical power decreases to 0.85, but is still reasonable. Note that the large statistical power in the calculation above is a result of the relatively small standard deviation of the PGE_2 compared with our working assumption on the mean reduction. This assumption is supported by the data in Abu Dayyeh et al.[20] If this pilot study is successful, demonstrating a statistically significant indomethacin-related decrease in PJ PGE_2 by at least 1/3, we will conduct a future study that focuses on patient centered outcomes; that study is expected to have a larger sample size because those outcomes are expected to be less sensitive to the treatment than biomarkers. Only if indomethacin treatment achieves this result would longer-term trials of indomethacin at this dose be warranted. The data from this pilot study will provide critical preliminary and feasibility data for the future investigation.

Timeline and Feasibility: Both Mayo Clinic Rochester (MCR) and Ohio State University (OSU) medical centers feature busy medical pancreatology practices. Average monthly new patient

volumes in GI and pancreas clinics at both sites are shown in **Table 1**. Based on these patient volumes we anticipate that 30 study participants will be easily accrued within 18 months (at a rate of approximately 1 participant/site/month), providing 6 months in the second year for biospecimen assays and data analysis. Both sites have established clinical research infrastructure for enrollment of persons with CP into the PROCEED natural history cohort study of the CPDPC Consortium; PAIR study participants may be co-enrolled in PROCEED or may enroll in PROCEED after completing PAIR. Endoscopic pancreatic function tests (ePFT) are routinely performed for clinical indications at both MCR and OSU, and we have previously performed and reported results of PJ PGE2 assays.

Table 1: Monthly New Patient Volumes at PAIR Study Sites

	MCR	OSU	TOTAL
CP	12	8	24

Synergy with CPDPC Consortium: This protocol will benefit from synergies due to the presence of PROCEED study infrastructure at Mayo Rochester and Ohio State, including established methods of subject enrollment and biospecimen handling.

Potential Biases, Pitfalls, Limitations and Possible Solutions: The small study sample size may prevent us from obtaining statistically significant results. However this is a pilot study designed to collect novel pharmacological information for which preliminary data does not exist. The study is designed to collect such data while minimizing the cost, time, and number of research interventions required.

Potential confounders that could affect the pancreatic juice PGE_2 concentration include concomitant use of aspirin or additional NSAIDs during the study. We have attempted to mitigate this possibility by excluding persons who habitually use aspirin or NSAIDs, and we will advise study participants to limit their use of these drugs to occasional prn use, when absolutely needed. Participants may nevertheless use occasional aspirin or NSAIDs, and this will be captured in the study drug diaries. Participant use of these drugs will be characterized using descriptive statistics, and if appropriate included in study analyses. Other potential confounders include occurrence of acute pancreatitis. Participants who are hospitalized with acute pancreatitis between baseline and completion of day 28 will be withdrawn from the study, and not considered accrued. Milder fluctuations in underlying pancreatic inflammation may or may not be symptomatic, and we cannot directly control this source of variation, but the blinded and randomized allocation of study subjects should minimize the impact of this confounder on study results. We doubt that administration of either steroids or oral pancreatic enzyme supplements would decrease PJ PGE_2 levels, but this can also be assessed using study data if sufficient numbers of subjects use these medications.

Pharmacologically the study design assesses the effect of steady-state (rather than single-dose) IN dosing on PJ PGE_2 concentrations. A single-dose study design would permit a pharmacokinetic analysis including time to peak physiologic effect after a single dose of study medication, and this

data might impact decisions regarding drug dosage and frequency of administration. However such a study would be difficult to perform, because PJ cannot be repeatedly assayed at various time points after single dose drug administration in the same subject, hence requiring construction of composite time curves utilizing multiple subjects to assess the single-dose pharmacokinetics of each drug and dose assessed. In addition the results of a single-dose study would be less relevant to subsequent therapeutic trials than the steady-state study design proposed here.

Subject accrual may be hindered by the need to return to the study center for a repeat endoscopic exam done for research purposes. However given the size of the clinical pancreatitis practices at Mayo Clinic and Ohio State University, complete study accrual within 2 years should be readily accomplished. We anticipate that reimbursement of study participants for completion of the study protocol will improve compliance with study interventions and accrual of complete study data.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is presented in the Introduction section of this protocol. A placebo control group was chosen to adequately control for changes in PJ PGE_2 that might occur over time due to other clinical and disease factors. A physiologic primary endpoint is being studied and the study is powered to identify superiority of IN over placebo.

