**COVER PAGE**

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# STATIN THERAPY TO REDUCE THE RISK OF RECURRENT PANCREATITIS

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# SCHEMA
## Statin Therapy to Reduce the Risk of Recurrent Pancreatitis

**Patients with acute or chronic pancreatitis**

▼

**Pre-Screen Eligibility Review – Initial determination of eligibility**

Inpatients and outpatients at study sites. Clinical research staff will review medical records of patients hospitalized for pancreatitis, and of patients who have an upcoming appointment with a study gastroenterologist, to assess potential eligibility: pancreatitis history, statin use, prohibited concomitant medications, medical contraindications. Referrals from physicians at outside institutions and self-referrals (medical records not available). Research staff will field questions from patients who call to request more information. Staff will describe the study and review the eligibility criteria using an IRB-approved phone script to assess potential eligibility.

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**Screen 1 – Consent and Secondary determination of eligibility**

Interested pre-screen eligible patients will be recruited and consented into the trial before any research related procedures are initiated. Trial gastroenterologists will confirm recurrent pancreatitis using the Atlanta Classification and will review computed tomography (CT) and magnetic resonance imaging (MRI) results in the past 12 months. *Patients with CT or MRI evidence of advanced chronic pancreatitis will be excluded.*

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**Screen 2 – Final determination of eligibility**

Consented patients who are eligible after Screen 1 will undergo the following procedures to confirm eligibility: physical exam, blood draw, pregnancy test (for women of child-bearing potential), and an endoscopic ultrasound (EUS) and endoscopic pancreatic function test (ePFT). *Patients with EUS evidence of advanced chronic pancreatitis, patients with lab results outside the eligibility range, and women who are pregnant will be excluded.*

▼

**Eligible, consented patients with recurrent pancreatitis randomized to simvastatin or placebo (n=30)**

| Simvastatin 40 mg, daily for 6 months (N=20) | Placebo identical in color, consistency, and appearance to simvastatin 40 mg, daily for 6 months (N=10) |
|---|---|

▼

**Study Visit 1 – Baseline / initiation of the intervention (0-14 days following Screen 2)**

Review medical history, medications, and laboratory test results; vital signs; symptom assessment; ECOG performance status; blood draw; self-collected fecal specimen; interviewer-administered risk questionnaire; self-administered QLQ-C30 and QLQ-PAN28(CP); review inclusion/exclusion criteria; dispense study drug and diary

▼

**Study Visit 2 (3 months ± 1 month after initiation of the intervention)**

Review medical history, medications, and laboratory test results; physical exam; vital signs; symptom assessment; ECOG performance status; blood draw; EGD and ePFT; self-collected fecal specimen; pregnancy test for women of child-bearing potential; self-administered QLQ-C30 and QLQ-PAN28(CP); review inclusion/exclusion criteria; collect study drug and diary; assess compliance and adverse events; review diary; dispense study drug and diary

▼

**Study Visit 3 (6 months ± 1 month after initiation of the intervention)**

Review medical history, medications, and laboratory test results; physical exam; vital signs; symptom assessment; ECOG performance status; blood draw; EUS and ePFT; self-collected fecal specimen; pregnancy test for women of child-bearing potential; interviewer-administered risk questionnaire; self-administered QLQ-C30 and QLQ-PAN28(CP); collect study drug and diary; assess compliance (pill count); review study diary; assess adverse events

▼

**Follow-up telephone calls to assess adverse events (30, 60, and 90 days ± 7 after completion of Study Visit 3)**

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**Endpoints – Evaluate the effect of simvastatin versus placebo after 6 months of treatment on:**

1) Change in pancreas exocrine function (secretin-stimulated peak bicarbonate concentration in the pancreatic fluid) as measured by ePFT
2) Change in EUS score
3) Change in serum and pancreatic fluid levels of cytokines, chemokines, and adhesion molecules
4) Change in pancreatitis-related readmissions
5) Change in quality of life score as measured by the QLQ-C30 and QLQ-PAN28(CP)

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# 1. OBJECTIVES

## 1.1 Primary Objectives

To evaluate the effect of a simvastatin intervention versus placebo on the change in secretin-stimulated peak bicarbonate concentration in the pancreatic fluid at 6 months post-treatment in patients with a history of at least two episodes of acute pancreatitis in the past 12 months.

## 1.2 Secondary Objectives

To evaluate the effect of a simvastatin intervention versus placebo at 6 months from baseline (Study Visit 1) on:

(1) Change in the endoscopic ultrasound score (EUS);
(2) Change in serum and pancreatic fluid levels of cytokines, chemokines, and adhesion molecules;
(3) Change in pancreatitis-related readmissions; and
(4) Change in quality of life score as measured by the QLQ-C30 and QLQ-PAN28(CP).

# 2. BACKGROUND

## 2.1 Study Disease

Pancreatic cancer is the fourth leading cause of cancer death in the US, and it has an extremely high fatality rate [1]. The incidence for pancreatic cancer in the US has been increasing for more than a decade, in parallel with the rates of pancreatitis, and both are driven by the epidemic of obesity and diabetes [2]. Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas, characterized by chronic pancreatic inflammation and scarring, irreversibly damaging the pancreas and resulting in loss of exocrine and endocrine function. The primary symptoms of CP are abdominal pain, maldigestion, and steatorrhea [3]. Chronic pancreatitis, which results from repeated episodes of acute pancreatitis, is the strongest identified risk factor for pancreatic cancer and increases the risk by at least 13.3 fold [4]. Pancreatitis and pancreatic cancer exist in a disease continuum; patients with an episode of acute pancreatitis have a 20-30% likelihood of one or more recurrent episodes, with progression to chronic pancreatitis in an estimated 10% of the recurrent cases [2, 5, 6]. Interventions that have the ability to prevent the development of pancreatic cancer in this high-risk population would therefore address a currently unmet major public health problem and would have a high clinical impact. Despite this need, and the associated high impact potential, few studies have investigated the effectiveness of a chemopreventive strategy for pancreatic cancer.

## 2.2 Study Agent

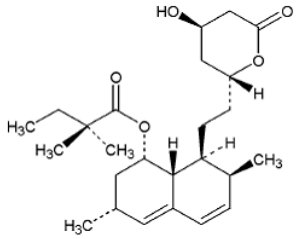


**Figure 1. Molecular structure of simvastatin**

Simvastatin (butanoic acid, see Figure 1) is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol. The empirical formula of simvastatin is $C_{25}H_{38}O_5$ and its molecular weight is 418.57. Simvastatin USP is a white to off-white powder that is practically insoluble in water; freely soluble in chloroform, in methanol and in alcohol; sparingly soluble in propylene glycol; very slightly soluble in hexane.

Simvastatin tablets for oral administration contain either 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg simvastatin and the following inactive ingredients: ascorbic acid, citric acid, hydroxypropyl cellulose, hypromellose, iron oxides, lactose, magnesium stearate, microcrystalline cellulose, starch, talc, and titanium dioxide. Butylated hydroxyanisole is added as a preservative.

Simvastatin is the most commonly prescribed HMG-CoA reductase inhibitor, which has a widely accepted tolerability profile with few serious side effects [7]. Potential, but uncommon side effects include muscle, liver, and kidney problems. Elevated levels of creatine kinase and rhabdomyolysis occur in <1% of consumers. In a clinical trial database in which 41,413 patients were treated with simvastatin, 60% of whom were enrolled in studies with a median follow-up of at least 4 years, the incidence of myopathy was approximately 0.03% and 0.08% at 20 and 40 mg/day, respectively. The incidence of myopathy with 80 mg (0.61%) was disproportionately higher than that observed at the lower doses [8].

Simvastatin is prescribed for primary and secondary prevention of cardiovascular disease and thus is indicated for long-term use. We propose to administer simvastatin 40 mg daily for 6 months in this trial.

## 2.3 Rationale

**Hypotheses:**

1) Participants randomized to simvastatin will experience a greater increase from baseline (Study Visit 1) in peak bicarbonate concentration measured at 6 months after initiation of the intervention compared to the placebo group.

2) Compared to the placebo group, participants randomized to simvastatin will experience
   (a) A greater reduction from baseline in EUS score;
   (b) A greater decrease in pro-inflammatory markers and a greater increase in anti-inflammatory markers;
   (c) Fewer episodes of pancreatitis-related readmissions; and
   (d) Improvement in quality of life score.

Pancreatic cancer is amenable to a chemoprevention strategy. The progression from acute pancreatitis to chronic pancreatitis to pancreatic cancer is characterized by a progressive desmoplastic reaction and an associated inflammatory injury to pancreatic cells, induced by factors such as a high fat diet, smoking, and alcohol. Both fibrotic and inflammatory processes involve paracrine cross-talk between the extracellular matrix (ECM), pancreatic epithelial cells and non-epithelial cells, including fibroblasts, stellate cells, and immune cells [9]. Of particular importance is the pancreatic stellate cell which, when activated by pro-fibrogenic mediators [10], in turn produces excess i.e., desmoplasia-associated ECM, growth factors, such as transforming growth factor-β [TGF-β], and inflammatory factors, including IL-1β and IL-6. These factors collectively promote proliferation and invasion via triggering the epithelial-to-mesenchymal transition [EMT] [11], which gives rise to cancer cells with stem-like properties, leading to formation of a localized cancer to metastatic disease [9, 12]. Emerging literature shows that microRNAs, such as miR-217, may also play a role in this pathogenic process by activating EMT [13]. Several cytokines and C-reactive protein (CRP) are increased in the blood during moderate to severe acute pancreatitis. Serum IL-6 is an established pro-inflammatory marker in acute pancreatitis [14-19], and it also predicts disease severity and duration [20-23]. Levels of IL-6 increase early and remain elevated in severe acute pancreatitis [20-23]. In contrast, IL-10 is an anti-inflammatory cytokine that increases later in the disease process and remains elevated with protracted disease [20-23]. IL-10 is thus associated with resolution of acute inflammation [15, 24-27].. Circulating biomarkers associated with chronic pancreatitis are not as established. However, there are two studies showing that chronic pancreatitis patients have increased levels of TGF-β1 [28, 29]. Individual studies report increases in tumor necrosis factor-α (TNF-α) [28], and soluble fractalkine [29].

**Exocrine insufficiency and endoscopic pancreatic function test (ePFT).** Pancreatic inflammation and fibrosis that result from unresolved pancreatitis directly cause a decrease in exocrine function, reflected in a reduced secretion of bicarbonate and pancreatic enzymes [30]. Although fibrosis, inflammation, and loss of parenchymal tissue are best measured by *tissue-based histology*, an invasive biopsy procedure can cause pancreatitis [31] and is therefore *not an option for biological measurement*. The current gold standard for diagnosing chronic pancreatitis is the endoscopic pancreatic function test (ePFT) which measures secretin-stimulated production of bicarbonate ion from pancreatic ductal cells during an endoscopic ultrasound procedure (EUS) [3, 32]. Clinically, ePFT-based peak bicarbonate levels can distinguish mild and severe chronic pancreatitis, and is correlated with the extent of histologically determined fibrosis (r=-0.57) [33]. Because ePFT is based on an endoscope-guided collection of pure pancreatic fluid, it provides a direct measurement of pancreatic function that is superior to indirect measurements in stool i.e., fecal elastase [34]. Endoscope-based specimen collection will also allow for measurement of immune cytokines and other potential biomarkers in the pancreatic fluid. Pancreatic fluid cytokine levels have been shown to discriminate chronic pancreatitis from milder disease and pancreatic cancer from normal pancreas [35, 36].

**Statins and the prevention of recurrent pancreatitis.** Because of the paracrine and self-perpetuating nature of the desmoplastic process in the promotion of pancreatic carcinogenesis, it constitutes a key process whose early disruption is a logical target for preventing pancreatic cancer. HMG-CoA reductase inhibitors, commonly known as statins, are cardioprotective drugs that also have immunomodulatory properties relevant to pancreatic carcinogenesis. Animal models of pancreatitis demonstrate that statins decrease pancreatitis in association with a reduction in pro-inflammatory factors [37, 38]. Following induction of chronic pancreatitis in rats, 10 mg/kg/day of *pravastatin* substantially attenuated the progression of pancreatic inflammation, fibrosis, and exocrine dysfunction [37]. Increased levels of the anti-inflammatory cytokine, IL-10, and decreased levels of the pro-inflammatory cytokine, TNF-α, in the intervention group compared to the control group suggests that pravastatin may mediate early inflammatory reactions.

Biochemically, statins directly bind leukocyte function antigen-1 (LFA-1), resulting in reduced leukocyte adhesion to sites of injury, and subsequent suppression of the inflammatory response [39]. A carboxylic moiety of statins also bind to the catalytic site of histone deacetylase (HDAC) protein 2 [40], leading to attenuation of HDAC-mediated inflammation [41], and may also downregulate HDAC-mediated epithelial to mesenchymal transition [42], which plays an important role in invasion and metastases of cancer cells. Indirectly, inhibition of HMG-CoA reductase also results in reduced production of isoprenyl groups that directly modify key small GTPase proteins (i.e., RhoA, Ras) involved in inflammation and fibrogenesis [43, 44]. Taken together, these studies demonstrate that statins inhibit, either directly or indirectly, several signaling pathways implicated in pancreatic carcinogenesis. Coupled with the fact that statins have been used clinically for a long time, and have a very favorable toxicity profile, these studies support the hypothesis that statins may effectively prevent or reduce the risk of pancreatic cancer.

Consistent with this notion, we have recently reported that patients taking simvastatin, the most commonly prescribed statin, experience a dramatic reduction in pancreatitis incidence. Simvastatin was independently associated with a 70% reduced risk of pancreatitis, with a rate ratio of 0.29 (95% CL 0.27, 0.31) after adjustment for age, sex, race/ethnicity, gallstone disorders, hypertriglyceridemia, and alcohol and tobacco use [45]. While our investigation suggests that statins may attenuate pancreatitis and pancreatitis-associated carcinogenesis, this needs to be rigorously tested in the context of a prospective clinical trial. We hypothesize that statins will improve pancreatic function in high-risk patients, as defined by those with two or more episodes of acute pancreatitis. Our multi-disciplinary research team will randomize pancreatitis patients with recurrent pancreatitis to simvastatin versus placebo, and will evaluate the impact of statin treatment on pancreatic function and inflammation implicated in pancreatic

carcinogenesis. Measures will include pancreatic exocrine function (secretin-stimulated peak bicarbonate concentration; the primary endpoint), endoscopic ultrasound measures of pancreatitis, inflammation-associated cytokines, chemokines, and adhesion molcules (serum and pancreatic secretion), and clinical recurrence. Our randomized trial will elucidate pathophysiological pathways of pancreatitis, and is designed to provide badly needed new prevention strategies for those at high risk for pancreatic cancer.

## 3. SUMMARY OF STUDY PLAN

We will conduct a randomized double-blinded, placebo-controlled Phase II trial of statin to evaluate the impact of statin treatment on pancreatic function and inflammation in patients diagnosed with recurrent pancreatitis who are undergoing treatment at four study sites: Cedars-Sinai Medical Center (CSMC), Kaiser Southern California Permanente Medical Group (KPMC), the University of Pittsburgh (UP), and Stanford University (SU). Thirty patients will be randomized to simvastatin or placebo (20 in the simvastatin arm, 10 in the control). Assuming that ~20% of the study participants drop-out, we expect to have data on a final sample of 24 men and women (16 simvastatin, 8 control) completing the 6-month follow-up period. Clinical and research measurements will be taken at Baseline (Study Visit 1), Month 3 (Study Visit 2), and Month 6 (Study Visit 3). Three and 6 months were chosen, given that patients have variable recovery times in the order of months after an acute pancreatitis event [46]. Therefore, the repeated measures at 3 and 6 months will be essential for determining the trajectory of change in the clinical and research measurements during the recovery period.

Patients with at least two episodes of acute pancreatitis in the past 12 months will be recruited for the study. We will recruit study participants among several pools of patients: patients hospitalized for acute or chronic pancreatitis at the study sites, patients who have an upcoming appointment scheduled with a study gastroenterologist, patients referred by other physicians or staff through outpatient clinics, and patients who self-refer. All patients will receive their usual care under the guidance of their physician.

**Pre-Screen Eligibility Review – Initial determination of eligibility and recruitment**

Inpatients and outpatients at study sites. The clinical research staff at each site will review the medical records of patients hospitalized for pancreatitis to determine if they have had at least one previous episode of acute pancreatitis in the past 12 months; have a history of use, adverse effects and/or contraindications to statin medication (e.g., current systemic use of gemfibrozil, cyclosporine, danazol, or strong CYP3A4 inhibitors); and to rule out medical contraindications and prohibited concomitant medications specified in the eligibility criteria. The medical records of patients who have an upcoming appointment with one of the study gastroenterologists, and the medical records of patients who are referred by other physicians at the institution, will also be reviewed for eligibility. The research staff will notify one of the trial gastroenterologists that a patient is potentially eligible for the trial based on the pre-screen evaluation.

Potentially eligible patients who are hospitalized will be approached by one of the trial gastroenterologists or a study team member. After describing the trial and answering the patient's questions, patients who express an interest in participating in the trial will be given a study information packet that includes the IRB-approved study consent form and HIPAA authorization, and IRB-approved recruitment materials (e.g., introductory letter, study brochure; each participating site will choose what materials to include). Patients will be encouraged to review the consent documents with family, friends, and/or other physicians.