4.3 JUSTIFICATION FOR DOSE

There is no published data on the effect of IN on human pancreatic COX-2 activity. Usual clinical doses of oral indomethacin are 25-50 mg BID to TID. This study's dose of oral IN was chosen based on standard clinical dosing, published literature showing that similar blood levels are achieved with oral vs rectal administration, and the fact that steady-state administration of IN 50 mg BID orally should result in higher blood and tissue drug levels than 100 mg administered rectally once. Common side effects of IN such as dyspepsia are often dose related. Five doses of drug are required to achieve pharmacological steady state.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities (SoA), Section 1.3.

The end of the study is defined as completion of the last visit or procedure shown in the SoA in the trial globally.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

1. Any gender, age ≥ 18 years and ≤ 700 years

2. Diagnosed with chronic pancreatitis per American Pancreatic Association guidelines (pancreatic calcifications and/or Cambridge 3-4 changes on CT, MRI, and/or ERCP)
3. Scheduled for an upper GI endoscopic procedure (EGD or EUS) for clinical or research) indications (not conflicting with current investigation).
4. Able to provide written informed consent.
5. Serum creatinine within normal laboratory range, as measured within 30 days of the baseline study endoscopy.
6. For females of reproductive potential: willing to use highly effective contraception while taking study medication and for an additional 5 days after completing study medication.

5.2 EXCLUSION CRITERIA

1. Diagnosed with acute pancreatitis requiring hospitalization within the 6 weeks prior to study enrollment.
2. Habitual use of aspirin or non-steroidal anti-inflammatory medications (NSAIDs), defined as use more than once per week.
3. Any use of aspirin or NSAIDs within 1 week of baseline study endoscopy procedure.
4. Allergy to secretin, indomethacin or NSAIDs.
5. History of known chronic renal insufficiency or cirrhosis.
6. History of coronary artery disease, angina pectoris, myocardial infarction, cerebrovascular accident (stroke), or transient ischemic accident (TIA).
7. History of peptic ulcer or gastrointestinal bleeding.
8. Incarcerated.
9. Found to have active GI ulceration at the time of baseline endoscopy.
10. Hospitalized for acute pancreatitis while participating in this research protocol. Participants who are hospitalized for an episode of acute pancreatitis during study participation will be withdrawn from the study, and considered non-accrued.
11. Patients with indwelling pancreatic duct stents.
12. Patients status post Whipple procedures or Roux-en-Y gastric bypass due to inability to collect pancreatic fluid via the natural ampulla, unless having an EDGE procedure for clinical reasons.

5.3 LIFESTYLE CONSIDERATIONS

During this study, participants are asked to avoid taking aspirin or NSAIDs. Participants will be given a list of NSAID generic and brand names for their reference.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but from whom baseline pancreas juice specimens are not obtained and study drug is never dispensed. 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 (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a modifiable factor may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Target study sample size is 32 participants who complete all aspects of the study protocol. Up to 300 potential participants may be screened to achieve target enrollment. Participants will be recruited from the clinical gastroenterology and endoscopy practices at Mayo Clinic Rochester and Ohio State University.

Potential participants may be approached in person or by telephone. Participants will be recruited without regard to race, ethnicity or gender. Vulnerable populations (children, incarcerated persons, persons unable to provide informed consent) are excluded from participation.

Participants who complete the study protocol, including 28 days of study medication and follow-up endoscopy with pancreas juice collection, will be paid $250 remuneration, and up to an additional $250 reimbursement for travel expenses including mileage, parking, hotel and airfare. In order to receive reimbursement, you must provide a copy of the original receipts for those expenses.

Participants who complete the first pancreatic juice collection but who do not complete the entire protocol will receive $50 remuneration and no additional reimbursement. Participants who do not complete the first pancreatic juice collection will not receive remuneration or reimbursement.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

The study intervention is oral indomethacin or identical placebo. Indomethacin is an FDA approved, commonly prescribed NSAID. Commercially available indomethacin will be utilized in this study and over-encapsulated to match the placebo capsules. A package insert for indomethacin is attached to this protocol.

6.1.2 DOSING AND ADMINISTRATION

Participants in both study arms will receive study medication, one capsule orally BID for 28 days. Those in the indomethacin arm will receive indomethacin 50 mg BID, and those in the placebo arm will receive placebo capsules BID.

Participants will be advised not to make up missed doses. They will be advised to take a dose of study medication on the morning of their follow-up endoscopy, 2 hours prior to their scheduled procedure time, with a sip of water. At the time of follow-up endoscopy they will return any unused study medication.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

6.2.1 ACQUISITION AND ACCOUNTABILITY

Indomethacin capsules are purchased by Mayo Clinic Research Pharmacy. Mayo Clinic Production Lab overencapsulates indomethacin capsules and creates matching lactose placebo capsules in bulk supply. After preparation, blinded medication is returned to Research Pharmacy and stored at 20-25C.
Research Pharmacy utilizes an electronic inventory management system (Vestigo) to maintain investigational drug inventory and prescription dispensing records.