Clinical research staff will prepare and mail the study information packet to potentially eligible patients who are outpatients (e.g., patients who have an upcoming appointment with a study gastroenterologist, patients hospitalized for pancreatitis who are discharged before the study team has an opportunity to approach them, referrals from other physicians). One of the study gastroenterologists or clinical research

staff will call potentially eligible patients within 14 days after the packet is mailed to introduce the study and answer questions.

Referrals from physicians at outside institutions and self-referrals (medical records not available). Additional recruitment strategies such as leaflets placed in outpatient clinics, study announcements sent to physicians at outside institutions, flyers and half-page ads posted at outside institutions and at community clinics, and video bulletins displayed on screens at the study sites and outside institutions, will be employed to increase awareness of the trial and aid in our recruitment goals. The recruitment materials will contain contact information for the study. A member of the study team will field questions from patients who respond to direct advertisement and outside referrals who call to request more information. Staff will describe the study and review the eligibility criteria with the patient using an IRB-approved phone script to assess potential eligibility. If the patient is potentially eligible and interested in the trial, they will be mailed the study information packet including the consent form and HIPAA authorization. Patients who are interested in participating in the study will be scheduled for a visit to sign the study consent documents. Clinical research staff will follow-up with a phone call to potentially eligible patients who are undecided within 14 days after the packet is mailed to evaluate interest in study participation and answer additional questions. Patients who want to volunteer for the study will be scheduled come to the clinic to sign the study consent documents.

**Screen 1 – Consent and Secondary determination of eligibility**. One of the trial gastroenterologists will review the study details and consent documents with interested pre-screen eligible patients after all clinical options have been presented to the patient. After the patient's questions have been answered, the gastroenterologist will obtain signatures on the study consent form and HIPAA authorization. Copies of each form will be given to the patient and placed in the medical record. The patient will be told that the decision to join or not join the study will not affect the medical treatment that s/he receives, and that s/he can withdraw from the study at any time. Written consent will be obtained before any research related procedures are initiated.

After consent has been obtained, a secondary assessment of eligibility will be conducted. If not available at the study site, the clinical research staff will retrieve medical records from other institutions for pancreatitis history. One of the trial gastroenterologists will review the patient's pancreatitis history and confirm the diagnosis of recurrent pancreatitis (at least two episodes of acute pancreatitis in the past 12 months) using the Atlanta Classification. The diagnosis of acute pancreatitis will be confirmed by any two of the following three features: (1) Typical upper abdominal pain often radiating to the back; (2) Elevation in serum amylase or lipase ≥3 times upper limit of normal; (3) Features of acute pancreatitis on cross-sectional imaging [47]. The gastroenterologist will also review the patient's computed tomography (CT) and magnetic resonance imaging (MRI) results from the past 12 months. Patients with evidence of advanced chronic pancreatitis by CT or MRI will be excluded.

**Screen 2 – Final determination of eligibility**. Consented patients who are eligible after Screen 1 will undergo an endoscopic ultrasound (EUS) and endoscopic pancreatic function test (ePFT) within 8 weeks after consent to rule out advanced chronic pancreatitis. Patients will also have a physical exam, vital signs assessment, symptom assessment, ECOG performance status, and a blood draw to confirm eligibility.

We will exclude patients with advanced chronic pancreatitis as determined by the following criteria:

a) EUS score greater than or equal to 6,
b) calcifications in combination with atrophy and/or dilation of ≥5 mm, or
c) evidence of advanced chronic pancreatitis by computed tomography (CT) or magnetic resonance imaging (MRI) results in the past 12 months.

Diagnosis of advanced chronic pancreatitis is based on satisfying one or more of the following criteria

[3]:

a) Intra-ductal or pancreatic parenchymal calcification(s) on cross-sectional imaging;
b) 6 or more standard criteria for chronic pancreatitis on endoscopic ultrasound (EUS) (**Table 1**);

**Table 1. EUS criteria for chronic pancreatitis**

| Ductal Features | Parenchymal Features |
|---|---|
| Duct well echogenicity | Echogenic foci |
| Side branch dilation | Cysts (>3 mm in size) |
| Calculi | Accentuation of the lobular pattern |
| Irregular pancreatic duct margins | Focal regions of reduced echogenicity |
| Main duct (dilation and narrowing) | |

c) Findings on MRI/MRCP: major duct abnormalities (Cambridge Classification 3 or greater) (**Table 2**).

**Table 2. Cambridge classification for chronic pancreatitis**

| Grade | Main pancreatic duct | Side branches |
|---|---|---|
| Normal (Grade 0) | Normal | Normal |
| Equivocal (Grade I) | Normal | <3 Abnormal |
| Mild (Grade II) | Normal | ≥3 Abnormal |
| Moderate (Grade III) | Abnormal | >3 Abnormal |
| Severe (Grade IV) | Abnormal with at least one of the following:<br>Large cavity >10 mm<br>Duct obstruction<br>Intraductal filling defect<br>Severe dilatation or irregularity | >3 Abnormal |

Because statins are known to be teratogenic, women of child-bearing potential will be required to have a pregnancy test during Screen 2. Women who are pregnant will be excluded from the trial. Patients with lab results outside the eligibility range will also be excluded.

Screen 2 eligible/consented patients will be registered and randomized to the study drug (either simvastatin or placebo). The Screen 2 EUS and ePFT results will be used as Study Visit 1 baseline measurements.

**Study Visits**

Study Visit 1 (Baseline measurements and initiation of the intervention). The first study visit will occur 0-14 days after Screen 2. The following procedures will be performed during this visit:

a) Review of medical history, medications, and laboratory test results; vital signs assessment, symptom assessment, and ECOG performance status
b) Blood collection for clinical labs and research
c) Collection of a fecal specimen (self-collected at home)
d) Interviewer-administered comprehensive questionnaire (demographics, risk factor and clinical assessment (Appendix E)
e) Self-administered QLQ-C30 and QLQ-PAN28(CP) to assess quality of life and pain level (Appendix D)
f) Review of inclusion /exclusion criteria
g) Dispense study drug and review instructions for how to take it
h) Dispense study diary and review instructions for how to complete it

Study Visit 2. The first follow-up visit will occur 3 months (± 1 month) after initiation of the intervention. The following procedures will be performed during this visit:

a) Review of medical history, medications, and laboratory test results; physical exam, vital signs assessment, symptom assessment, and ECOG performance status
b) Blood collection for clinical labs and research
c) Endoscopic pancreatic function test (ePFT) and simultaneous esophagogastroduodenoscopy (EGD)
d) Collection of a fecal specimen (self-collected at home)
e) Pregnancy test for women of child-bearing potential
f) Self-administered QLQ-C30 and QLQ-PAN28(CP) to assess quality of life and pain level
g) Review of conformance with inclusion /exclusion criteria
h) Dispense study drug and review instructions for how to take it
i) Review study drug diary and assess medication compliance and adverse events

Study Visit 3. The final visit will occur 6 months (± 1 month) after initiation of the intervention. The following procedures will be performed during this visit:

a) Review of medical history, medications, and laboratory test results; physical exam, vital signs assessment, symptom assessment, and ECOG performance status
b) Blood collection for clinical labs and research
c) Endoscopic pancreatic function test (ePFT) and simultaneous endoscopic ultrasound (EUS)
d) Collection of a fecal specimen (self-collected at home)
e) Pregnancy test for women of child-bearing potential
f) Interviewer-administered follow-up questionnaire to obtain information about changes in exposures and behaviors since the baseline visit (Appendix F)
g) Self-administered QLQ-C30 and QLQ-PAN28(CP) to assess quality of life and pain level
h) Compliance assessment (pill count) and collection of study agent and study diary
i) Assess adverse events

**Post-intervention follow-up**. Clinical research staff will make follow-up telephone calls to study participants on days 30 ± 7, 60 ± 7, and 90 ± 7 after completion of Study Visit 3 to assess symptoms and adverse events.

Accrual will occur within 24 months with an expected accrual rate of 1-2 subjects per month across four study sites. We anticipate that all evaluable participants will have completed all study procedures within three years.

**Study Measurements**

**Physician assessment.** Study subjects will have an assessment by a gastroenterologist at the time of screening and enrollment, and at the subsequent planned study visits at Months 3 and 6. Each assessment will include an interval symptom history; vital signs, including blood pressure, heart rate, respiratory rate, and temperature; and measurement of weight. Height will be measured at Study Visit 1 only.

**Baseline and follow-up questionnaires.** A structured interview (Appendix E), developed for this investigation and including risk factor and clinical assessment, will be administered by the staff at Study Visit 1. The questionnaire will obtain information regarding date of birth; detailed race/ethnicity; and education; medical history, including pancreatic diseases and diabetes; medications, including analgesics and antibiotics; physical activity; history of alcoholic beverage consumption; tobacco smoking history; and anthropometry. A shorter questionnaire (Appendix F) will be administered at the 6-month visit to assess alcohol use and surgical procedures that will impact the risk of recurrent pancreatitis.

**Quality of life and pain assessment**. We will measure quality of life and pain level using the QLQ-C30 and QLQ-PAN28(CP) (Appendix D). The European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 is a 30-item measure developed to assess the quality of life of cancer patients [48]. The measure includes three scales: global health status, functional status (physical, role, emotional, cognitive, and social), and physical symptoms. The EORTC QLQ-PAN26 is a 26-item measure specifically for patients with pancreatic cancer that assesses pain, dietary changes, disease symptoms, and emotional problems related to pancreatic cancer [49]. The QLQ-PAN28(CP) is a modified version of the QLQ-PAN26 for patients with chronic pancreatitis [50]. Participants will self-administer the QLQ-C30 and QLQ-PAN28(CP) assessments.

**Endoscopic pancreatic function test (ePFT) and simultaneous endoscopic ultrasound (EUS) and fasting pancreatic fluid.** Patients will be instructed to fast overnight (8 hours) before the endoscopic testing. Pancreatic fluid through the ePFT will be collected at Screen 2 (will be used as Study Visit 1 baseline measurement), Month 3 (Study Visit 2), and Month 6 (Study Visit 3) to measure secretin-stimulated peak bicarbonate concentration; cytokines, , chemokines, and adhesion molecules. EUS will be performed at Screen 2 and at Study Visit 3. Esophagogastroduodenoscopy (EGD), a simpler endoscopic procedure without the ultrasound imaging, will be performed at Study Visit 2.

**Fecal specimen.** A fecal specimen will be collected from participants at Study Visits 1, 2, and 3 for measurement of fecal elastase. A stool collection kit and instructions will be provided to the participant before the scheduled visit. The specimen will be self-collected at home and brought to the study visit.

**Blood specimen.** A blood specimen (approximately 10 mL) will be collected from patients at the Screen 2 visit for blood tests to confirm eligibility. A Complete Blood Count and Automated Differential (CBDF) [for hemoglobin, leukocytes, neutrophils, and platelets] and a Comprehensive Metabolic Panel (CMPL) [for total bilirubin, liver enzymes (AST/ALT), and creatinine] will be done to confirm that laboratory levels for acceptable organ, hepatic, and renal function are within the eligibility requirements. Alkaline phosphatase and glucose are also required at this visit to establish baseline levels but are not necessary for eligibility verification. See Appendix A for Clinical Laboratory Minimum Test Requirements. If a patient's lab results within 35 days before the Screen 2 visit are available in the medical record and are within eligibility range, their blood will not be drawn at the Screen 2 visit. Otherwise, the patient's blood will be drawn to confirm eligibility.

A blood specimen (approximately 36 mL) will be collected from each participant at Study Visits 1, 2, and 3. Approximately 10 mL of blood will be drawn for laboratory blood tests to monitor for potential adverse effects of the intervention and to confirm that laboratory levels meet the eligibility requirements for continuation in the trial. A Lipid Panel will be done at all study visits; a CBDF and a CMPL will be done at Study Visits 2 and 3; hemoglobin A1C will be measured at Study Visits 1 and 3; and creatine phosphokinase (CPK) will be measured at Study Visit 1 only. See Appendix A for Clinical Laboratory Minimum Test Requirements. Twenty-six mL of blood will be collected for research purposes. Six mL of blood will be drawn for measurement of serum concentrations of protocol-specific biomarkers (cytokines, chemokines, and adhesion molecules), and 20 mL of blood will be drawn for DNA extraction and use in future studies.

**Pregnancy test.** Because statins are known to be teratogenic, women of child-bearing potential will be required to have a confirmed negative pregnancy test prior to enrollment and at Study Visits 2 and 3. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.

## 4. PARTICIPANT SELECTION

## 4.1 Inclusion Criteria

4.1.1 At least two episodes of acute pancreatitis in the past 12 months. Acute pancreatitis is defined as any 2 of the following: (1) Typical upper abdominal pain; (2) Elevation in serum amylase or lipase ≥3 times upper limit of normal; (3) Features of acute pancreatitis on cross-sectional imaging.

4.1.2 Age ≥18 years.

4.1.3 ECOG performance status ≤1 (Karnofsky ≥70%; see Appendix B).

4.1.4 Participants must have acceptable organ, hepatic and renal function as defined below:

| | |
|---|---|
| Leukocytes | ≥2,500/microliter |
| Absolute neutrophil count | ≥1,500/microliter |
| Platelets | ≥100,000/microliter |
| Hemoglobin | >10 g/dL |
| Total bilirubin | ≤3 × institutional upper limit of normal (ULN) |
| AST (SGOT)/ALT (SGPT) | ≤1.5 × institutional ULN |
| Creatinine | <1.5 mg/dL |

Patients whose lab levels meet the inclusion criteria by Screen 2 will be included in the trial.

4.1.5 Women of child-bearing potential must have a confirmed negative pregnancy test result prior to enrollment.

4.1.6 The effects of simvastatin on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because statins are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her study physician immediately. It is not known whether simvastatin is excreted into human milk; however, a small amount of another drug in this class does pass into breast milk. Because statins have the potential for serious adverse reactions in nursing infants, women who receive treatment with simvastatin should not breastfeed their infants.

4.1.7 Ability to understand and the willingness to sign a written informed consent document and medical release.

4.1.8 Willing and able to comply with trial protocol and follow-up.

## 4.2 Exclusion Criteria

4.2.1 Prior or current use of statin medication, or current systemic use of gemfibrozil, cyclosporine, danazol, lomitapide, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, ranolazine, or strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, or cobicistat-containing products).

4.2.2 History of chronic myopathy

4.2.3 Current use of any other investigational agents

4.2.4 History of adverse effects, intolerance, or allergic reactions attributed to compounds of similar chemical or biologic composition to simvastatin (i.e., other statin medications).

4.2.5 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

4.2.6 Women who are pregnant or breastfeeding. Pregnant women are excluded from this study because simvastatin is a lipid-lowering agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with simvastatin, breastfeeding should be discontinued if the mother is treated with simvastatin.

4.2.7 Presence of gallstones or hypertriglyceridemia (level greater than 800 mg/dl) that requires medical or surgical intervention. *Note: We will include patients who had an independent episode of pancreatitis after a cholecystectomy, but exclude patients who are candidates for cholecystectomy.*

4.2.8 History of pancreatic adenocarcinoma (at any time)

4.2.9 History of active malignancy in the past 2 years (excluding basal/squamous cell skin cancer or prostate cancer with a Gleason score 6 or less)

4.2.10 Known active infection with HIV

4.2.11 Concurrent illness, such as known psychiatric disorders or substance abuse (i.e., average alcohol consumption of more than 5 drinks per day), which in the opinion of the investigators would compromise either the patient or the integrity of the data

4.2.12 Lab results do not meet inclusion criteria 4.1.4 by Screen 2.

4.2.13 Recurrent pancreatitis episode is iatrogenic (endoscopic retrograde cholangiopancreatography (ERCP) induced)

4.2.14 Advanced chronic pancreatitis as determined by the following criteria: EUS score greater than or equal to 6, calcifications in combination with atrophy and/or dilation of ≥5 mm, or evidence of advanced chronic pancreatitis by computed tomography (CT) or magnetic resonance imaging (MRI) results in the past 12 months.

### 4.3 Inclusion of Women and Minorities

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

### 4.4 Recruitment and Retention Plan

Patients with recurrent pancreatitis will be recruited for the study from the CSMC Pancreatic and Biliary Diseases Program, the KPMC Center for Pancreatic Care, the SU Gastroenterology and Digestive Health Clinic, and Presbyterian/Montefiore and Shadyside Hospitals at the UP Medical Center. Gastroenterologists at the four institutions jointly treat approximately 1,600 patients with acute pancreatitis annually, of whom approximately 600 (38%) are recurrent acute pancreatitis cases. We estimate that 40% (240) will not be eligible because they have not had at least two episodes of pancreatitis in the past 12 months, and that 40% will not be eligible due to current or prior statin use, presence of

gallstones, or other medical contraindications. We project that 120 potentially eligible patients will be approached for consent annually across four study sites (240 patients during the 24-month accrual period). Based on this patient population and the importance of our objectives to the gastroenterology community, **our recruitment goal of 30 patients** with two or more episodes of pancreatitis in the past 12 months is highly feasible. The sample size of 30 will include an estimated 14 women (10 white, 2 black, 2 Asian) and 16 men (11 white, 3 black, 2 Asian) with confirmed recurrent pancreatitis. Each of the investigators has substantial experience with patient recruitment and/or clinical trials of pancreatic diseases and will insure that our recruitment goals are met. Neither the repeated endoscopies nor the ePFT are considered barriers to recruitment as there is minimal risk (minor pain, discomfort, and few other sequelae) associated with the procedure. Healthy subjects have been subjected to cross-over studies of endoscopic and Dreiling tube pancreatic function tests, performed in tandem with a 1-week washout, and no procedure- or medication-related complications were reported [51]. Trial gastroenterologists will work closely with their gastroenterology teams in the recruitment effort.