Investigator issues an electronic prescription for study medication and sends to Research Pharmacy. The prescription is processed, patient is randomized by pharmacy staff, and a blinded pharmacy label is generated and attached to the study medication bottle. Study medication prescriptions are picked up by study team at Research Pharmacy, or mailed to patient's home address upon request.
Unused study medication is returned to Research Pharmacy where capsules are counted, return count is recorded in Vestigo, and capsules are destroyed per policy. Expired medications are removed from inventory and destroyed per policy.

Investigator may prescribe up to 31 days of study medication, so that in case of rescheduling of the Day 28 endoscopy the subject may continue to take study medication for up to an additional 3 days.

6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Generic indomethacin 50 mg capsules are obtained from Cardinal Health by Research Pharmacy. Research pharmacy sends indomethacin bottles to Production Lab where they are encapsulated and matching placebo capsules are created. Blinded batches are labeled and returned to Research Pharmacy for storage until dispensation. When a prescription is received, pharmacy staff randomizes patient and places ordered quantity of study medication into a prescription bottle. Bottle is labeled in a blinded fashion, and dispensed to study team for dispersal to patient.

6.2.3 PRODUCT STORAGE AND STABILITY

Indomethacin and placebo capsules are stored in Research Pharmacy at room temperature (20-25C). Daily min/max temperatures are recorded manually every business day, and electronic temperature data is captured continuously via TempTrak. Temperature data is available for viewing upon request.

6.2.4 PREPARATION

Described above.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

Randomization: Subjects will be assigned to receive IN or placebo according to a computer generated randomization list composed of randomized blocks of sizes of 2 or 4. Two separate sets of blocks will be created, one for subjects with alcoholic CP and the other for those with other causes of CP. Within each block, equal number of subjects will be assigned to IN and placebo. Separate sets of blocks will be provided for Mayo and Ohio State. The randomization lists will be computer generated by the study statistician (Dr Li), and kept in a secure computer file and paper study binder in the Mayo and Ohio State Research Pharmacies. No investigators or study personnel other than Dr Li and staff at Mayo/OSU research pharmacies will have knowledge of the randomization list. Dr Li will not participate in any aspect of subject recruitment, subject allocation, conduct of the study, or data ascertainment, but will perform data analysis with de-identified data.

Subject allocation will be known only to the staff of the Mayo and Ohio State Research Pharmacies, who will assign subjects to IN or placebo according to their randomization list provided by Dr. Li. Allocation will be performed by matching the subject's study number with the randomization list. Allocation will not be revealed to subjects, investigators, other study personnel, or clinicians caring for subjects until all subjects have completed the clinical trial or for medical emergency. Because subjects, investigators, and study personnel will be blinded, they will not be able to determine subject allocation before or during data ascertainment.

Allocation will be performed on the day of the participant's baseline endoscopy with pancreas juice collection. One container of study medication containing 28 days of medication (56 capsules) will be dispensed to the participant that day.

In case a subject is allocated to receive study medication, but is withdrawn from the study before completing the protocol, study medication will be returned to the Research Pharmacy for disposal.

Blinding: Study medication will be labelled "indomethacin 50 mg or placebo capsule" with the subject's name, hospital or clinic number, study IRB number, and subject number. Placebo and IN capsules will be identical in appearance. The investigators, study coordinator, and clinical caregivers will remain blinded to subject allocation throughout the data ascertainment and data entry phase of the study.

The success of blinding will be evaluated by asking the investigator, the study coordinator, and the subject the following question during each telephone follow-up visit: "Which treatment group is this subject/were you assigned to: placebo, active drug, or unsure?"

6.4 STUDY INTERVENTION COMPLIANCE

Participants will complete a daily symptom and medication diary. Unused study drug will be returned by the participant on the day of their follow-up endoscopy procedure. Unused capsules will be counted, documented and returned to the research pharmacy for disposal. Indomethacin levels will be measured in blood collected on the morning of the follow-up endoscopy procedure.

6.5 CONCOMITANT THERAPY

Participants who have taken aspirin or NSAIDs at any time during the 7 days prior to their baseline endoscopy procedure are excluded from participation. Participants will be asked to refrain from taking aspirin or NSAIDs throughout the 28 days of study drug administration.

6.5.1 RESCUE MEDICINE

Not applicable.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

Study interventions (endoscopy, pancreas juice collection, dispensing of study medication) will be halted if there are 2 or more SAEs attributable to study interventions, pending IRB review. If study interventions are halted, participants who are actively taking study medication may continue to take study medication and complete the study protocol, but no new study medication will be dispensed.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation at any time upon request. An investigator may withdraw a participant from the study for the following reasons:

1. Found to have active gastrointestinal ulceration at the time of their baseline, clinically indicated GI endoscopy procedure.
2. Positive pregnancy test in a woman of child bearing potential.
3. Significant study medication non-compliance (defined as failure to take at least 66% of study medication doses, as determined during telephone follow-up calls).
4. Hospitalized for acute pancreatitis during study participation.
5. Other acute illness that requires breaking study blinding and discontinuing study medication for clinical reasons.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to complete more than one telephone follow-up visit within 48 hours of its scheduled time, or fails to return or reschedule study visit 3.