Patients who are eligible for the trial based on the pre-screen eligibility review by the clinical research staff (initial determination of eligibility) will be provided with a study information packet that includes the IRB-approved study informed consent form and HIPAA authorization, and IRB-approved recruitment materials (each participating site will choose what materials to include). Patients will be encouraged to review the consent documents with family, friends, and/or other physicians. One of the trial gastroenterologists will review the study details and consent documents with interested pre-screen eligible patients after all clinical options have been presented to the patient. After the patient's questions have been answered, the gastroenterologist will obtain signatures on the consent documents. Written consent will be obtained before any research related procedures are initiated. After consent has been obtained, Screen 1, the secondary assessment of eligibility, will be conducted by trial gastroenterologists (review of computed tomography (CT) and magnetic resonance imaging (MRI) results and confirmation of recurrent pancreatitis). Consented patients who are eligible after Screen 1 will undergo Screen 2 (final determination of eligibility to rule out advanced chronic pancreatitis and pregnancy) within 8 weeks after consent. Screen 2 eligible/consented patients will be registered and randomized to the study drug. Study Visit 1 (Baseline measurements), the beginning of the intervention (study agent dispensed), will occur 0-14 days after Screen 2.

Research visits, scheduled at the participating clinic, will coincide whenever practicable with usual care to reduce travel time and increase compliance with the study protocol. Participants will receive $50 when they complete the Screen 2 testing and $150 at the time they complete each study visit for their time, transportation, parking, and other expenses related to the study. Participants who complete the entire study – the Screen 2 testing, and three study visits – will receive $500.

**Compensation schedule**

| Screen 2 | Study Visit 1 | Study Visit 2 | Study Visit 3 |
|---|---|---|---|
| $50 | $150 | $150 | $150 |

Study visits will be scheduled at 3 months (± 1 month) and 6 months (± 1 month) to avoid protocol violations. A day or two prior to the scheduled follow-up visit, the participant will be contacted by telephone to confirm or reschedule his/her visit. Patients who develop intercurrent pancreatitis will receive usual medical care by their gastroenterologist, and their next study visit will be rescheduled if necessary. The study coordinator will have a database which tracks active participants who do not have a scheduled visit or who have missed their targeted visit date. Study visits will be rescheduled for up to 2 months until the participant is considered lost to follow-up.

## 5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events (AEs) and potential risks are described in Section 6.2.

## 5.1 Dose Regimen and Dose Groups

Thirty participants with recurrent pancreatitis will be randomized into one of 2 groups: 20 participants will receive 40 mg simvastatin per day and 10 participants will receive a placebo identical in color, consistency, and appearance to simvastatin 40 mg. Simvastatin and placebo will be provided as over-encapsulated tablets. Dosing will extend for 6 months.

- Agent(s): Simvastatin and placebo
- Daily dose(s) and regimen(s) for each agent: One 40 mg capsule per day
- Duration for each agent: Daily treatment for 6 months

The usual recommended dose of simvastatin is 10-40 mg/day, and the toxicity and tolerability are comparable for 20 mg and 40 mg [8].

## 5.2 Study Agent Administration

Patients will self-administer the 40 mg capsule of simvastatin or placebo daily in the evening. Patients will be instructed to take the study agent at bedtime or with an evening meal. Each participant will be given 1 bottle of 120 capsules at Study Visit 1 and 1 bottle of 120 capsules at Study Visit 2 (Month 3).

## 5.3 Run-in Procedures

None.

## 5.4 Contraindications

Patients are advised not to consume any form of grapefruit (e.g., juice, fruit, grapefruit seed extract, dietary supplements containing grapefruit) while on simvastatin as grapefruit may increase the blood levels of simvastatin [52]. Participants enrolled in the study will be instructed to avoid all forms of grapefruit.

The combined use of simvastatin with systemic formulations of gemfibrozil, cyclosporine, danazol, lomitapide, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, ranolazine, or strong CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors, boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone, and cobicistat-containing products) is contraindicated due to an increased risk for myopathy. Patients will be screened for contraindications to simvastatin prior to enrollment in the study. Patients with known active infection with HIV will be excluded from the study. Patients will be advised not to use contraindicated medications during the study and will be excluded if systemic use of any contraindicated medication is unavoidable. Concomitant medications will be reviewed at study visits and during follow-up telephone calls. Participants will be closely monitored for symptoms and side effects to the study drug and will be instructed to call the study doctor immediately if they have a serious adverse reaction.

## 5.5 Concomitant Medications

All medications (prescription and over-the-counter), vitamin and mineral supplements, and/or herbs taken by the participant will be documented on the concomitant medication CRF and will include: 1) start and

stop date, dose and route of administration, and indication. Medications taken for a procedure (e.g., biopsy) should also be included.

## 5.6 Dose Modification

No dose modifications are planned. The study agent will be stopped in the event of an AE ≥ grade 3 considered possibly, probably, or definitely related to the study agent. The study agent will be restarted after resolution. One of the common side effects of statin medication is myalgia (muscle pain with normal creatine phosphokinase (CPK) level), and rarely this is associated with statin myopathy (muscle weakness or other muscle injury with or without elevation in CPK level). In randomized controlled trials of standard dose statin therapy, the risk is very low (<1%). We will measure levels of CPK in the blood drawn at the first study visit to establish a patient-specific reference for this indicator of muscle toxicity. During the trial, if the participant reports unexplained muscle pain or weakness, CPK will be tested again to check for elevation. The study agent will be temporarily discontinued in subjects experiencing grade 1 or greater myopathy (unexplained muscle symptoms *and* creatine phosphokinase (CPK) > 2.5 times institutional ULN) or hepatotoxicity (ALT or AST > 1.5 times institutional ULN) that is considered possibly, probably, or definitely related to the study agent. Resolution of myopathy or hepatotoxicity will be evaluated with follow-up laboratory blood tests 4 weeks after the elevated levels occur. If the lab test results are still elevated after 4 weeks, the study agent will be discontinued permanently and the participant's primary care physician will be notified of the abnormal tests. If the lab test results return to normal levels, participant will go back on the study agent.

Because dose modification could lead to lack of dose homogeneity that may impair the research objectives, we will stop the intervention in patients who initiate drugs that require dose modifications of simvastatin below 40 mg: lomitapide, verapamil, diltiazem, dronedarone, amiodarone, amlodipine, or ranolazine.

## 5.7 Adherence/Compliance

Compliance will be measured by pill counts and patient diaries. Compliance is defined as 80% of the total dose with all doses of the study agent taken during the week before Study Visit 2 and Study Visit 3 (final visit). A patient diary will be used to monitor daily compliance (Appendix C). Participants will be instructed to record the time the study drug was taken each day in the diary, as well as any potential side effects.

Phone calls will be made to study participants every four weeks (± 7 days) to monitor compliance. Participants will be asked if they missed any doses of medication, and the dates of all missed doses will be recorded. The study agent diary will be reviewed with participants at every visit. Participants who report having taken < 80% of the study drug doses between phone calls, or whose pill count at a study visit reveals < 80% compliance, will be called every two weeks (± 3 days) to monitor compliance.

The participant will be asked at registration if they would like to receive reminder emails or text messages regarding the study medication. Messages will be sent daily for the first week; in following weeks, messaging will be targeted to participants having difficulty remembering their dose. Since agent compliance is very important during the final week of the intervention, text/email messages will be sent to all study participants who opt to receive these reminders. In addition, phone calls will be made to all study participants during the week before their final visit (Visit 3) to remind them to take the study drug every day until the last study visit when the final endoscopic procedure will be performed. Participants will also be reminded to bring any leftover study drugs and the study diary with them to each visit.

Pill (capsule) counts will be performed at Study Visits 2 and 3 to assess compliance. All participants that receive a study agent for any period of time will be evaluable for toxicity.

## 6. PHARMACEUTICAL INFORMATION

### 6.1 Study Agent (IND # [redacted] (Exempt), IND Sponsor: NCI/Division of Cancer Prevention)

Simvastatin is a lipid-lowering agent that is derived synthetically from a fermentation product of *Aspergillus terreus*. After oral ingestion, simvastatin, which is an inactive lactone, is hydrolyzed to the corresponding β-hydroxyacid form, which is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in the biosynthesis of cholesterol.

The empirical formula of simvastatin is C25H38O5 and its molecular weight is 418.57. Simvastatin USP is a white to off-white powder that is practically insoluble in water; freely soluble in chloroform, in methanol and in alcohol; sparingly soluble in propylene glycol; very slightly soluble in hexane. Simvastatin tablets for oral administration contain 40 mg simvastatin and the following inactive ingredients: ascorbic acid, citric acid anhydrous, hydroxypropyl cellulose, hypromellose, lactose anhydrous, magnesium stearate, pregelatinized starch, talc, titanium dioxide and iron oxide red. Butylated hydroxyanisole is added as a preservative. The botanical source for pregelatinized starch is corn starch. Simvastatin and placebo will be provided as overencapsulated tablets.

### 6.2 Reported Adverse Events and Potential Risks

The most common (incidence ≥5.0% patients) reported adverse events (AEs) are upper respiratory infection, headache, abdominal pain, constipation, and nausea. Other AEs reported in clinical trials (<5%) were diarrhea, rash, dyspepsia, flatulence, and asthenia.

Persistent increases in serum transaminases (to more than 3 x ULN) have occurred in approximately 1% of patients who received simvastatin in clinical studies. When drug treatment was interrupted or discontinued in these patients, the transaminase levels usually fell slowly to pretreatment levels. The increases were not associated with jaundice or other clinical signs or symptoms. It is recommended that liver function tests be performed before the initiation of treatment, and thereafter when clinically indicated.

Simvastatin occasionally causes myopathy manifested as muscle pain, tenderness or weakness with creatine kinase above 10 x ULN. Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. Predisposing factors for myopathy include advanced age (≥65 years), female gender, uncontrolled hypothyroidism, and renal impairment. The risk of myopathy, including rhabdomyolysis, is dose related. The risk of myopathy and rhabdomyolysis is increased by high levels of statin activity in plasma. Simvastatin is metabolized by the cytochrome P450 isoform 3A4 (CYP3A4). Certain drugs which inhibit this metabolic pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. These include itraconazole, ketoconazole, posaconazole, voriconazole, the macrolide antibiotics erythromycin and clarithromycin, and the ketolide antibiotic telithromycin, HIV protease inhibitors, boceprevir, telaprevir, the antidepressant nefazodone, cobicistat-containing products, or grapefruit products. Combination of these drugs with simvastatin is contraindicated. If short-term treatment with strong CYP3A4 inhibitors is unavoidable, therapy with simvastatin must be suspended during the course of treatment.

Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors, including simvastatin.

## 6.3 Availability

Simvastatin and matching placebo are investigational agents supplied to investigators by NCI/DCP through MRIGlobal.

Simvastatin 40 mg and matching placebo will be supplied as overencapsulated tablets for oral administration. Simvastatin and matching placebo will be packaged with 120-count 40 mg overencapsulated tablets/bottle. Each participant will receive one bottle at Study Visit 1 and one bottle at Study Visit 2 (Month 3).

## 6.4 Agent Distribution

Agents will only be released by NCI, DCP after documentation of IRB approval of the DCP-approved protocol and consent is provided to DCP and the collection of all Essential Documents is complete (see DCP website for description of Essential Documents).

NCI, DCP-supplied agents may be requested by the Investigator (or their authorized designees) at each Organization. DCP guidelines require that the agent be shipped directly to the institution or site where the agent will be prepared and administered. DCP does not permit the transfer of agents between institutions (unless prior approval from DCP is obtained). DCP does not automatically ship agents; the site must make a request. Agents are requested by completing the DCP Clinical Drug Request form (NIH-986) (to include complete shipping contact information) and faxing or mailing the form to the DCP agent repository contractor:

John Cookinham
MRIGlobal
DCP Repository
1222 Ozark Street
North Kansas City, MO 64116
Phone: (816) 360-3805
FAX: (816) 753-5359
Emergency Telephone: (816) 360-3800

## 6.5 Agent Accountability

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCP using the NCI Drug Accountability Record Form (DARF). The Investigator is required to maintain adequate records of receipt, dispensing, and final disposition of study agent. This responsibility has been delegated to the study pharmacists: Annie Yi, Pharm.D., Investigational Drug Pharmacist at Cedars-Sinai Medical Center; Joseph Chang, Pharm.D., Pharmacy Manager at Kaiser Southern California Permanente Medical Group; Linda Gibson, R.Ph., Investigational Pharmacist at the University of Pittsburgh; and Scott Mayeda, Diem Tran, and Khanh Nguyen, Pharmacists at Stanford University. The receipt record will include from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. The dispensing record will note quantities and dates study agent was dispensed to and returned by each participant. The study agent will be dispensed to the subject at Study Visit 1 and Study Visit 2.

## 6.6 Packaging and Labeling

Simvastatin and placebo will be packaged and labeled by NCI DCP.

Each bottle will be labeled with a one-part label identifying study specific information, such as Study title, DCP protocol number, dosing instructions, recommended storage conditions, the name and address of the distributor, randomization number, and a caution statement indicating that the agent is limited by United States law to investigational use only and the agent should be kept out of reach of children.

## 6.7 Storage

The DCP Drug Repository, MRIGlobal, will distribute the study agent directly to each participating site. Study agents will be stored in a safe, secure, temperature monitored limited access drug storage area specifically for research medication at the Research Pharmacy at each site. Study agents shall be maintained at a controlled room temperature [between 15-30°C] by the Research Pharmacy at each site and once dispensed, the subjects will be instructed to store the drug in their homes protected from light, heat, and moisture. MRIGlobal will be notified in the event of a temperature excursion below 15°C or above 30°C for 24 hours continuously. MRIGlobal will evaluate the temperature excursions on a case-by-case basis.

## 6.8 Registration/Randomization

The Lurie Cancer Center Clinical Trials Management System (CTMS) will be the database of record. The study coordinator must upload (via CTMS), a signed and complete informed consent along with HIPAA authorization and a completed registration form for each participant identified as eligible to be entered into the study.

All participants must be registered in CTMS Monday-Friday between the hours of 9:30 a.m. and 5:00 p.m., Central Time (CT). Participants must not start protocol treatment prior to registration in CTMS.

After registration, participants will be randomized by a member of the Quality Assurance Team of the Northwestern University Lurie Cancer Center (NU) to treatment with the study agent or placebo. Investigators and participants will be blinded as to the result of randomization. The following people will be un-blinded: the study statistician at Northwestern University (NU); the quality assurance team at NU; and the investigational pharmacists at CSMC, KPMC, UP, and SU. Full unblinded randomization information will be emailed to the investigational pharmacist at each study site. The study statistician will set up randomization blocks.

The clinical research coordinators at CSMC, KPMC, UP, and SU will receive a blinded Participant ID code for the patient via email.

Randomization procedures are also provided in Section 13.

## 6.9 Blinding and Unblinding Methods

The research pharmacist will manage the investigational agent. The blind will be maintained through the effort of the research pharmacist, and the pharmacy. Unblinding will only occur when it is deemed medically necessary, and will only take place after consultation with the NCI, DCP Task Order Monitor. If the NCI Task Order Monitor cannot be reached and the participant requires emergency care, the Study Chairman may authorize the site PI to break the blind. The date and reason for breaking the blind must be submitted by the site PI to the Study Chairman and the NCI Task Order Monitor as soon as possible.

DCP Medical/Task Order Monitor
Luz Maria Rodriguez, MD, FACS
NCI/Division of Cancer Prevention

9609 Medical Center Dr.
Rm 5E-228
Bethesda, MD 20892
Telephone (240) 276-7039
Fax (240) 276-7848
Email: rodrigul@mail.nih.gov

### 6.10 Agent Destruction/Disposal

At the completion of investigation, all unused study agent will be destroyed according to local institutional procedures. Destruction records must be provided to MRIGlobal at the end of the study.

## 7. CLINICAL EVALUATIONS AND PROCEDURES

### 7.1 Schedule of Events

| Procedure | Pre-Screen[1] | Screen 1[2] | Screen 2[3] | Study Visit 1[4] | Months 1–3 | Study Visit 2[5] | Months 4-6 | Study Visit 3[6] | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|
| Assess eligibility | X | X | X | | | | | | |
| Informed consent form and HIPAA authorization | | X | | | | | | | |
| Registration and randomization to simvastatin or placebo | | | X | | | | | | |
| Review medical history, medications, and lab test results | | X | X | X | | X | | X | |
| Review CT and MRI results | | X | | | | | | | |
| Blood Hematology: Complete Blood Count with Differential (CBDF) | | | X | | | X | | X | |
| Blood Chemistry: Comprehensive Metabolic Panel (CMPL) | | | X | | | X | | X | |
| Pancreatic fluid via endoscopic pancreatic function test (ePFT) | | | X | | | X | | X | |
| Endoscopic ultrasound (EUS) | | | X | | | | | X | |
| Esophagogastroduodenoscopy (EGD) | | | | | | X | | | |
| Urine pregnancy test[7] | | | X | | | X | | X | |
| Demographics (date of birth, race, ethnicity, education) | | | | X | | | | | |
| Physical exam | | | X | | | X | | X | |
| Vital signs assessment, measure weight, symptom assessment, and ECOG performance status | | | X | X | | X | | X | |
| Blood test: Lipid Panel | | | | X | | X | | X | |
| Blood test: Hemoglobin A1C (HbA1C) | | | | X | | | | X | |
| Blood test: Creatine phosphokinase (CPK) | | | | X | | | | | |
| Collect blood specimen for | | | | X | | X | | X | |

| Procedure | Pre-Screen[1] | Screen 1[2] | Screen 2[3] | Study Visit 1[4] | Months 1–3 | Study Visit 2[5] | Months 4-6 | Study Visit 3[6] | Follow-Up |
|---|---|---|---|---|---|---|---|---|---|
| research[8] | | | | | | | | | |
| Fecal specimen (self-collected) | | | | X | | X | | X | |
| Risk factor questionnaire | | | | X | | | | X | |
| QLQ-C30 and QLQ-PAN28(CP) | | | | X | | X | | X | |
| Imaging studies, as needed | | | | X | | X | | X | |
| Review eligibility criteria | | | | X | | X | | | |
| Dispense study agent and diary | | | | X | | X | | | |
| Collect study agent and diary | | | | | | X | | X | |
| Review study diary | | | | | | X | | X | |
| Assess compliance | | | | | X | X | X | X | |
| Assess adverse events | | | | | X | X | X | X | X |
| Telephone contact[9] | X | X | X | X | X | X | X | X | X |

[1] Pre-Screen eligibility review by clinical research staff to determine initial eligibility. Research staff will review medical records of patients hospitalized for pancreatitis, and of patients who have an upcoming appointment with a study gastroenterologist. For patients who respond to direct advertisement and outside referrals who call to request more information (whose medical records are not available), research staff will describe the study, field questions, and assess potential eligibility using an IRB-approved phone script.

[2] Consent and secondary determination of eligibility by trial gastroenterologists. Review of patient's CT and MRI results from past 12 months and confirmation of recurrent pancreatitis (at least two episodes of acute pancreatitis in the past 12 months) using the Atlanta Classification. The diagnosis of acute pancreatitis requires two of the following three features: (1) abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back); (2) serum lipase activity (or amylase activity) at least three times greater than the upper limit of normal; and (3) characteristic findings of acute pancreatitis on contrast-enhanced computed tomography (CECT). Patients with CT or MRI evidence of advanced chronic pancreatitis will be excluded from the trial.

[3] Consented patients who are eligible after Screen 1 will undergo an endoscopic ultrasound (EUS) and endoscopic pancreatic function test (ePFT), clinical labs, and pregnancy test (for women of child-bearing potential) within 8 weeks after consent. Patients with EUS evidence of advanced chronic pancreatitis, patients with lab results outside the eligibility range, and women who are pregnant will be excluded from the trial.

[4] Screen 2 eligible/consented patients will be registered and randomized. Study Visit 1 (baseline measurements and initiation of the intervention) will occur 0-14 days after Screen 2. The Screen 2 EUS and ePFT results will be used as Visit 1 measurements.

[5] Study Visit 2 will occur 3 months (± 1 month) after the initiation of the intervention.

[6] Study Visit 3 (last day of study drug) will occur 6 months (± 1 month) after initiation of the intervention.

[7] Pregnancy test for women of child-bearing potential at the Screen 2 visit and at Study Visits 2 and 3. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.

[8] Blood collection for research (26 mL): 6 mL for measurement of protocol-specific biomarkers and 20 mL banked for DNA extraction and future studies

[9] Telephone contact with patients during the screening period to assess eligibility, introduce the study, answer questions, and schedule pre-study evaluations. Telephone contact every four weeks (± 7 days) during the intervention to assess compliance and adverse events. Follow-up telephone contact on days 30 ± 7, 60 ± 7, and 90 ± 7 after completion of Study Visit 3 to assess adverse events.

## 7.2 Pre-Study Evaluation and Baseline Testing

### 7.2.1 Pre-Screen Eligibility Review – Initial determination of eligibility and recruitment

Inpatients and outpatients at study sites. The medical records of patients hospitalized for acute or chronic pancreatitis will be reviewed by the clinical research staff to determine initial eligibility as specified in the

inclusion and exclusion criteria. The medical records of patients who have an upcoming appointment with one of the study gastroenterologists, and the medical records of patients who are referred by other physicians at the institution, will also be reviewed for eligibility. The following information will be reviewed:

1. History of acute pancreatitis in the past 12 months
2. History of use and/or adverse effects to statin medication, and contraindications to statin use
3. Medical contraindications and medications that impact inclusion in the study

Potentially eligible patients who are hospitalized will be approached by one of the trial gastroenterologists or a study team member. After describing the trial and answering the patient's questions, patients who express an interest in participating in the trial will be given a study information packet that includes the IRB-approved study informed consent form and HIPAA authorization, and IRB-approved recruitment materials (e.g., introductory letter, study brochure; each participating site will choose what materials to include). Patients will be encouraged to review the consent documents with family, friends, and/or other physicians.

Clinical research staff will prepare and mail the study information packet to potentially eligible patients who are outpatients (e.g., patients who have an upcoming appointment with a study gastroenterologist, patients hospitalized for pancreatitis who are discharged before the study team has an opportunity to approach them, referrals from other physicians). One of the study gastroenterologists or clinical research staff will call potentially eligible patients within 14 days after the packet is mailed to introduce the study and answer questions.

Referrals from physicians at outside institutions and self-referrals (medical records not available). Additional recruitment strategies such as leaflets placed in outpatient clinics, study announcements sent to physicians at outside institutions, flyers and half-page ads posted at outside institutions and at community clinics, and video bulletins displayed on screens at the study sites and outside institutions, will be employed to increase awareness of the trial and aid in our recruitment goals. The recruitment materials will contain contact information for the study. A member of the study team will field questions from patients who respond to direct advertisement and outside referrals who call to request more information. Staff will describe the study and review the eligibility criteria with the patient using an IRB-approved phone script to assess potential eligibility. If the patient is potentially eligible and interested in the trial, they will be mailed the study information packet including the consent form and HIPAA authorization. Patients who are interested in participating in the study will be scheduled for a visit to sign the study consent documents. Clinical research staff will follow-up with a phone call to potentially eligible patients who are undecided within 14 days after the packet is mailed to evaluate interest in study participation and answer additional questions. Patients who want to volunteer for the study will be scheduled come to the clinic to sign the study consent documents.

### 7.2.2 Screen 1 – Consent and Secondary determination of eligibility

Interested pre-screen eligible patients will be recruited and consented into the trial. One of the trial gastroenterologist will review the study details and consent documents with potentially eligible patients after all clinical options have been presented to the patient. After the patient's questions have been answered, the gastroenterologist will obtain signatures on the study consent form and HIPAA authorization. Copies of each form will be given to the patient and placed in the medical record. Written consent will be obtained before any research related procedures are initiated.

After consent has been obtained, a secondary assessment of eligibility will be conducted.

1. If not available at the study site, the clinical research staff will retrieve medical records from other institutions for pancreatitis history.
2. Trial gastroenterologists will review the patient's pancreatitis history and confirm the diagnosis of recurrent pancreatitis (at least two episodes of acute pancreatitis in the past 12 months) using the Atlanta Classification. They will also review the patient's computed tomography (CT) and magnetic resonance imaging (MRI) results from the past 12 months.

Patients with CT or MRI evidence of advanced chronic pancreatitis will be excluded from the trial.

### 7.2.3 Screen 2 – Final determination of eligibility, Registration, and Randomization

Consented patients who are eligible after Screen 1 will undergo the following procedures within 8 weeks after consent to rule out advanced chronic pancreatitis and pregnancy. Patients will be instructed to fast overnight (8 hours) before the endoscopic testing.

1. Clinical labs for a Complete Blood Count with Differential (CBDF) and a Comprehensive Metabolic Panel (CMPL) will be done to confirm that laboratory levels for acceptable organ, hepatic, and renal function are within the eligibility requirements. See Appendix A for Clinical Laboratory Minimum Test Requirements. If a patient's lab results within 35 days before the Screen 2 visit are available in the medical record and are within eligibility range, their blood will not be drawn at the Screen 2 visit. Otherwise, the patient's blood will be drawn to confirm eligibility.
2. Pregnancy test for women of child-bearing potential. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
3. Physical exam including vital signs assessment, symptom assessment, and ECOG performance status
4. Endoscopic ultrasound (EUS)
5. Endoscopic pancreatic function test (ePFT)

Based on Screen 2 results, patients with EUS evidence of advanced chronic pancreatitis, patients with lab results outside the eligibility range, and women who are pregnant will be excluded from the trial. Patients with EUS evidence of advanced chronic pancreatitis will not undergo the ePFT. See Section 3. Summary of Study Plan for advanced chronic pancreatitis diagnostic criteria.

Consented patients who qualify for the study after the Screen 2 eligibility evaluations will be registered and randomized to the study drug (simvastatin or placebo). The Screen 2 EUS and ePFT results will be used as Study Visit 1 baseline measurements. The pancreatic fluid will be used to measure secretin-stimulated peak bicarbonate concentration; cytokines, chemokines, and adhesion molecules.

### 7.2.4 Study Visit 1 – Baseline Testing and Initiation of the Statin Intervention

Study Visit 1 (Baseline measurements) will occur 0-14 days after Screen 2. Participants will be told to fast for 8 hours before the study visit. Fasting instructions will be provided to participants prior to their study visit, and participants will receive a phone call reminder the day before the visit to fast overnight. The following procedures will be performed during this visit:

1. Review medical history, medications, and laboratory test results
2. Measure height and weight and symptom assessment
3. Vital signs assessment: blood pressure, heart rate, respiratory rate, and oral temperature
4. ECOG performance status

5. Blood collection for clinical labs (approximately 10 mL). Laboratory blood tests will be done for a Lipid Panel, hemoglobin A1C, and creatine phosphokinase (CPK) to establish baseline levels prior to initiating the study agent. CBDF and CMPL lab results from the Screen 2 eligibility visit will be used to establish patient-specific references prior to initiation of therapy. If blood tests were not done at the Screen 2 visit for a CBDF and CMPL; and lab results within 30 days prior to this visit for these tests are not available in the medical record, a CBDF and CMPL will be done at this visit. See Appendix A for Clinical Laboratory Minimum Test Requirements.
6. Blood collection for research purposes (26 mL): 6 mL will be collected for measurement of protocol-specific biomarkers (serum concentrations of cytokines, chemokines, and adhesion molecules), and 20 mL will be banked for DNA extraction and future studies.
7. Fecal specimen for measurement of fecal elastase. A stool collection kit and instructions will be provided to the participant before the scheduled visit. The specimen will be self-collected at home. The participant will receive a phone call reminder the day before the visit to collect the fecal specimen and bring it to the study visit.
8. Interviewer-administered questionnaire to obtain demographic information (date of birth, detailed race and ethnicity, education); medical history, including pancreatic diseases and diabetes; medications, including analgesics and antibiotics; physical activity; history of alcoholic beverage consumption; tobacco smoking history; and anthropometry
9. Self-administered QLQ-C30 and QLQ-PAN28(CP) to assess quality of life and pain level
10. Review of inclusion /exclusion criteria
11. Dispense study agent and review instructions for how to take the study drug. Each participant will be given a 3-month supply of the study agent (1 bottle of 120 capsules).
12. Dispense study diary and review instructions for how to complete it

## 7.3 Evaluation During Study Intervention

### 7.3.1 Study Visit 2

Study Visit 2 will occur 3 months (± 1 month) after the initiation of the intervention. Participants will be told to fast for 8 hours before the study visit. Fasting instructions will be provided to participants prior to their study visit, and participants will receive a phone call reminder the day before the visit to fast overnight. The following procedures/evaluations will be performed during this visit:

1. Review medical history, medications, and laboratory test results
2. Physical exam including measurement of weight and symptom assessment
3. Vital signs assessment: blood pressure, heart rate, respiratory rate, and oral temperature
4. ECOG performance status
5. Pregnancy test for women of child-bearing potential. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
6. Blood collection for clinical labs (approximately 10 mL). Laboratory blood tests will be done for a Complete Blood Count and Automated Differential (CBDF), a Complete Metabolic Panel (CMPL), and a Lipid Panel to monitor for potential adverse effects of the intervention and to confirm that laboratory levels meet the eligibility requirements for continuation in the trial (See Appendix A). If lab results within 30 days prior to this visit for any of these tests are available in the medical record, the blood test(s) will not be done.
7. Blood collection for research purposes (26 mL): 6 mL will be collected for measurement of protocol-specific biomarkers (serum concentrations of cytokines, chemokines, and adhesion molecules), and 20 mL will be banked for DNA extraction and future studies.

8. Fecal specimen for measurement of fecal elastase. A stool collection kit and instructions will be provided to the participant before the scheduled visit. The specimen will be self-collected at home. The participant will receive a phone call reminder the day before the visit to collect the fecal specimen and bring it to the study visit.
9. Self-administered QLQ-C30 and QLQ-PAN28(CP) to assess quality of life and pain level
10. Review of conformance with inclusion /exclusion criteria
11. Collect study agent and diary
12. Assess compliance (pill count)
13. Review study diary
14. Assess adverse events
15. Dispense study agent and diary. Each participant will be given a 3-month supply of the study agent (1 bottle of 120 capsules).
16. Endoscopic pancreatic function test (ePFT) and simultaneous esophagogastroduodenoscopy (EGD) and fasting pancreatic fluid to measure secretin-stimulated peak bicarbonate concentration; cytokines, chemokines, and adhesion molecules.

### 7.3.2 Telephone Calls and Email/Text Messages

Study participants will be followed during intervention via telephone calls every four weeks (± 7 days) by the clinical research staff to assess compliance and adverse events. Participants who report having taken < 80% of the study drug doses between phone calls, or whose pill count at a study visit reveals < 80% compliance, will be called every two weeks (± 3 days) to monitor compliance. In addition, participants will receive a phone call the day before each scheduled study visit to remind them to fast overnight and to collect a fecal specimen and bring it to the study visit. Participants will also be reminded to bring any leftover study drugs and the study diary with them to the visit. Study participants will also be called during the week before their final visit (Visit 3) to remind them to take the study drug every day until the visit appointment.

Participants who opt to receive reminders for study medication intake via email or text messages will be contacted by the study staff during the first week of study and further as needed. The study staff will send emails or text messages on cellular phone; participants will be encouraged to respond to these messages indicating if the study drug has been taken. These responses will be used to assess compliance and will be reviewed at weekly phone contact. For participants who miss more than one dose in a week, the email/text reminders will continue further into dosing period. Since agent compliance is very important during the final week of the intervention, text/email messages will be sent to all study participants who opt to receive these reminders.

The following information with be collected during the telephone calls:

1. Medication compliance review. Participants will be asked if they missed any doses of medication, and the dates of all missed doses will be recorded.
2. Concomitant medication review
3. Adverse events. Participants will be asked if they have experienced any of the following symptoms to assess adverse events:
    a. Upper respiratory infections
    b. Headache
    c. Abdominal pain
    d. Constipation
    e. Nausea / Vomiting

4. Additional symptoms experienced by participants will be recorded to assess adverse events

## 7.4 Evaluation at Completion of Study Intervention

### 7.4.1 Study Visit 3

The final study visit will occur 6 months (± 1 month) after initiation of the intervention. Participants will be told to fast for 8 hours before the study visit. Fasting instructions will be provided to participants prior to their study visit, and participants will receive a phone call reminder the day before the visit to fast overnight. The following procedures will be performed during this visit:

1. Review medical history, medications, and laboratory test results
2. Physical exam including measurement of weight and symptom assessment
3. Vital signs assessment: blood pressure, heart rate, respiratory rate, and oral temperature
4. ECOG performance status
5. Pregnancy test for women of child-bearing potential. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
6. Blood collection for clinical labs (approximately 10 mL). Laboratory blood tests will be done for a Complete Blood Count and Automated Differential (CBDF), a Complete Metabolic Panel (CMPL), a Lipid Panel, and hemoglobin A1C to monitor for potential adverse effects of the intervention and to confirm that laboratory levels meet the eligibility requirements for continuation in the trial (See Appendix A). If lab results within 30 days prior to this visit for any of these tests are available in the medical record, the blood test(s) will not be done.
7. Blood collection for research purposes (26 mL): 6 mL will be collected for measurement of protocol-specific biomarkers (serum concentrations of cytokines, chemokines, and adhesion molecules), and 20 mL will be banked for DNA extraction and future studies.
8. Fecal specimen for measurement of fecal elastase. A stool collection kit and instructions will be provided to the participant before the scheduled visit. The specimen will be self-collected at home. The participant will receive a phone call reminder the day before the visit to collect the fecal specimen and bring it to the study visit.
9. Interviewer-administered follow-up questionnaire to obtain information about changes in exposures and behaviors since the baseline visit, and to assess alcohol use and surgical procedures that will impact the risk of recurrent pancreatitis
10. Self-administered QLQ-C30 and QLQ-PAN28(CP) to assess quality of life and pain level
11. Collect study agent and diary
12. Assess compliance (pill count)
13. Review study diary
14. Assess adverse events
15. Endoscopic pancreatic function test (ePFT) and simultaneous endoscopic ultrasound (EUS) and fasting pancreatic fluid to measure secretin-stimulated peak bicarbonate concentration; inflammatory cytokines, chemokines, and adhesion molecules

## 7.5 Post-intervention Follow-up Period

Clinical research staff will make follow-up telephone calls to study participants on days 30 ± 7, 60 ± 7, and 90 ± 7 after completion of Study Visit 3 to assess symptoms and adverse events.