The following actions must be taken if a participant fails to return to the clinic or is not available by telephone for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 24 hours, and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary,

a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts will be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

The *endoscopic pancreatic function test (ePFT)* will be performed at baseline and on day 28. ePFT is a standardized test used in medical pancreatology clinical practice that involves administration of intravenous secretin (0.2 mcg/kg slowly over one minute) to stimulate pancreatic juice secretion, followed by aspiration of pancreatic juice from the duodenum via an endoscope. Some subjects will undergo a baseline ePFT as part of their routine clinical care; other subjects, who are having upper GI endoscopy or endoscopic ultrasound (EUS) performed as part of their clinical care, will undergo ePFT for research purposes during their baseline, clinically indicated endoscopy. Fluid will be aspirated from the duodenum via an endoscope at baseline and from 0-10 and 10-20 minutes following secretin administration, and processed per CPDPC pancreas juice/fluid SOP. Participants will be instructed take their study drug with a sip of water 2 hours prior to their follow-up research endoscopy with ePFT on day 28.

PJ bicarbonate and lipase concentrations will be measured on duodenal aspirates from each time point using a previously validated method.[18] *PGE2 concentrations* will be measured in saliva, blood, and pancreatic juice from baseline and day 28 using a tandem mass spectroscopy assay developed and validated at Mayo Clinic Rochester. *Peak IN drug levels* will be measured in blood on day 28, providing an assessment of participant compliance with study drug administration. Exploratory analysis of molecular analytes (cytokine and microbiome) in blood and saliva will be done to measure effect of IN administration.

The *Brief Pain Inventory (BPI)* and the *PROMIS-10* are validated scales that quantify pain and quality of life, respectively, and will be completed at baseline and day 28.

A *medication and pain diary* will be completed daily by all subjects at baseline and during the 28-day treatment period, including all narcotics and over-the-counter medications used. Oral opioid usage will be expressed in oral morphine equivalents for purposes of data analysis.

8.2 SAFETY AND OTHER ASSESSMENTS

Screening of potential participants for eligibility will be done during the screening visit. Additional elements (serum creatinine result, presence of active GI ulceration) will be determined subsequent to the screening visit when laboratory results are available, and during the baseline endoscopy.

Physical Examination, including chest, cardiac, and abdominal exams, will be documented in the patient's medical record within 30 days of their baseline endoscopy procedure.

Height and weight will be measured within 30 days of the participant's baseline endoscopy procedure.

Serum creatinine will be measured within 30 days of the participant's baseline endoscopy procedure. This test will be performed for research purposes, and the result placed in the patient's medical record, if it is not being performed clinically. Participants with serum creatinine outside of the laboratory normal range will be withdrawn from the study and considered non-accrued.

Blood draw will be up to 30 cc at study visit 1 (baseline) and up to 20 cc at study visit 3 (day 28). This includes up to 10 cc for measurement of serum PGE2 at both time points. Baseline blood draw also includes up to 10 cc for measurement of serum creatinine if not already measured for clinical purposes, and up to 10 cc for aspirin and NSAID screens. Day 28 blood draw also includes up to 10 cc for indomethacin level. Details of biospecimen handling are documented in the study biospecimen SOP.

Endoscopic procedures will be performed on clinical GI Endoscopy Units at the current standard of clinical care at Mayo Clinic Rochester and Ohio State University, including the use of monitored anesthesia care (MAC) or general anesthesia (GA) at the discretion of the attending gastroenterologist and anesthesiologist. Participants will receive pre-procedure evaluation, intra-procedural monitoring, and post-procedural recovery care identical to that provided to patients undergoing endoscopy in these units. Staff nurses, anesthetists, and GI endoscopists will be available to assess symptoms and adverse events and provide appropriate treatment during endoscopic procedures and their recovery period. Participants will be discharged from the endoscopy unit when they meet the unit's standard discharge criteria.

Secretin Administration: Secretin will be administered intravenously during GI endoscopy procedures at baseline and day 28 at a weight-based dose of 0.2 mcg/kg administered slowly over one minute. Fluid will be aspirated from the duodenum via an endoscope at baseline and from 0-10 and 10-20 minutes following secretin administration, and processed per CPDPC pancreas juice/fluid SOP. Participants will be instructed take their study drug 2 hours prior to their follow-up research endoscopy with ePFT on day 28. Details of biospecimen handling are documented in the study biospecimen SOP.

Medical History and Endoscopic Findings: Subjects with a history of cirrhosis, chronic renal insufficiency, gastroduodenal ulceration, GI bleeding, stroke, myocardial infarction, or hospitalization for acute pancreatitis within 6 weeks of enrollment are excluded from participation. Subjects found to have active gastric or duodenal ulceration at the time of baseline endoscopy are also excluded. Women who are pregnant or nursing and persons older than 70 years of age, who are at higher risk for aspirin or NSAID-related adverse events, are also excluded from this study.

Women of child bearing potential must have a negative serum or urine pregnancy test within 48 hours of initiating study drug treatment, and must agree to remain sexually abstinent or use birth control measures for the duration of their study participation and for 5 days afterward.

A woman is NOT considered to be of "child-bearing potential" if their menses ceased within the past 2 years or if they have undergone hysterectomy.

The following birth control methods are acceptable for study purposes:

- Hormonal methods, such as birth control pills, patches, injections, vaginal ring, or implants
- Barrier methods (such as a condom or diaphragm) used with a spermicide (a foam, cream, or gel that kills sperm)
- Intrauterine device (IUD)
- Abstinence (no sex)

Weekly Follow-up: Subjects will be contacted weekly by telephone by a study coordinator weekly during study drug administration, as well as several days following completion of study drug administration. The coordinator will ask about compliance with study medication, completion of the daily symptom and medication diary, and new or worsening symptoms or health concerns. Subjects will be encouraged to report new symptoms or health problems to study staff, which will result in communication between a physician-investigator and the subject. Subjects will be able to report symptoms or ask questions at other times by telephone. A study physician will be available to respond to subjects by telephone at all times.

Study enrollment logs containing individually identifiable private information will be stored in secure non-public sites at each study site, as detailed above.

Incidental findings noted during study endoscopy will be described in the clinical endoscopy report generated after each endoscopy exam, which is placed in the patient's medical record. Subjects will be informed of incidental findings and encouraged to follow-up with their clinical care professional about any incidental findings.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

"Adverse event" means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, 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, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. Examples relevant to this trial include adverse effects of GI endoscopy and its associated sedation that result in hospitalization, or gastrointestinal hemorrhage or vascular events in subjects receiving indomethacin.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- **Potentially Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

8.3.3.3 EXPECTEDNESS

Drs. Vege and Han, the study co-PIs, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

Expected adverse events include (but are not limited to) allergic reactions to study medication, adverse effects of indomethacin such as upset stomach, vomiting, heartburn, diarrhea, constipation, bloating, flatus, rash, itching, tinnitus, lightheadedness. Serious adverse events may include gastrointestinal ulceration, bleeding, perforation or obstruction as well as renal insufficiency or known complications of GI endoscopy. However the protocol has been designed to minimize the risk of these SAEs by excluding persons with risk factors for endoscopic adverse events, NSAID-induced gastrointestinal ulceration or renal insufficiency.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits or weekly scheduled telephone interviews of a study participant, by communication to study staff initiated by the study participant, or when a participant presents for medical care.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The study coordinators will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

AEs will be reported to the study PIs within 24 hours, and summarized in quarterly reports to the study DSMB as well as annual reports to the IRB, FDA and NIH. Furthermore, AEs will be reported to additional regulatory agencies (such as the FDA) if and as required.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

According to 21 CFR 312.64(b), "An investigator must immediately report to the sponsor any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor…"

According to 21 CFR 312.32(c)(1), "the sponsor must notify FDA and all participating investigators…in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting… In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction, and must analyze the significance of the suspected adverse reaction in light of previous, similar reports or any other relevant information. The sponsor must report any suspected adverse reaction that is both serious and unexpected. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

> *(A) A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);*
> *(B) One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture);*
> *(C) An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group."*

Furthermore, according to 21 CFR 312.32(c)(2), "the sponsor must also notify FDA of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information."

The study clinicians will immediately report to the DSMB any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or ICF, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the DSMB, IRB, FDA, or NIH and should be provided as soon as possible.

The study PI is responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar

days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the PI determines that the information qualifies for reporting.

SAEs will be summarized in quarterly reports to the DSMB and in annual reports to the IRB, NIH and FDA.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

A de-identified summary of AEs and SAEs will be included in published results of this trial, and this information will be made available to study subjects.