## 7.6 Methods for Clinical Procedures

**Endoscopic pancreatic function test (ePFT) and simultaneous endoscopic ultrasound (EUS) and fasting pancreatic fluid**. Patients will be instructed to fast overnight (8 hours) before the endoscopic testing. Instructions regarding preparing for the ePFT and the simultaneous EUS will be provided to the participants before each study measurement at Screen 2 and Study Visit 3 (6 months). Esophagogastroduodenoscopy (EGD), a simpler endoscopic procedure without the ultrasound imaging, will be performed at Study Visit 2 (3 months) in tandem with an ePFT. The ePFT/EUS (or ePFT/EGD) requires intravenous sedation with propofol that has a demonstrated safety profile [53]. A 6-mm ultrasound-adapted endoscope will be passed into the stomach and the duodenum. Experienced endoscopists will visualize the pancreas to determine the presence or absence of nine ductal and parenchymal criteria for chronic pancreatitis: hyperechoic foci, hyperechoic strands, cysts, lobularity, calcifications, hyperechoic duct margins, visual side branches, main pancreatic duct dilation, and main pancreatic duct irregularity, which sum to a score ranging from 0 to 9 (*secondary endpoint*) [32]. As soon as the EUS is completed, one of the trial gastroenterologists will perform the ePFT. The gastroenterologists are experienced with ePFT, and Drs. Afghani (CSMC) and Wu (KPMC) have written review articles on its validity and utility [32, 54]. Briefly, the ultrasound-adapted endoscope will be replaced with a standard endoscope and fluid from the stomach and duodenum will be removed by aspiration. A test dose of ChiRhoStim® human synthetic secretin 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies. After one minute, if there are no signs of allergic reaction, ChiRhoStim® at a dose of 0.2 mcg/kg of body weight is injected intravenously over 1 minute. Pancreatic fluid will be collected at five time points over one hour (at 0-10 minutes, 10-20 minutes, 20-30 minutes, 30-45 minutes, and 45-60 minutes). Each collection will contain at least 3 mL of fluid, which is sufficient for analysis of peak bicarbonate concentration (*primary endpoint*) and cytokine concentrations (*secondary endpoint*). For each time point, 1.0 mL of pancreatic fluid will be placed into a plastic collection vial without preservatives and placed in wet ice. The samples will be transported to the designated processing lab for bicarbonate analysis. The remainder of the pancreatic fluid specimen will be stored for later assays of cytokines, chemokines, and adhesion markers (*secondary endpoints*). [55]. Immediately upon receipt of the pancreatic fluid, lab personnel will process the specimen as specified in the Laboratory Manual. Processed specimens will be stored in a -80$^{o}$ C freezer awaiting batch analysis.

**Fecal specimen.** A stool collection kit and instructions regarding the collection of the fecal specimen will be provided to participants prior to their study visit. The fecal specimen will be self-collected at home and brought to the study visit. Participants will receive a phone call reminder the day before the visit to collect the fecal specimen and bring it to the study visit. The fecal specimen will be processed as specified in the Laboratory Manual and stored at -80$^{o}$C.

**Blood specimen.** A blood specimen (approximately 10 mL) will be collected from each participant at the Screen 2 visit for blood tests to confirm eligibility. A Complete Blood Count (CBC) and a Comprehensive Metabolic Panel (CMPL) will be done to confirm that laboratory levels for acceptable organ, hepatic, and renal function are within the eligibility requirements. See Appendix A for Clinical Laboratory Minimum Test Requirements. If a patient's lab results within 35 days before the Screen 2 visit are available in the medical record and are within eligibility range, their blood will not be drawn at the Screen 2 visit. Otherwise, the patient's blood will be drawn to confirm eligibility.

Approximately 36 mL of blood will be collected from each participant at Study Visits 1, 2, and 3 using a standard phlebotomy protocol. Fasting instructions will be provided to participants prior to their study visit, and participants will receive a phone call reminder the day before the visit to fast overnight (8 hours). The date and time of the blood draw and of the participant's last meal will be recorded.

Approximately 10 mL of blood will be drawn for laboratory blood tests to monitor for potential adverse effects of the intervention and to confirm that laboratory levels meet the eligibility requirements for continuation in the trial. A fasting Lipid Panel will be done at all study visits. A CBDF and a CMPL will

be done at Study Visits 2 and 3. Fasting hemoglobin A1C will be measured at Study Visits 1 and 3. Creatine phosphokinase (CPK) will be measured at Study Visit 1. See Appendix A for Clinical Laboratory Minimum Test Requirements.

The CMPL and CBDF test results will be utilized to screen for any issues that could be related to an adverse event or affect eligibility for the trial. CBDF and CMPL lab results from the Screen 2 eligibility visit will be used to establish patient-specific references prior to initiation of therapy. If blood tests were not done at the Screen 2 visit for a CBDF and CMPL; and lab results within 30 days prior to Study Visit 1 for these tests are not available in the medical record, a CBDF and CMPL will be done at Study Visit 1. The Lipid Panel includes tests for cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglycerides. Since the study agent is a cholesterol lowering agent, we feel that it is important to establish baseline lipid levels prior to initiating the study agent (Study Visit 1) and to monitor lipids at subsequent study visits. Hemoglobin A1C is used to assess glucose control in insulin-dependent diabetics whose glucose levels are very labile and in whom single blood glucose measurements may not accurately reflect the level of control present over the preceding few weeks. Glucose and hemoglobin A1C will be used to establish a baseline (Study Visit 1) for monitoring adverse events (incident diabetes) during the trial. CPK will be tested to establish a baseline for monitoring myopathy, a rare complication associated with the study agent (<1%). CPK will be measured at Study Visit 1 to establish a patient-specific reference for this indicator of muscle toxicity. If the participant reports unexplained muscle pain or weakness during the trial, CPK will be tested again to check for elevation.

Twenty-six mL of blood will be collected for research purposes. Six mL of blood will be drawn into a red top serum vacutainer tube for measurement of protocol-specific biomarkers (cytokines, chemokines, and adhesion molecules). Twenty mL of blood will be drawn into three vacutainer tubes, including one 6 mL red top serum tube and two 7 mL lavender top EDTA tubes, for DNA extraction and use in future studies. The blood will be collected and processed as specified in the Laboratory Manual. Processed specimens will be stored at -80ºC.

**Biomarkers.** Pancreatic fluid will be analyzed for secretin-stimulated peak bicarbonate levels. Study assays for blood and pancreatic fluid concentrations of cytokines, chemokines, and adhesion moleculeswill be performed in Dr. Pandol's laboratory at CSMC. Inflammatory cytokines will be measured in pancreatic fluid collected 30 minutes after secretin stimulation and in serum samples collected at each visit using our Luminex-based MAGPIX multiplexing analysis system in Dr. Pandol's lab using methods previously described [36].

## 8. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

The overall objective of this trial is to examine the effect of simvastatin use versus placebo at 6 months from baseline (Study Visit 1) on pancreatic function and inflammatory mediators in patients with recurrent acute pancreatitis (at least two episodes of acute pancreatitis in the past 12 months). Participants will be on the study drug from Study Visit 1 until the last study visit (Study Visit 3 at 6 months) when the final endoscopic procedure will be performed. Primary and secondary endpoints are measured in specimen samples taken after 8 hours of fasting.

### 8.1 Primary Endpoint

**Primary:** To measure changes in pancreas exocrine function (secretin-stimulated peak bicarbonate concentration in the pancreatic fluid) as measured by the endoscopic pancreatic function test (ePFT). We hypothesize that participants randomized to simvastatin will experience a greater increase from baseline in peak bicarbonate concentration measured at 6 months from baseline compared to the placebo group.

## 8.2 Secondary Endpoints

8.2.1 To measure changes in endoscopic ultrasound score (EUS), a measure of pancreatitis. We hypothesize that compared to the placebo group participants randomized to simvastatin will experience a greater reduction from baseline in EUS score.

8.2.2 To measure changes in serum and pancreatic secretions of the following targets: interleukins (IL; 1α, 1β, 1RA, 2, 4, 5, 6, 7, 8, 9, 10, 12p40, 12p70, 13, 15, 17A, 17F, 18, 21, 22, 27, 23, 31), BDNF, CD40L, EGF, ENA78, Eotaxin, FASL, FGFβ, GCSF, GMCSF, GROA, HGF, ICAM1, IFNα, IFNβ, IFNγ, IP10, LIF, Leptin, MCP1, MCP3, MCSF, MIG, MIP1α, MIP1β, PDGFβ, PIGF1, NGF, Rantes, Resistin, PAI1, SCF, SDF1α, TGFα, TGFβ, TNFα, TNFβ, TRAIL, VCAM1, VEGF, VEGFD. . We hypothesize that participants randomized to simvastatin will experience a greater decrease in pro-inflammatory markers and a greater increase in anti-inflammatory markers.

8.2.3 To assess changes in pancreatitis-related readmissions. We hypothesize that participants randomized to simvastatin will experience fewer episodes of pancreatitis-related readmissions. A pancreatitis-related readmission will be defined as a hospital readmission that is due to complications from the previous pancreatitis episode, as determined by a physician; or an independent episode of acute pancreatitis defined by at least two of the following 1) Typical upper abdominal pain; 2) Elevation in serum amylase or lipase ≥3 times ULN; 3) Features of acute pancreatitis on cross-sectional imaging. Source documents include: 1) lipase or amylase levels; 2) physician notes; 3) imaging results.

8.2.4 To assess changes in quality of life measures using the QLQ-C30 and QLQ-PAN28(CP). We hypothesize that participants randomized to simvastatin will experience improvement in quality of life scores.

## 8.3 Off-Agent Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate agent supply, noncompliance, concomitant medications, or medical contraindication. Participants who experience complications of pancreatitis or develop intercurrent pancreatitis during the study will be instructed to continue taking the study agent unless they are unable to take oral medications. The study agent will be resumed as soon as they are able to tolerate oral medications. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events.

As described in section 7.5, clinical research staff will make follow-up telephone calls to the participants on days 30 ± 7, 60 ± 7, and 90 ± 7 after the participant discontinues the study agent to assess symptoms and adverse events. Standard of care data (medical history, laboratory test results, concomitant medications, imaging results) will continue to be collected via review of the participant's electronic medical record at the time points specified in the Schedule of Time and Events. If feasible, we will conduct a research visit to collect final measurements for participants who permanently discontinue the study agent early. An end-of-study research visit will be conducted 6 months after initiation of the statin intervention (Study Visit 3). The blood collections for clinical labs and banked samples future research, and the follow-up risk questionnaire will not be done. The following procedures will be performed during the end-of-study visit:

1. Review medical history, medications, and laboratory test results
2. Vital signs assessment, measurement of weight, and symptom assessment
3. ECOG performance status

4. Pregnancy test for women of child-bearing potential. Women who have had a hysterectomy, both ovaries removed, or a tubal ligation will not be required to have a pregnancy test.
5. Blood collection for measurement of protocol-specific biomarkers (6 mL): serum concentrations of the following targets: interleukins (IL; 1α, 1β, 1RA, 2, 4, 5, 6, 7, 8, 9, 10, 12p40, 12p70, 13, 15, 17A, 17F, 18, 21, 22, 27, 23, 31), BDNF, CD40L, EGF, ENA78, Eotaxin, FASL, FGFβ, GCSF, GMCSF, GROA, HGF, ICAM1, IFNα, IFNβ, IFNγ, IP10, LIF, Leptin, MCP1, MCP3, MCSF, MIG, MIP1α, MIP1β, PDGFβ, PIGF1, NGF, Rantes, Resistin, PAI1, SCF, SDF1α, TGFα, TGFβ, TNFα, TNFβ, TRAIL, VCAM1, VEGF, VEGFD.
6. Fecal specimen for measurement of fecal elastase. A stool collection kit and instructions will be provided to the participant before the scheduled visit. The specimen will be self-collected at home.
7. Self-administered QLQ-C30 and QLQ-PAN28(CP) to assess quality of life and pain level.
8. Endoscopic pancreatic function test (ePFT) and simultaneous endoscopic ultrasound (EUS) and fasting pancreatic fluid to measure secretin-stimulated peak bicarbonate concentration; and concentrations of the following targets: interleukins (IL; 1α, 1β, 1RA, 2, 4, 5, 6, 7, 8, 9, 10, 12p40, 12p70, 13, 15, 17A, 17F, 18, 21, 22, 27, 23, 31), BDNF, CD40L, EGF, ENA78, Eotaxin, FASL, FGFβ, GCSF, GMCSF, GROA, HGF, ICAM1, IFNα, IFNβ, IFNγ, IP10, LIF, Leptin, MCP1, MCP3, MCSF, MIG, MIP1α, MIP1β, PDGFβ, PIGF1, NGF, Rantes, Resistin, PAI1, SCF, SDF1α, TGFα, TGFβ, TNFα, TNFβ, TRAIL, VCAM1, VEGF, VEGFD.

### 8.4 Off-Study Criteria

Participants may go 'off-study' for the following reasons:

- Adverse Event
- Death
- Disease Progression
- Lost to follow-up/Participant Withdrawal
- Participant Refused Follow-up
- Physician Decision
- Protocol Defined Follow-up Completed
- Protocol Violation
- Study Complete
- Ineligible
- Other

### 8.5 Study Termination

NCI, DCP as the study sponsor has the right to discontinue the study at any time.

## 9. CORRELATIVE/SPECIAL STUDIES

### 9.1 Rationale for Methodology Selection

*Endoscopic pancreatic function test:* The current gold standard for diagnosing chronic pancreatitis is the endoscopic pancreatic function test (ePFT) which measures secretin-stimulated production of bicarbonate ion from pancreatic ductal cells during an endoscopic ultrasound procedure (EUS) [3, 32]. Clinically, ePFT-based peak bicarbonate levels can distinguish mild and severe chronic pancreatitis, and is correlated with the extent of histologically determined fibrosis (r=-0.57) [33]. Because ePFT is based on an endoscope-guided collection of pure pancreatic fluid, it provides a direct measurement of pancreatic

function that is superior to indirect measurements in stool i.e., fecal elastase [34].

*Endoscopic ultrasound:* The endoscopic ultrasound is an imaging tool for evaluating the presence or absence of nine ductal and parenchymal criteria for chronic pancreatitis: hyperechoic foci, hyperechoic strands, cysts, lobularity, calcifications, hyperechoic duct margins, visual side branches, main pancreatic duct dilation, and main pancreatic duct irregularity, which sum to a score ranging from 0 to 9 [32]. It is the current standard of care imaging method for determining the extent of chronic pancreatitis.

*Immunological cytokines and C-reactive protein:* A panel of immunological cytokines will be measured to evaluate the effect of statin on immune profiling markers in the pancreatic fluid and in the blood. We will use the MILLIPLEX MAP Human Cytokine/Chemokine Magnetic Bead Panel- Immunology Multiplex to measure interleukins (IL; 1α, 1β, 1RA, 2, 4, 5, 6, 7, 8, 9, 10, 12p40, 12p70, 13, 15, 17A, 17F, 18, 21, 22, 27, 23, 31), BDNF, CD40L, EGF, ENA78, Eotaxin, FASL, FGFβ, GCSF, GMCSF, GROA, HGF, ICAM1, IFNα, IFNβ, IFNγ, IP10, LIF, Leptin, MCP1, MCP3, MCSF, MIG, MIP1α, MIP1β, PDGFβ, PIGF1, NGF, Rantes, Resistin, PAI1, SCF, SDF1α, TGFα, TGFβ, TNFα, TNFβ, TRAIL, VCAM1, VEGF, and VEGFD.

### 9.2 Comparable Methods

Proposed methods represent standard technology for measuring the study biomarkers.

## 10. SPECIMEN MANAGEMENT

### 10.1 Laboratories

1) Study blood tests will be done for a Complete Blood Count and Automated Differential (CDF), a Complete Metabolic Panel (CMPL), a Lipid Panel, hemoglobin A1C, and creatine phosphokinase (CPK) at the clinical laboratories at each study site; or the blood tests will be done at an external CLIA-certified clinical laboratory as required by the participant's health insurance carrier.

2) Measurement of bicarbonate concentrations in pancreatic fluid will be performed by Cedars-Sinai Department of Pathology and Laboratory Medicine.

3) Study assays for blood and pancreatic fluid concentrations of interleukins (IL; 1α, 1β, 1RA, 2, 4, 5, 6, 7, 8, 9, 10, 12p40, 12p70, 13, 15, 17A, 17F, 18, 21, 22, 27, 23, 31), BDNF, CD40L, EGF, ENA78, Eotaxin, FASL, FGFβ, GCSF, GMCSF, GROA, HGF, ICAM1, IFNα, IFNβ, IFNγ, IP10, LIF, Leptin, MCP1, MCP3, MCSF, MIG, MIP1α, MIP1β, PDGFβ, PIGF1, NGF, Rantes, Resistin, PAI1, SCF, SDF1α, TGFα, TGFβ, TNFα, TNFβ, TRAIL, VCAM1, VEGF, and VEGFDwill be performed in the Stanford Human Immune Monitoring Core (HIMC). The lab is equipped with a Luminex MAGPIX multiplexing system which will be used in combination with specific antibody based magnetic bead assays to measure each of the analytes.

### 10.2 Collection and Handling Procedures

Research study staff at participating study sites will receive specific instructions for collection, processing, and shipment of specimens.