8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

8.3.9 REPORTING OF PREGNANCY

If a study participant reports that they are pregnant they will be advised to immediately discontinue study drug use. Study endoscopic procedures will not be performed on pregnant participants. Pregnant participants will be withdrawn from the study.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

An incident, experience, or outcome that meets the definition of an UP may warrant consideration of changes to the protocol or consent in order to protect the safety, welfare, or rights of participants or

others. Other UPs may warrant corrective actions at a specific study site. Examples of corrective actions or changes that might need to be considered in response to an UP include:

- Modification of inclusion or exclusion criteria to mitigate the newly identified risks
- Implementation of additional safety monitoring procedures
- Suspension of enrollment of new participants or halting of study procedures for enrolled participants
- Modification of informed consent documents to include a description of newly recognized risks
- Provision of additional information about newly recognized risks to previously enrolled participants.

8.4.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the DSMB. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or ICF, or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the DSMB immediately, and to the IRB within 7 days of the investigator becoming aware of the event.
- Any other UP will be reported to the DSMB within 30 days of the investigator becoming aware of the problem, and summarized in quarterly reports to DSMB and annual reports to the IRB, FDA and NIH.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) within 3 months of the IRB's receipt of the report of the problem from the investigator.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

UPs that are SAEs may require revision of the study informed consent form (ICF). In that case, study participants who are active participants (taking study drug or scheduled for study endoscopy) will be informed of the revisions to the ICF and re-consented.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint:

- Decrease in mean pancreatic juice PGE_2 concentration after indomethacin treatment, to no more than 66% of baseline, and statistically significant in comparison to placebo.

Secondary Efficacy Endpoints:

- Changes in salivary and blood PGE_2 concentrations after study drug administration will have statistically significant correlation with changes in PJ PGE_2 concentrations and blood IN levels.
- Salivary and blood PGE_2 concentrations will have statistically significant correlation with PJ PGE_2 concentrations.
- Improvement in pain and quality of life of study participants will have statistically significant correlation with post-treatment changes in PJ PGE_2 concentrations.
- Exploratory analysis of molecular analytes (cytokine and microbiome) in blood and saliva will be done to measure effect of IN administration.

9.2 SAMPLE SIZE DETERMINATION

We plan a sample size of 16 patients per treatment arm. Since this is a pilot study, this sample size is largely limited by budgetary restraint and is too small for a sequential study design. However, this sample size is adequate for studying the primary hypothesis with a two-sample two-sided t-test on the mean PGE_2 level at day 28 between the randomized groups. We expect to show that the treatment group has significantly lower mean PGE_2 than the placebo group. In our previous publication on PJ PGE_2,[20] we reported that median PJ PGE_2 level in 10 CP patients was 307 pg/ml with IQR of 249-362 pg/ml and standard deviation of 84 pg/ml. The boxplot of that data suggests that normality is a reasonable distributional assumption for the PGE_2 data. That study also found that mean PJ PGE_2 in a healthy control group was 104 pg/ml, about one third of the mean level of the CP group. If we conservatively assume that the control group in the proposed trial has 50% decrease in mean, with a Type I error of 0.05, the power of the t-test is 0.998. If we use an even more conservative mean for the control group, with 1/3 reduction in mean PGE_2, the power is 0.94. If we additionally assume that there is some data loss (due to consent withdrawal, dropout, or specimen mishandling) so that the sample size per treatment group is 12 instead of 16, the statistical power decreases to 0.85, but is still reasonable. Note that the large statistical power in the calculation above is a result of the relatively small standard deviation of the PGE_2 compared with our working assumption on the mean reduction. This assumption is supported by the data in Abu Dayyeh et al.[20] If this pilot study is successful, we will conduct a future study that focuses on patient centered outcomes; that study is expected to have a larger sample size because those outcomes are expected to be less sensitive to the treatment than biomarkers. The data from this pilot study will provide critical preliminary and feasibility data for the future investigation.

9.3 POPULATIONS FOR ANALYSES

Given the small sample size of this pilot study, the entire study population completing the study protocol will be utilized for most analyses. Per-Protocol analysis will be used primarily (e.g., participants who took at least 80% of study intervention for 80% of the days within the treatment period).

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

For descriptive statistics, categorical and continuous data will be presented as percentages or medians with ranges as appropriate. P-values < 0.5 will be considered statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

For the Primary Endpoint/Specific Aim 1, the primary analysis will be a linear random intercept model that incorporates PJ PGE_2 data from both baseline and day 28 from all randomized patients. Transformation will be used as appropriate to reduce the skewness of data and satisfy modeling assumption. The model includes randomized groups, time, and their interactions as fixed effect covariates, from which the mean change in PJ PGE2 will be estimated for each randomized group. Effects of additional covariates, such as sex and sites, will be explored. The intra-subject correlation will be estimated from the variances of the random intercepts and residuals. Other outcome variables, such as other biomarkers and questionnaire data, can be analyzed in a similar way. The estimates about the variability of data and intrasubject correlations will be useful for designing a subsequent larger study.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