**Endoscopic pancreatic function test (ePFT) for collection of fasting pancreatic fluid.**
Instructions regarding the endoscopic procedures (Esophagogastroduodenoscopy (EGD) or endoscopic

ultrasound (EUS)) and the collection of fasting pancreatic fluid will be given to participants prior to their study visit. Subjects will be instructed to fast overnight (8 hours) before the testing. Briefly, the ultrasound-adapted endoscope will be replaced with a standard endoscope and fluid from the stomach and duodenum will be removed by aspiration. A test dose of ChiRhoStim® human synthetic secretin 0.2 mcg (0.1 mL) is injected intravenously to test for possible allergies. After one minute, if there are no signs of allergic reaction, ChiRhoStim® at a dose of 0.2 mcg/kg of body weight is injected intravenously over 1 minute. Pancreatic fluid will be aspirated from the descending duodenum at five time points over one hour (at 0-10 minutes, 10-20 minutes, 20-30 minutes, 30-45 minutes, and 45-60 minutes) following hormonal stimulation. Each collection will contain at least 3 mL of pancreatic fluid, which is sufficient for analysis of peak bicarbonate concentration (*primary endpoint*) and cytokine, chemokine, adhesion molecule concentrations (*secondary endpoint*). For each time point, 1.0 mL of pancreatic fluid will be placed into a plastic collection vial without preservatives and placed in wet ice. The samples will be transported to the designated processing lab for bicarbonate analysis. The remainder of the pancreatic fluid specimen will be stored for later assays of cytokines, chemokines, and adhesion molecules. Immediately upon receipt of the pancreatic fluid, lab personnel will process the specimen as specified in the Laboratory Manual. Processed specimens will be stored in a -80º C freezer awaiting batch analysis.

**Fecal specimen**. A stool collection kit that includes instructions and supplies for collecting the fecal sample at home will be provided to participants prior to their study visit. The fecal specimen will be self-collected at home and brought to the study visit. Participants will receive a phone call reminder the day before the visit to collect the fecal specimen and bring it to the study visit. The fecal specimen will be processed as specified in the Laboratory Manual and stored at -80ºC. .

**Blood specimen.** A blood specimen (approximately 10 mL) will be collected from each participant at the Screen 2 visit for blood tests to confirm eligibility. A Complete Blood Count (CBC) and a Comprehensive Metabolic Panel (CMPL) will be done to confirm that laboratory levels for acceptable organ, hepatic, and renal function are within the eligibility requirements. See Appendix A for Clinical Laboratory Minimum Test Requirements. If a patient's lab results within 35 days before the Screen 2 visit are available in the medical record and are within eligibility range, their blood will not be drawn at the Screen 2 visit. Otherwise, the patient's blood will be drawn to confirm eligibility.

Approximately 36 mL of blood will be collected from each participant at Study Visits 1, 2, and 3 using a standard phlebotomy protocol. Fasting instructions will be provided to participants prior to their study visit, and participants will receive a phone call reminder the day before the visit to fast overnight (8 hours). The date and time of the blood draw and of the participant's last meal will be recorded.

Approximately 10 mL of blood will be drawn for laboratory blood tests to monitor for potential adverse effects of the intervention and to confirm that laboratory levels meet the eligibility requirements for continuation in the trial. A fasting Lipid Panel will be done at all study visits. A CBDF and a CMPL will be done at Study Visits 2 and 3. If blood tests were not done at the Screen 2 visit for a CBDF and CMPL; and lab results within 30 days prior to Study Visit 1 for these tests are not available in the medical record, a CBDF and CMPL will also be done at Study Visit 1. Fasting Hemoglobin A1C will be measured at Study Visits 1 and 3. Creatine phosphokinase (CPK) will be measured at Study Visit 1. See Appendix A for Clinical Laboratory Minimum Test Requirements.

Twenty-six mL of blood will be collected for research purposes. Six mL of blood will be drawn into a red top serum vacutainer tube for measurement of protocol-specificinterleukins (IL; 1α, 1β, 1RA, 2, 4, 5, 6, 7, 8, 9, 10, 12p40, 12p70, 13, 15, 17A, 17F, 18, 21, 22, 27, 23, 31), BDNF, CD40L, EGF, ENA78, Eotaxin, FASL, FGFβ, GCSF, GMCSF, GROA, HGF, ICAM1, IFNα, IFNβ, IFNγ, IP10, LIF, Leptin, MCP1, MCP3, MCSF, MIG, MIP1α, MIP1β, PDGFβ, PIGF1, NGF, Rantes, Resistin,

PAI1, SCF, SDF1α, TGFα, TGFβ, TNFα, TNFβ, TRAIL, VCAM1, VEGF, and VEGFD. Twenty mL of blood will be drawn into three vacutainer tubes, including one 6 mL red top serum tube and two 7 mL lavender top EDTA tubes, for DNA extraction and use in future studies. The blood will be collected and processed as specified in the Laboratory Manual. Processed specimens will be stored at -80ºC for later measurement of cytokine concentrations, DNA extraction, and use in future studies.

### 10.3 Shipping Instructions

Blood samples for laboratory blood tests (Complete Blood Count and Automated Differential (CBDF), Complete Metabolic Panel (CMPL), Lipid Panel, hemoglobin A1C, and creatine phosphokinase (CPK)) will be transported to the clinical laboratories at each study site for processing; or the blood will be drawn and processed at an external CLIA-certified clinical laboratory as required by the participant's health insurance carrier.

Blood samples for research, pancreatic fluid samples, and fecal specimens collected at CSMC, UP, and SU will be transported to the designated laboratories at the respective study site for processing. All samples collected at KPMC will be delivered via courier to CSMC immediately after collection for processing. KPMC research blood samples may be processed at KPMC or at CSMC. If processed at KPMC, the processed aliquots will be couriered to CSMC with the pancreatic fluid samples and fecal specimens.

CSMC Laboratories
Blood samples collected for research will be transported to the Cedars Sinai Clinical and Translational Research Center (CTRC) Laboratory for processing.

Clinical and Translational Research Center (CTRC) Laboratory
Steven Spielberg Building, Room 280
8723 Alden Drive
Los Angeles, CA 90048
Telephone: 310-423-7445

Pancreatic fluid samples and fecal specimens collected at CSMC and KPMC will be transported to Dr. Pandol's laboratory at CSMC. Personnel in the Pandol Laboratory will prepare all samples for analyses.

Pandol Laboratory, Attn: Richard Waldron, Ph.D.
Cedars-Sinai Medical Center
110 N. George Burns Rd.
Davis Building, Room 3096
Los Angeles, CA 90048
Telephone: 310-423-4731
E-mail: Richard.Waldron@cshs.org

The Pandol Laboratory will aliquot pancreatic fluid samples for measurement of bicarbonate levels. The pancreatic fluid samples will be transported to the Cedars Sinai Clinical Laboratory for bicarbonate analysis.

Cedars-Sinai Department of Pathology and Laboratory Medicine
8700 Beverly Blvd., Room 8725
Los Angeles, CA 90048
Telephone: 310-423-5431

The Pandol Laboratory will package and ship serum and pancreatic fluid samples to the Stanford Human Immune Monitoring Center (HIMC) for assays of cytokines, chemokines, and adhesion molecules.

Holden T. Maecker, PhD

Director, Human Immune Monitoring Center (HIMC)
phone: +1.650.723.1671
email: maecker@stanford.edu
Stanford School of Medicine
Fairchild Science Bldg, D039
299 Campus Drive
Stanford, CA 94305-5124
fax: +1.650.498.7495

UP Research Laboratory

Kim Stello, Lab Manager and Sample Processing
841 Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261
Telephone: 412-648-8060

SU Research Laboratory

Peili Hsu, Acting Manager
Clinical and Translational Research Unit (CTRU) lab
Freidenrich Center for Translational Research
800 Welch Road
Palo Alto, CA 94305
Telephone: 650-724-1175

All leftover research blood samples, pancreatic fluid samples, and fecal samples collected and processed at UP and SU will be shipped to CSMC at end of trial. Shipping address for CSMC specimen manager:

Geoffrey Houghton, MSc.
Clinical Research Specialist, Prevention and Control
Samuel Oschin Comprehensive Cancer Institute
Cedars-Sinai Medical Center
Davis Building, Room 3096
8700 Beverly Blvd.
Los Angeles, CA 90048
Telephone: 310-423-9670
Cellular: 310-384-8281
E-mail: Geoffrey.Houghton@cshs.org

All samples will be shipped in compliance with the International Air Transport Association (IATA) Dangerous Goods Regulations. Cedars-Sinai will send a quarterly manifest of specimens collected and/or received to the Northwestern Cancer Prevention Consortium (NCPC).

### 10.4 Tissue Banking

Leftover pancreatic fluid, tissue, and fecal samples will be stored and maintained for future research. Banked samples for use in future research will include blood (20 mL collected from the participant at each visit), and surplus pancreatic fluid, tissue, and fecal samples leftover after all study analyses are completed. Future research may include: 1) studies to identify genes and/or biomarkers and proteins that influence an individual's risk of getting pancreatitis, pancreatic cancer, or other diseases; 2) studies to identify specific pathways and mechanisms that promote pancreatic cancer. All banked specimens will be coded with the unique Biobank subject identifier and stored in -80°C freezers located in the Shuman Basement of the Davis Research Building at CSMC.

Appropriate administrative, physical, and technical safeguards are in place to ensure the confidentiality, integrity, and security of the banked specimens. Investigators with future IRB approved studies who are approved to receive specimens will not be given access to any information that can establish the identity of the donor. All data and specimens sent to approved investigators will be coded and de-identified, and will contain no direct identifiers. The data will always be published using aggregate statistics and no participant will be identified in any reports or publications.

Biologic specimens collected during the conduct of each clinical trial that are not used during the course of the study will be considered deliverables under the contract and thus the property of the NCI. At study completion, NCI reserves the option to either retain or relinquish ownership of the unused biologic specimens. If NCI retains ownership of specimens, the Contractor shall collect, verify and transfer the requested biologic specimens from the site to a NCI-specified repository or laboratory at NCI's expense.

## 11. REPORTING ADVERSE EVENTS

DEFINITION: AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign), symptom, or disease temporally associated with participation in a study, whether or not related to that participation. This includes all deaths that occur while a participant is on a study.

Please note that all abnormal clinical laboratory values that are determined to be of clinical significance based on a physician's assessment are to be reported as AEs. Those labs determined to be of no clinical significance or of unknown clinical significance (per the physician's assessment) should not be reported as AEs. Any lab value of unknown clinical significance should continue to be investigated/followed-up further for a final determination, if possible.

A list of AEs that have occurred or might occur can be found in §6.2 Reported Adverse Events and Potential Risks, as well as the Investigator Brochure or package insert.

### 11.1 Adverse Events

#### 11.1.1 Reportable AEs

All AEs that occur after the informed consent is signed and Study Visit 1 (baseline) assessments are completed must be recorded on the AE CRF (paper and/or electronic) whether or not related to study agent.

#### 11.1.2 AE Data Elements:

The following data elements are required for adverse event reporting.

- AE verbatim term
- NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) AE term (MedDRA lowest level term)
- CTCAE (MedDRA) System Organ Class (SOC)
- Event onset date and event ended date
- Treatment assignment code (TAC) at time of AE onset
- Severity grade
- Attribution to study agent (relatedness)
- Whether or not the event was reported as a serious adverse event (SAE)

- Whether or not the subject dropped due to the event
- Outcome of the event

11.1.3 Severity of AEs

11.1.3.1 Identify the AE using the CTCAE version 4.0. The CTCAE provides descriptive terminology (MedDRA lowest level term) and a grading scale for each AE listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs will be assessed according to the grade associated with the CTCAE AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.0. as stated below.

**CTCAE v4.0 general severity guidelines:**

| Grade | Severity | Description |
|---|---|---|
| 1 | Mild | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 | Moderate | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*. |
| 3 | Severe | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**. |
| 4 | Life-threatening | Life-threatening consequences; urgent intervention indicated. |
| 5 | Fatal | Death related to AE. |

**ADL**

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, *etc*.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.4 Assessment of relationship of AE to treatment

The possibility that the adverse event is related to study agent will be classified as one of the following: not related, unlikely, possible, probable, definite.

11.1.5 Follow-up of AEs

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such. Adverse Events which occur in participants who are screened but not enrolled in the study will be followed for one week.

## 11.2 Serious Adverse Events

11.2.1 DEFINITION: Regulations at 21 CFR §312.32 (revised April 1, 2014) defines an SAE as any untoward medical occurrence that at any dose has one or more of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to perform normal life functions
- A congenital abnormality or birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization should also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require intervention to prevent one of the other outcomes.

11.2.2 Reporting SAEs to DCP

11.2.2.1 The Lead Organization and all Participating Organizations will report SAEs on the DCP SAE Report Form found at http://prevention.cancer.gov/clinical-trials/clinical-trials-management/protocol-information-office/pio-instructions-and-tools/2012-consortia.

11.2.2.2 Contact the DCP Medical Monitor by phone within 24 hours of knowledge of the event.

DCP Medical/Task Order Monitor
Luz Maria Rodriguez, MD, FACS
NCI/Division of Cancer Prevention
9609 Medical Center Dr.
Rm 5E-228
Bethesda, MD 20892
Telephone (240) 276-7039
Fax (240) 276-7848
Email: rodrigul@mail.nih.gov

Include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- DCP protocol number
- Title of protocol
- Description of the SAE, including attribution to drug and expectedness

11.2.2.3 The Lead Organization and all Participating Organizations will email written SAE reports to the following within 48 hours of learning of the event using the fillable PDF SAE Report Form.

- DCP's Regulatory Contractor CCS Associates, Inc. (CCSA; phone: 650-691-4400) at safety@ccsainc.com
- NCI DCP Medical Monitor, Dr. Luz Rodriguez (rodrigul@mail.nih.gov)
- Northwestern Cancer Prevention Consortium (ncpc@northwestern.edu)

11.2.2.4 The DCP Medical Monitor and CCSA regulatory staff will determine which SAEs require FDA submission as IND safety reports.

11.2.2.5 The Lead Organization and all Participating Organizations will comply with applicable regulatory requirements related to reporting SAEs to the IRB/IEC.

11.2.3 Follow-up of SAE

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the DCP SAE Report Form in the appropriate format. Follow-up information should be sent to DCP as soon as available. All SAEs will be followed according to standard of care. SAEs possibly, probably, or definitely related to the study agent will be followed until resolved.

## 12. STUDY MONITORING

### 12.1 Data Management

Data will be managed by the study statistician, Dr. Jovanovic, according to standard operating procedures, which meet the guidelines of DCP Requirements for Data Management and which follow the Data Management Plan that Northwestern University has on file with the Division of Cancer Prevention, NCI. Source data verification will be performed by the Northwestern Cancer Prevention Consortium. The Consortia 2012 Data Management Plan, submitted as part of a contract agreement with the NCI (HHSN261201200035I), was approved.

Clinical data will be reported to Northwestern University through the Lurie Cancer Center Clinical Trials Management System (CTMS), which will be the database of record.

### 12.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRFs) developed from the standard set of DCP Chemoprevention CRF Templates and utilizing NCI-approved Common Data Elements (CDEs). The approved CRFs will be used by Northwestern University to create the electronic CRFs (e-CRFs) screens in the CTMS-RDC application. Site staff will enter data into the e-CRFs for transmission to DCP according to DCP standards and procedures.

All specimen results that are batch analyzed will be collected and stored on excel spreadsheets. The excel spreadsheets will constitute the database of record.

### 12.3 Source Documents

All source documents will be collected and stored by the research staff at the site of accrual. Any data recorded directly in CTMS that constitute no prior written or electronic record of data, will be specifically identified as source data. Quality of Life questionnaires completed in person may be completed on the paper and entered into CTMS.

### 12.4 Data and Safety Monitoring Plan

A comprehensive Data Safety and Monitoring Plan has been submitted by Northwestern University, approved by the DCP, and is on file there. Any future changes will be forwarded for review.

This trial is subject to review by the Lurie Cancer Center Data Monitoring Committee (DMC). Semi-Annual reports, SAEs, and protocol deviations will be reviewed by the DMC at bi-weekly meetings. This trial is also subject to possible annual audits by the Lurie Cancer Center Clinical Trials Audit Committee (CTAC).

## 12.5 Sponsor or FDA Monitoring

The NCI, DCP (or their designee), pharmaceutical collaborator (or their designee), or FDA may monitor/audit various aspects of the study. These monitors will be given access to facilities, databases, supplies and records to review and verify data pertinent to the study.

## 12.6 Record Retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, *etc*.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with Health Insurance Portability and Accountability Act (HIPAA), Office of Human Research Protections (OHRP), Food and Drug Administration (FDA) regulations and guidances, and NCI/DCP requirements, unless the standard at the site is more stringent. The records for all studies performed under an IND will be maintained, at a minimum, for two years after the approval of a New Drug Application (NDA). For NCI/DCP, records will be retained for at least three years after the completion of the research. NCI will be notified prior to the planned destruction of any materials. The records should be accessible for inspection and copying by authorized persons of the Food and Drug Administration. If the study is done outside of the United States, applicable regulatory requirements for the specific country participating in the study also apply.

## 12.7 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agent(s) supplied by DCP, NCI, used in this protocol, is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as Collaborator(s)) and the NCI Division of Cancer Prevention. Therefore, the following obligations/guidelines, in addition to the provisions in the “Intellectual Property Option to Collaborator@ contained within the terms of award, apply to the use of Agent(s) in this study:

12.7.1 Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a patient participating on the study or participant’s family member requests a copy of this protocol, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from the DCP website.

12.7.2 For a clinical protocol where there is an Investigational Agent used in combination with (an) other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-party Data”).

12.7.3 NCI must provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

12.7.4 Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval, or commercialize its own investigational agent.

12.7.5 Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational agent.