For Secondary Endpoints/Specific Aim 2, we will use multivariate analysis of variance model (MANOVA) with repeated measures. The multivariate outcomes include patient-related outcomes (BPI and PROMIS-10 scores) and PJ PGE_2 concentrations at baseline and day 28. Fixed effect covariates include randomized groups, time, and their interactions. Additional secondary analyses include descriptive analysis and statistical comparison of PJ PGE_2 concentrations at baseline and after secretin administration between the various study groups, and correlations between baseline PJ PGE_2 levels, clinical features, and changes in plasma and saliva PGE_2 levels. Changes in daily pain ratings and narcotic use (in morphine equivalents) will be analyzed in comparison to changes in PJ PGE_2 concentrations. Any dropout before Day 28 will be documented and descriptively summarized. Sensitivity analysis on dropout will be conducted in an exploratory manner according to standard missing data analysis procedure for longitudinal data.[19] As a pilot study, we will collect and descriptively analyze data on feasibility, patient compliance and satisfaction, and attrition, in order to inform the possible future study.

9.4.4 SAFETY ANALYSES

The frequency and severity of AEs in the placebo and IN groups will be calculated and compared statistically. Because IN is a common medication that has been in use for many decades its adverse effect profile is already well known, and we do not expect data from this pilot study to materially change our understanding of its adverse effects.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive statistics will compare the IN and placebo groups on variables including age, gender, cause of pancreatitis (if known), time since the most recent episode of acute pancreatitis requiring

hospitalization, presence and duration of diabetes, exocrine insufficiency, pancreas enzyme replacement therapy (PERT) and history of occasional NSAID or ASA use.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

Not applicable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Study data will be tabulated in electronic databases and spreadsheets.

9.4.9 EXPLORATORY ANALYSES

Analyses of patient-reported outcomes (PRO) and quality of life (QOL) data are exploratory, and meant to form a basis for sample size calculation for subsequent larger clinical studies.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention. Consent materials are attached to this study protocol and IRB application.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

[Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their family or

surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the IRB, FDA, and NIH. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a password-protected study RedCap database that is accessible to the study teams at both Mayo Clinic and OSU. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at Mayo Clinic.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at Mayo Clinic and Ohio State University. After the study is completed, the de-identified, archived data will be transmitted to and stored at Mayo Clinic and/or Ohio State University, for use by other researchers including those outside of the study. Permission to transmit data to Mayo Clinic will be included in the informed consent.

With the participant's approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at Mayo Clinic and/or Ohio State University with the same goal as the sharing of data. These samples could be used to research the causes of pancreatic disease, its complications and other conditions for which individuals with pancreatitis are at increased risk, and to improve treatment. Biospecimens will be labelled with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage may not be possible after the study is completed.

When the study is completed, access to study data and/or samples will be provided by joint review and decision of the study PIs at Mayo Clinic and Ohio State University.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

PI – Mayo Clinic	**PI – Ohio State University**
Santhi Vege, M.D.	Samuel Han, M.D.
200 First St SW, Rochester, MN 55901	Room 201, 395 W. 12th Ave., Second FL, Columbus, OH, 43210
507-774-2175	614-366-6819
Vege.santhi@mayo.edu	*Samuel.Han@osumc.edu*

Project Leadership Plan:
Dr. Vege at Mayo Clinic will be responsible for the oversight and coordination of the project, including subject recruitment, enrollment, and conduct of the protocol at Mayo Clinic as well as communication with IRB, FDA, and NIH. Dr. Han at Ohio State University (OSU) will be responsible for all aspects of the project at OSU. Each PI will be responsible for his own fiscal and research administration, and for supervising the research team at their respective institutions.
The PIs will communicate bi-weekly, either by phone, e-mail, or in person, to discuss recruitment, enrollment, biospecimen collection, processing, and storage, data analysis, and all administrative responsibilities. They will share their respective research results and insights with each other. They will work together to discuss any changes in the direction of the research project and the reprogramming of funds, if necessary. They will agree together on a publication policy.
Dr. Vege will serve as contact PI and be responsible for submission of progress reports to NIH and all communication.
Intellectual Property
The Technology Transfer Offices at Mayo Clinic and OSU will be responsible for preparing and negotiating an agreement for the conduct of the research, including any intellectual property. An Intellectual Property Committee composed of representatives from each institution that is part of the grant award, will be formed to work together to ensure the intellectually property developed by the PIs is protected according to the policies established in the agreement.
Conflict Resolution
If a potential conflict develops, the PIs shall meet and attempt to resolve the dispute. If they fail to resolve the dispute, the disagreement shall be referred to an arbitration committee consisting of one impartial senior executive from each PI's institution and a third impartial senior executive mutually agreed upon by both PIs. No members of the arbitration committee will be directly involved in the research grant or disagreement.
Change in PI Location
If a PI moves to a new institution, attempts will be made to transfer the relevant portion of the grant to the new institution. In the event that a PI cannot carry out his/her duties, a new PI will be recruited as a replacement at one of the participating institutions.