12.7.6 Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

12.7.7 When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators of Collaborator's wish to contact them.

12.7.8 Any manuscripts reporting the results of this clinical trial must be provided to DCP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days (or as specified in the CTA) from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to DCP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to DCP prior to release. Copies of any manuscript, abstract, and/or press release/ media presentation should be sent to the Protocol Information Office at NCI_DCP_PIO@mail.nih.gov.

The Protocol Information Office will forward manuscripts to the DCP Project Officer for distribution to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/proprietary information.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Design/Description

This is a phase II randomized, double-blinded, placebo-controlled trial of statin to evaluate the impact of statin treatment on pancreatic function and inflammation implicated in pancreatic carcinogenesis in patients with recurrent acute pancreatitis. The primary objective of this study will be to demonstrate that statins will improve pancreatic function in high-risk patients, as defined by those with two or more episodes of acute pancreatitis in the past 12 months.

The primary outcome for this study is change from baseline (Study Visit 1) at 6 months of *peak bicarbonate concentration* as measured by *ePFT.* Sample size calculations follow from computations PASS 11 (www.ncss.com). Means and standard deviations of peak bicarbonate concentrations are derived from the literature on the validity and utility of ePFT for diagnosis of chronic pancreatitis [56, 57]. We expect baseline peak bicarbonate levels to be 60 mEq/L in these patients with recurrent pancreatitis, with a standard deviation of 13 mEq/L. We expect the peak bicarbonate levels to increase in both simvastatin and placebo groups as the groups recover from the acute pancreatitis event, with the simvastatin group showing a greater increase to full recovery compared to the placebo group. An analytic sample size of 24 (after 20% drop out) will have 82% power to detect a statistically significant one-sided difference of 15 mEq/L (25 vs. 10 mEq/L) at an alpha level of 0.05. The anticipated changes are well within the range of

peak bicarbonate levels of patients with mild to severe pancreatitis [56, 57] whose median peak bicarbonate levels range from 40 mEq/L to 100 mEq/L.

### 13.2 Randomization/Stratification

Patients will be randomized by the study statistician at Northwestern University. Randomization will be carried out among consented patients meeting the Screen 2 eligibility criteria at each study site with a 2:1 ratio for simvastatin and placebo assignment.

### 13.3 Accrual and Feasibility

Sample size: Intervention = 30 (20:10) randomized sample; after 20% drop out = 24 (16:8) analytic sample. The expected accrual rate is 1-2 participants per month across four study sites, and the planned recruitment duration is 24 months. We anticipate that all evaluable participants will have completed all study procedures within three years. Power and precision arguments are provided below.

### 13.4 Primary Objective, Endpoint(s), Analysis Plan

The primary outcome for this study is change from baseline (Study Visit 1) at 6 months of peak bicarbonate concentration as measured by ePFT. For the primary endpoint, we will consider differences D(T) and D(P) for D=After-Before, for Treatment and Placebo (Control) groups respectively. Then we will use a nonparametric two-sample Wilcoxon-Mann-Whitney test to address the hypothesis H0: mean [D (T)] =mean [D (P)] versus H1: mean[D(T)] > mean[D(P)], and report a one-sided p-value, as presented in **Table 3**. If $p<0.05$ we will consider this to be evidence of activity in the simvastatin group.

**Table 3. Numeric Results for Mann-Whitney Test (Uniform Distribution)**

| Power | N1 | N2 | Ratio | Alpha | Beta | Mean1 | Mean2 | S1 | S2 |
|---|---|---|---|---|---|---|---|---|---|
| 0.82 | 16 | 8 | 0.5 | 0.05 | 0.18 | 25 | 10 | 13 | 13 |

Null Hypothesis: Mean1=Mean2. Alternative Hypothesis: Mean1>Mean2.
The standard deviations were assumed to be equal at 13 mEq/L.

### 13.5 Secondary Objectives, Endpoints, Analysis Plans

For secondary endpoints, we will consider D(T) and D(P) as well as percent change relative to baseline as well, namely, D (T)/B (T) and D (P)/B (P). For all secondary variables, we will use descriptive statistics and graphics at 3 months and at 6 months, as well as study random effects regression trends along the timeline Baseline → 3 months → 6 months for further hypotheses generation. In particular, we will look into cytokines, chemokines, and adhesion molecules and quality of life scores from the QLQ-C30 and QLQ-PAN28(CP) assessment after possible log-transformation of continuous data. In particular, we will be interested in the relation between a) pairs of secondary variables and differences D=After-Before in pairs of secondary variables in the Treatment group, b) same as a) but in the control group, c) comparing pairwise changes between the Treatment and the Control groups, and d) relationship of secondary outcomes with recurrent pancreatitis. In this way, we will be able to study co-dependence among various secondary variables and their possible relationship with recurrent pancreatitis. We will thus fit various regression models, estimate relevant parameters (e.g., intercept, slope) and explore the apparent magnitudes of change in these parameters in the treatment and the control group.

Analyses will be performed with Stata software. All analyses will be conducted on an intention to treat basis (all randomized participants will be included in the assigned group) and will begin with univariate cross-sectional statistics for profiling the study population and bivariate tabulations as a preliminary step to possible model building. We will not control for overall Type I error due to small number of

observations and the preliminary nature of the study.

### 13.6 Reporting and Exclusions

We anticipate some contamination from the simvastatin intervention to placebo due to non-compliance. We do not expect cross-over from the placebo to statin group as participants will be aware that they might be on statins already and would not want to jeopardize their safety and care. However, new clinical guidelines for prescription of statins may also influence drop-outs among participants who wish to reduce the risk of cardiovascular disease [58]. These guidelines recommend targeting men and women with cardiovascular disease, LDL cholesterol ≥ 190 mg/dL, and persons 40-75 years with diabetes or a 10-year cardiovascular disease risk ≥ 7.5%. Most of these people would not meet the eligibility criteria for study participation. The drop-out rate is expected to be 4 subjects in the treatment arm and 2 subjects in the placebo arm at 6 months follow-up.

### 13.7 Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first dose of simvastatin.

### 13.8 Evaluation of Response

Changes in peak bicarbonate concentration as measured by ePFT will be evaluated for all randomized participants.

### 13.9 Interim Analysis

There will be no planned interim analyses.

### 13.10 Ancillary Studies

N/A

## 14. ETHICAL AND REGULATORY CONSIDERATIONS

### 14.1 Form FDA 1572

Prior to initiating this study, the Protocol Lead Investigator at the Lead or Participating Organization(s) will provide a signed Form FDA 1572 stating that the study will be conducted in compliance with regulations for clinical investigations and listing the investigators, at each site that will participate in the protocol. All personnel directly involved in the performance of procedures required by the protocol and the collection of data should be listed on Form FDA 1572.

### 14.2 Other Required Documents

14.2.1 Current (within two years) CV or biosketch for all study personnel listed on the Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.2 Current medical licenses (where applicable) for all study personnel listed on Form FDA 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.3 Lab certification (*e.g.*, CLIA, CAP) and lab normal ranges for all labs listed on Form FDA 1572 for the Lead Organization and all Participating Organizations.

14.2.4 Documentation of training in "Protection of Human Research Subjects" for all study personnel listed on the FDA Form 1572 and Delegation of Tasks form for the Lead Organization and all Participating Organizations.

14.2.5 Documentation of Federalwide Assurance (FWA) number for the Lead Organization and all Participating Organizations.

14.2.6 Signed Investigator's Brochure/Package Insert acknowledgement form

14.2.7 Delegation of Tasks form for the Lead Organization and all Participating Organizations signed by the Principal Investigator for each site and initialed by all study personnel listed on the form

14.2.8 Signed and dated NCI, DCP Financial Disclosure Form for all study personnel listed on Form FDA 1572 for the Lead Organization and all Participating Organizations

## 14.3 Institutional Review Board Approval

Prior to initiating the study and receiving agent, the Investigators at the Lead Organization and the Participating Organization(s) must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study become necessary, protocol amendments will be submitted to the DCP PIO according to DCP Amendment Guidelines. The DCP-approved amended protocol must be approved by the IRB prior to implementation

## 14.4 Informed Consent

All potential study participants will be given a copy of the IRB-approved Informed Consent to review. The investigator will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant decides to participate in the study, he/she will be asked to sign and date the Informed Consent document. The study agent(s) will not be released to a participant who has not signed the Informed Consent document. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

Participants must be provided the option to allow the use of blood samples, other body fluids, and tissues obtained during testing, operative procedures, or other standard medical practices for further research purposes. If applicable, statement of this option may be included within the informed consent document or may be provided as an addendum to the consent. A Model Consent Form for Use of Tissue for Research is available through a link in the DCP website.

Prior to study initiation, the informed consent document must be reviewed and approved by NCI, DCP, the Consortium Lead Organization, and the IRB at each Organization at which the protocol will be implemented. Any subsequent changes to the informed consent must be approved by NCI, DCP, the Consortium Lead Organization's IRB, and then submitted to each organization's IRB for approval prior to initiation.

## 14.5 Submission of Regulatory Documents

All regulatory documents are collected by the Consortia Lead Organization and reviewed for completeness and accuracy. Once the Consortia Lead Organization has received complete and accurate documents from a participating organization, the Consortium Lead Organization will forward the regulatory documents to DCP's Regulatory Contractor:

Paper Document/CD-ROM Submissions:
Regulatory Affairs Department
CCS Associates, Inc.
2001 Gateway Place, Suite 350 West
San Jose, CA 95110
Phone: 650-691-4400

E-mail Submissions:
regulatory@ccsainc.com

Regulatory documents that do not require an original signature may be sent electronically to the Consortium Lead Organization for review, which will then be electronically forwarded to DCP's Regulatory Contractor.

### 14.6 Other

This trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and the applicable regulatory requirements.

## 15. FINANCING, EXPENSES, AND/OR INSURANCE

All research related costs associated with participating in this study will be paid for, and will not be the responsibility of the participant. Individuals will receive $50 for completing the Screen 2 testing and $150 at the completion of each visit for their time, transportation, parking, and other expenses related to the study. Subjects who complete the entire study – the Screen 2 testing, baseline testing (Study Visit 1), and two follow-up visits (Study Visits 2 and 3) – will receive $500. Subjects will be paid only for the visits they complete.

It is possible that a research injury or illness may result from participating in this study. Subjects being treated for a research injury or illness will not pay for the costs of care provided by Cedars-Sinai Medical Center (CSMC); Kaiser Southern California Permanente Medical Group (KPMC); the University of Pittsburgh (UP); or Stanford University (SU); or in any emergency room provided that they are being treated for a research injury or illness. If a subject chooses to obtain non-emergency care elsewhere, the costs of that care will be the responsibility of the study participant and/or their health insurance carrier. Losses such as lost wages will not be paid.

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**CONSENT FORM**

*(Insert Institution name)*

# Consent Form

**Study Title for Study Participants: A Study Testing Simvastatin to Prevent Pancreatic Cancer in People with Recurrent Pancreatitis**

**Protocol Title:** NWU2014-04-01, Statin Therapy to Reduce the Risk of Recurrent Pancreatitis

**Principal Investigator:** Marc T. Goodman, Ph.D., M.P.H.

**Sponsored By:** National Cancer Institute (NCI)

## Introduction

You are being asked to take part in a research study. This document has important information about the reason for the study, what you will do if you choose to be in this research study, and the way we would like to use information about you and your health.

### What is the usual approach to my recurrent pancreatitis (pancreatitis that occurs more than once)?

You are being asked to take part in this study because you have recurrent pancreatitis and are at increased risk for pancreatic cancer. People who are at increased risk and choose not to participate in a study are usually followed closely by their doctor to watch for the development of cancer.

### What are my other choices if I do not take part in this study?

- You may choose to have the usual approach described above;
- You may choose to take part in a different study, if one is available; or
- You may choose to do nothing.

### Why is this study being done?

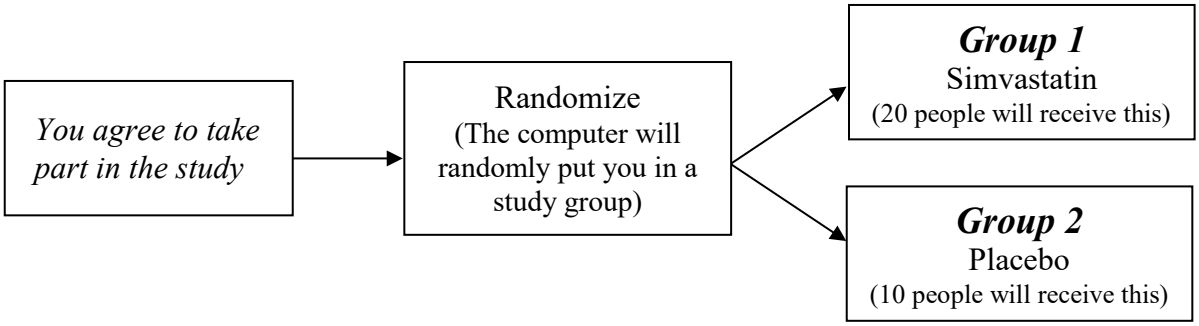
The purpose of this study is to compare the safety and effects of simvastatin in people with recurrent pancreatitis who are at an increased risk for pancreatic cancer. In this study, you will get either simvastatin or placebo, a pill that looks like the study drug but contains no medication. Simvastatin is approved by the U.S. Food and Drug Administration (FDA) to reduce the risk for heart attack, stroke, and chest pain in patients who have heart disease or risk factors for heart disease such as smoking, high blood pressure, low high-density lipoprotein (HDL), or family history of early heart disease. It is also approved to lower the risk for heart attack or stroke in patients with type 2 diabetes and risk factors such as diabetic eye or kidney problems, smoking, or high blood pressure. However, simvastatin is not approved by the FDA to decrease the risk of recurrent pancreatitis. Studies show that simvastatin lowers the risk of heart disease not only by decreasing cholesterol, but also by decreasing inflammation. We believe that this anti-inflammatory effect of simvastatin may help patients with pancreatitis. There will be about 30 people taking part in this study at Cedars-Sinai Medical Center (CSMC); Kaiser Southern California Permanente Medical Group (KPMC); the University of Pittsburgh (UP); and Stanford

University (SU).

**What are the study groups?**
This study has two study groups. Group 1 will receive the study drug simvastatin and Group 2 will receive a placebo, a pill that looks like the study drug but contains no medication. There will be 20 people in Group 1 and 10 people in Group 2.

A computer will randomly put you in a study group—like a coin toss—to decide what group you get placed into. This is done because no one knows if one study group is better, the same, or worse than the other group. Once you are put in a group, you cannot switch to the other group.

Neither you nor your doctor will know if you are receiving simvastatin or placebo. Your doctor cannot choose which group you will be in.




**How long will I be in this study?**
Your participation in the study will last 9 months. You will receive the study drug for 6 months, and your doctor will continue to watch you for side effects and follow your condition for 3 months after you stop taking the study drug. If you stop taking the study drug early, your doctor will continue to watch you for side effects for 3 months.

**What extra tests and procedures will I have if I take part in this study?**
If you agree to participate in this study, you will be required to sign this consent form before you have any tests or procedures that are done only for this study. Most of the exams, tests, and procedures you will have are part of the usual approach for your condition. However, there are some extra tests and procedures that you will need to have if you take part in this study, including review of your medical history and medications, blood tests, endoscopic tests of your gastrointestinal tract, collection of stool samples, completion of questionnaires, and pregnancy tests (only for women who are able to become pregnant). These extra tests and procedures are described in further detail below.

There are 4 main parts to this study: *Screening, Baseline Testing*, *Intervention*, and *Follow-up after Completion of Study Intervention*.

*Screening (Screening 1 and 2)*
Screening is a period during which tests and exams will be done to determine if you are eligible to participate in the study. Some of the tests and exams may have been recently done by one of your doctors and might not need to be repeated. You may be required to provide a medical

release to obtain medical records from clinical centers other than *(Insert institution name)* to review your pancreatitis history.

- *Screening 1*
  After you sign the consent form, you will need to have the following to determine if you are eligible for the study:
  - Review of your medical records and pancreatitis history by the study doctor to confirm that you have recurrent pancreatitis
  - Review of your computed tomography (CT) and magnetic resonance imaging (MRI) results in the past 12 months. If previous CT or MRI results show that you have advanced chronic pancreatitis, you will not be eligible for the study.

- *Screening 2*
  If you are still eligible after Screening 1, the following will occur:
  - Physical exam and vital signs assessment (blood pressure, heart rate, respiratory rate, and oral temperature)
  - Blood draw (about 2 teaspoons or 10 mL of your blood will be collected) for lab tests to check for a low blood count or clotting problems and to check your liver and kidneys
  - Endoscopic ultrasound (EUS) and endoscopic pancreatic function test (ePFT). These tests allow the doctor to see your upper gastrointestinal tract and check the function of your pancreas. You will be asked to fast overnight (8 hours) before the endoscopic testing.
  - Pregnancy test (for women who are able to become pregnant)

Endoscopic ultrasound (EUS) is a test that lets a doctor see your upper gastrointestinal tract. The doctor uses a long, flexible, lighted tube called an endoscope that has a video camera, as well as additional ultrasound tubes to visualize the digestive tract by sound waves. Images of the inside of the patient's body can be seen on a screen. Before the EUS is administered, a medicine will be sprayed into your mouth to prevent you from coughing or gagging when the endoscope is inserted. An intravenous (IV) needle will be inserted into your arm, and you will be given medicine through the IV to make you relaxed and sleepy. You should feel no pain. When you are sleepy, the endoscope will be guided through your mouth and throat, then through the esophagus, stomach, and duodenum (first part of the small intestine). This will allow the doctor to examine the inside of these organs.