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a Data and Safety Monitoring Board (DSMB) composed of individuals with the appropriate expertise, including one gastroenterologist at Mayo Clinic and one gastroenterologist at Ohio State University. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will meet (by telephone or video conference) at least quarterly to assess safety and efficacy data of the study, and will meet as needed when informed of study SAEs or UPs. The DSMB will provide its input to the study PIs and IRB, and generate a quarterly DSMB report.

The charter of the DSMB is to:

1) Review all SAEs and UPs in a timely fashion, as detailed in sections 8.3 and 8.4 of this protocol.
2) To halt study activities (including drug administration and endoscopic procedures) pending IRB and FDA review if 2 or more SAEs have occurred that, in the opinion of the DSMB, are definitely or probably related to study participation.

3) To advise the study PIs regarding changes to the study protocol and/or ICF in response to AEs, SAEs and UPs.
4) Generate a quarterly report based on data provided by study staff.

The quarterly DSMB report will be sent to the study staff including the PIs, and will be included in reports to IRB, FDA and NIH. The quarterly report will include:

a. A summary of study recruitment, enrollment, and participant completion
b. A summary of all AEs, SAEs and UPs that have occurred since the last quarterly report and in total for the study
c. Recommendations regarding study protocol or ICF modification, study suspension or discontinuation.

10.1.7 CLINICAL MONITORING

Site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

This section should give a general description of how monitoring of the conduct and progress of the clinical investigation will be conducted (i.e., who will conduct the monitoring, the type, frequency, and extent of monitoring, who will be provided reports of monitoring, if independent audits of the monitoring will be conducted). This section may refer to a separate detailed clinical monitoring plan.

A separate clinical monitoring plan (CMP) should describe in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports. A CMP ordinarily should focus on preventing or mitigating important and likely risks, identified by a risk assessment, to critical data and processes. The types (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification)) of monitoring activities will depend on a range of factors, considered during the risk assessment, including the complexity of the study design, types of study endpoints, clinical complexity of the study population, geography, relative experience of the PI and of the sponsor with the PI, electronic data capture, relative safety of the study intervention, stage of the study, and quantity of data.

If a separate CMP is not used, include all the details noted above in this section of the protocol.

*Example text when a **separate CMP is being used is provided as a guide, customize as needed**:*

[Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- Monitoring for this study will be performed by <insert text>.
- <Insert brief description of type of monitoring (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g.,

comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification or targeted data verification of endpoint, safety and other key data variables)>.

- <Insert text> will be provided copies of monitoring reports within <x> days of visit.
- Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of monitoring reports.
- Independent audits <will/will not> be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites and that monitors are following the CMP.]

OR

*Example text when a **separate CMP is <u>not</u> being used is provided as a guide, customize as needed**:*

[Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- <Insert detailed description of who will conduct the monitoring, the type of monitoring (e.g., on-site, centralized), frequency (e.g., early, for initial assessment and training versus throughout the study), and extent (e.g., comprehensive (100% data verification) versus targeted or random review of certain data (less than 100% data verification or targeted data verification of endpoint, safety and other key data variables)), and the distribution of monitoring reports>
- Independent audits <will/will not> be conducted by <insert text> to ensure monitoring practices are performed consistently across all participating sites.]

<Insert text>

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL*:*

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data forms and telephone interview scripts are attached to the protocol and IRB application.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into study electronic databases. Clinical data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the all study interventions have been completed and the study is closed. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 5 working days of identification of the protocol deviation, or within 5 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, and reported to the study DSMB in quarterly reports. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data from this study may be requested from other researchers 5 years after the completion of the primary endpoint by contacting Drs Vege and Han.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

10.2 ADDITIONAL CONSIDERATIONS

Not applicable.

10.3 ABBREVIATIONS

The list below includes abbreviations utilized in this template. However, this list should be customized for each protocol (i.e., abbreviations not used should be removed and new abbreviations used should be added to this list).

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CMP	Clinical Monitoring Plan
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data Safety Monitoring Board
DRE	Disease-Related Event
EC	Ethics Committee
eCRF	Electronic Case Report Forms
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FFR	Federal Financial Report
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
ISO	International Organization for Standardization
ITT	Intention-To-Treat
LSMEANS	Least-squares Means
MedDRA	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
MSDS	Material Safety Data Sheet
NCT	National Clinical Trial
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SMC	Safety Monitoring Committee

SOA	Schedule of Activities
SOC	System Organ Class
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.

Version	Date	Description of Change	Brief Rationale

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