The endoscopic pancreatic function test (ePFT) is a test that checks on the function of your pancreas. It is done after the EUS. Fluid from your stomach and duodenum will be removed when the endoscope is in place. Then secretin will be administered through your IV. Secretin is a digestive hormone that stimulates secretions by the liver and pancreas. A small dose of secretin will be administered first to observe and make sure you do not have strong adverse reactions to it before the full dose is administered. After the secretin is administered, pancreatic fluid will be collected at five time points over one hour (at 0-10 minutes, 10-20 minutes, 20-30 minutes, 30-45 minutes, and 45-60 minutes). Each collection will contain at least 3 mL (about 1/2 teaspoon) of fluid.

When EUS and ePFT testing is finished, the doctor will slowly remove the endoscope. The EUS and ePFT will be done by a highly trained, experienced doctor. The EUS will take about 30 minutes and the ePFT will take about one hour. The Screening 2 visit, including the EUS and ePFT, will last approximately 3-4 hours.

If the EUS results show that you have advanced chronic pancreatitis, if your lab test results are unacceptable, or if you are pregnant, you will not be eligible for the study.

*Baseline Testing (Study Visit 1)*

If the Screening 2 exams and tests show that you can take part in the study, and you choose to, then you will be randomized to a study group. You will also need the following extra procedures. These are not part of the usual approach for your condition. The baseline testing will take place at *(site specific clinic and address)* 0-14 days after the Screening 2 tests. You will be asked to fast overnight (8 hours) before the testing. The baseline testing will take approximately 2 hours.

- Review of your medical history, medications, and laboratory test results, and a vital signs assessment (blood pressure, heart rate, respiratory rate, and oral temperature)
- Blood tests (about 7 teaspoons or 36 mL of blood will be collected) to check your organ function, and for research purposes
- Collection of a stool sample for research purposes. A stool collection kit and instructions for collecting the sample at home will be provided before the scheduled visit. You will collect your stool sample at home and bring it to the baseline testing.
- Completion of a questionnaire that asks about your background (birthplace, race, education, marital status), health habits, physical activity, and tobacco and alcohol use. The questionnaire will be administered by a research staff person, who will ask you the questions and record the answers.
- Completion of a questionnaire that asks about your pain level and quality of life. This is a self-administered questionnaire.

The blood and stool samples are required in order for you to take part in this study because the research on the samples is an important part of the study. You will receive a phone call the day before the visit to remind you to fast overnight and to collect the stool sample and bring it to the baseline testing.

The study drug (either simvastatin or placebo) will be provided to you at the baseline testing. Study staff will review instructions for how and when to take the study drug. You will be given a study diary to fill out and record each dose of study drug that you take. You should mark any missed or skipped doses in this diary, as well as any side effects that you are experiencing.

*Intervention (Study Visits 2 and 3)*

During the *Intervention* portion of this study, you will be asked to take the study drug every day for 6 months and participate in 2 study visits. *Research staff will contact you approximately every four weeks by phone* to check on your progress and answer any questions regarding the study drug. You will also be asked questions about potential side effects of the study drug. These phone calls will last approximately 10 minutes.

*Reminders to take your study drug:* You will have the option of receiving email or text messages

from research staff to remind you about the study drug during the first week of the intervention period. We encourage you to respond to indicate if the dose has been taken. If you are having trouble remembering, these reminders can be extended beyond the first week. It is important that you stay on the study drug until the last study visit 6 months after you start intervention with the study drug. You will receive a phone call from research staff to remind you to stay on the study drug during the last week of the study intervention, as it is very important that you not miss any dose during this week so that we are able to fully use all data collected. Reminder messages to take the study drug will also be sent to you.

- *Study Visit 2*

  You will need to come to *(site specific clinic and address)* for a study visit 3 months after you start intervention with the study drug. You will be asked to fast overnight (8 hours) before this visit. The following procedures will be done during the visit:
  - Review of your medical history, medications, and laboratory test results, and a physical exam and vital signs assessment (blood pressure, heart rate, respiratory rate, and oral temperature)
  - Review of your study diary and side effects of the study drug you may be experiencing
  - Blood tests (about 7 teaspoons or 36 mL of blood will be collected)
  - Pregnancy test (for women who are able to become pregnant)
  - Collection of a stool sample for research purposes. A stool collection kit and instructions for collecting the sample at home will be provided before the scheduled visit. You will collect your stool sample at home and bring it to the study visit.
  - Completion of a self-administered questionnaire that asks about your pain level and quality of life
  - Esophagogastroduodenoscopy (EGD) and endoscopic pancreatic function test (ePFT)

  Esophagogastroduodenoscopy (EGD) is a test that lets a doctor see your upper gastrointestinal tract. EGD is a simpler procedure than the EUS performed in Screening 2 in that while it does involve an imaging scope, it will not require additional ultrasound probes to visualize the digestive tract using sound waves. ePFT will be performed after the EGD. The two procedures will take about 90 minutes.

  This visit, including the EGD and ePFT, will last approximately 4 hours. You will receive a phone call the day before the visit to remind you to fast overnight and to collect the stool sample and bring it to the study visit. We will also remind you to bring your study diary and any leftover study drugs to the visit.

- *Study Visit 3*

  You will need to come to *(site specific clinic and address)* for a final study visit 6 months after you start intervention with the study drug. You will be asked to fast overnight (8 hours) before this visit. The following procedures will be done during the visit:
  - Review of your medical history, medications, and laboratory test results, and a physical exam and vital signs assessment (blood pressure, heart rate, respiratory

rate, and oral temperature)
- Review of your study diary and side effects of the study drug you may be experiencing. The study diary and all unused study medication will be collected at this visit.
- Blood tests (about 7 teaspoons or 36 mL of blood will be collected)
- Pregnancy test (for women who are able to become pregnant)
- Collection of a stool sample for research purposes. A stool collection kit and instructions for collecting the sample at home will be provided before the scheduled visit. You will collect your stool sample at home and bring it to the study visit.
- Completion of a questionnaire that asks about changes in your health habits, physical activity, and tobacco and alcohol use since your baseline testing. The questionnaire will be administered by a research staff person.
- Completion of a self-administered questionnaire that asks about your pain level and quality of life
- Endoscopic ultrasound (EUS) and endoscopic pancreatic function test (ePFT)

The endoscopic ultrasound (EUS) and endoscopic pancreatic function test (ePFT) are the same tests as those performed during Screening 2.

The final study visit, including the EUS and ePFT, will last approximately 4 hours. You will receive a phone call the day before the visit to remind you to fast overnight and to collect the stool sample and bring it to the study visit. We will also remind you to bring your study diary and any leftover study drugs to the visit.

*Follow-up after Completion of Study Intervention*
We will continue to follow your condition for 3 months after you stop taking the study drug. Research staff will contact you by phone to check on potential symptoms and side effects you may be experiencing, and to answer any questions you may have. These phone calls will last approximately 10 minutes. You will be contacted approximately 30 days, 60 days, and 90 days after you complete the study.

**What possible risks can I expect from taking part in this study?**
Your involvement in this study may involve the following risks:

*Risks associated with simvastatin*
The study drug simvastatin used in this study may affect how different parts of your body work, such as your liver and kidneys. Simvastatin is not safe for people with active liver disease. You will have blood tests before and during the study to monitor your liver and kidney function. The study doctor will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects.

Here are important points about side effects:
- The study doctors do not know who will or will not have side effects.

- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may be serious and may even result in death

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.

The tables below show the most common side effects that we know about simvastatin, some of which may be serious. There might be other side effects that we do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

| **OCCASIONAL**<br>**(**out of every 100 people receiving simvastatin, from 4 to 20 may experience): |
|---|
| • Upper respiratory infections<br>• Headache<br>• Abdominal pain<br>• Constipation<br>• Nausea<br>• Myalgia (muscle aches)<br>• Dry skin |

| **RARE, SOME MAY BE SERIOUS**<br>**(**out of every 100 people receiving simvastatin, 3 or fewer may experience): |
|---|
| • Feeling weak and having no energy<br>• Confusion, forgetfulness, or memory problems<br>• Liver failure (signs and symptoms: fatigue, weight loss, yellowing of the skin or eyes)<br>• Rhabdomyolysis (a breakdown of muscle tissue), a rare condition that may cause kidney damage (signs and symptoms: muscle pain, tenderness, or weakness; dark colored urine)<br>• Elevations in blood glucose |

*Food and medication interactions:*
Grapefruit and grapefruit juice may interact with simvastatin and lead to potentially dangerous effects. Do not consume grapefruit products (grapefruit, grapefruit juice, grapefruit seed extract, or dietary supplements containing grapefruit) during the intervention portion of this study.

Simvastatin interacts with many other medications in ways that can increase or decrease the amount of medication in your blood. The interactions could result in increased levels that can be

dangerous, or decreased levels so that drugs don't work. Simvastatin also interacts with some medications in a way that increases the risk of muscle injury called myopathy (symptoms: unexplained muscle weakness or pain). Simvastatin should not be taken by people who are also taking the antibiotics erythromycin, clarithromycin, or telithromycin; the antidepressant nefazodone; the antifungal drugs itraconazole, ketoconazole, posaconazole, or voriconazole; the immunosuppressant cyclosporine; the endometriosis drug danazol; HIV protease inhibitors; the Hepatitis C protease inhibitors boceprevir or telaprevir; lomitapide (a drug used to treat high cholesterol that runs in families); or the cardiovascular drugs gemfibrozil, diltiazem, dronedarone, amiodarone, amlodipine, ranolazine, or verapamil (medications used to treat high cholesterol, high blood pressure, angina (chest pain), or heart rhythm problems). Oral formulations (i.e., tablets or capsules) of these medications should not be used during the intervention portion of this study. Topical formulations, including creams, shampoos, foams, and gels applied to the skin, are acceptable. Tell the study doctor immediately if you use any of these medications, or if any of these medications is prescribed for you during the study.

*Alcohol consumption*

Simvastatin should be used with caution in patients who consume more than 5 drinks per day of alcohol as simvastatin may cause liver injury. We will monitor your liver function every three months and inform you if your test results are abnormal.

*Reproductive risks*

Women who are pregnant or may become pregnant should not use simvastatin. When taken during pregnancy, simvastatin may cause harm to a developing baby. Women who are pregnant, attempting to become pregnant or breastfeeding may not participate in the study. Women of child-bearing potential will be required to have a pregnancy test before the study and at the follow-up visits, and must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Let the study doctor know immediately if you believe you might be pregnant.

*Esophagogastroduodenoscopy (EGD), endoscopic ultrasound (EUS), and endoscopic pancreatic function testing (ePFT)*

You may experience an infection, possibly somewhere along the path of the endoscope; piercing or tearing of an organ that could require subsequent surgery; or bleeding more than normally expected. There is a small risk of complications related to the sedative (medicine given to relax you during the procedure) such as an allergic reaction, nausea, or irregular heartbeats. During the ePFT procedure, secretin will be administered through your intravenous (IV) line. Secretin is a digestive hormone that stimulates secretions by the liver and pancreas. There is a small risk of complications related to the EGD, EUS, ePFT, or the secretin administration, such as nausea, flushing, abdominal pain, or vomiting. Secretin has the potential to cause a serious allergic reaction, which may include rash, low blood pressure, wheezing, shortness of breath, or swelling of the face or throat. A small dose of secretin will be administered first to observe and make sure you do not have strong adverse reactions to it before the full dose is administered. You should not drive after an EGD, EUS, or ePFT, and you should arrange transportation after the study visits where the EGD, EUS, or ePFT will be performed. The study doctor will discuss the risks of possible complications before your EGD, EUS, and ePFT procedures.

*Blood Collection*
There may be pain, swelling, or bruising around the vein where your blood is collected. You may feel faint. There is a small risk of infection at the place on your body from which the blood is collected. The blood will be drawn by a person trained to collect blood using sterile (clean) equipment, and a very small needle will be used for drawing your blood to minimize discomfort. The blood draw will be done after you haven't eaten for 8 hours. You may feel weak, light-headed, dizzy, and have palpitations.

*Questionnaires*
You may feel uncomfortable answering some of the questions you will be asked. If you feel uncomfortable answering any question, you can choose not to answer it.

**What possible benefits can I expect from taking part in this study?**
You should not expect to benefit from taking part in this research study. The results from this study will provide information that will help scientists to better understand how pancreatitis develops, and to learn whether simvastatin will improve pancreatic function in individuals with recurrent pancreatitis. This knowledge could help prevent pancreatic cancer in the future.

**Can I stop taking part in this study?**
Your participation in this research study is voluntary so you may decline to participate or to stop being in this study at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you choose not to participate in this study or decide to stop participating, you will not suffer any loss of benefits to which you would be entitled outside of the study. Choosing not to participate will not negatively affect the care you receive or any present or future medical treatment.

You will be told about any new information or changes in the study that could affect your health or your willingness to continue in the study.

Your participation in this study may be ended without your consent by the principal investigator or the study doctor for the following reasons:

- If you develop a dangerous side effect;
- If you become pregnant;
- If your health changes;
- If the study is no longer in your best interest;
- If you do not follow the study rules;
- If the study is stopped early for any reason by the sponsor, IRB, or FDA.

**What are my rights in this study?**
Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights. If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether or not you wish to continue or stop being in the study.

If you want to speak with someone who is not directly involved in this research, or have questions about your rights as a research subject, please contact the *(Insert institution name and*

*Institutional Review Board or other site specific entity)*. You can call them at *(insert phone number)* or contact them by email at *(insert email address)*. The *(site specific entity)* has been established to protect the rights and welfare of research participants. You may also contact the *(site specific entity)* if you want to offer input or obtain information regarding the study.

**What are the costs of taking part in this study?**
There will be tests and procedures that are done only for this study and other tests and procedures that are part of your routine medical care (not part of the research).

The simvastatin and placebo will be supplied at no charge while you take part in this study. The cost of study-specific exams, tests, and any other procedures performed for research purposes will be paid for by the study.

Some costs associated with your care may be considered standard of care, and will be billed to you or your insurance company. You will have to pay for any costs (including deductibles and co-payments) not covered by your health insurer. You should check with your health plan or insurance company to find out what they will pay for.

**Will I receive payment for taking part in this study?**
You will receive $50 for completing Screening 2 and $150 at the completion of each visit (Study Visit 1, Study Visit 2, and Study Visit 3) to reimburse you for your time, transportation, parking, and other expenses related to the study, as summarized in the table below. The total amount you will receive if you complete the whole study – Screening 2 and Study Visits 1, 2, and 3 – is $500. If you do not complete the entire research study, you will only be paid for those visits you do complete.

| **Research Visit** | **Covered** (done for research purposes at no cost to you) | **Not covered** (routine medical care, billed to you or your insurance) | **Payment to you when you finish the visit** |
|---|---|---|---|
| Screening 2 | Medical records and medications review, vital signs assessment, blood tests, pregnancy test, EUS and ePFT | Physical exam | $50 |
| Study Visit 1 | Medical history and medications review, vital signs assessment, blood tests, stool collection, questionnaires | | $150 |
| Study Visit 2 | Medical history and medications review, vital signs assessment, blood tests, stool collection, pregnancy test, questionnaire, EGD and ePFT | Physical exam | $150 |
| Study Visit 3 | Medical history and medications review, vital signs assessment, blood tests, stool collection, pregnancy test, questionnaires, EUS and ePFT | Physical exam | $150 |

You may be required to complete a W-9 Form in order to receive payment. The W-9 Form will be maintained by our accounting department at *(Insert institution name)*. If total payment is $600

or more from *(Insert institution name)* in a calendar year, a 1099 Form will be filed with the IRS in accordance with federal tax law. If you are a *(Insert institution name)* employee, you should provide your employee identification number to the research team so that your payment can be appropriately processed through Payroll. For your own protection and to comply with tax laws, your payment for participation will be reported to the IRS together with other compensation you receive from *(Insert institution name)*.

**What happens if I am injured or hurt because I took part in this study?**
If you feel you have been injured or hurt as a result of taking part in the study, it is important that you contact your study doctor immediately: *(Insert site specific study doctor's name and telephone number)*. If it is a medical emergency, call 911 or go to an emergency room. You will get medical treatment if you are injured or hurt as a result of taking part in this research study.

**Who will see my medical information?**
Your privacy is very important to us and we will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, we will do our best to make sure that any information that is released will not be able to identify you. Some of your health information, and information about your specimens, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The study sponsor, the National Cancer Institute (NCI)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the US.
- The National Cancer Institute will obtain information for this clinical trial under data collection authority Title 42 U.S.C. 285.

**Where can I get more information?**
***You may visit the NCI website at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).***

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Website will not include information that can identify you. At most, the Website will include a summary of the results. You can search this Website at any time.

**Who can answer my questions about this study?**
You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor *(insert name of site-specific study doctor(s)* at *(insert telephone number)*.

**This section is about optional studies you can choose to take part in.**

**Optional Sample Collections for Biobanking for Possible Future Studies**

Researchers are trying to learn more about cancer and other health problems. Much of this research is done using samples from your biopsies, blood, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

The researchers would like to ask your permission to store left over samples and health information obtained during your participation in this study for future medical research. Storing samples for future studies is called biobanking. If you agree, the blood, tissue, pancreatic fluid, and stool samples, and information collected about you during the study will be coded and kept at *(Insert institution name)*.

The research that may be done is unknown at this time. Future research may include: 1) studies to identify genes and/or biomarkers and proteins that influence an individual's risk of getting pancreatitis, pancreatic cancer, or other diseases; 2) studies to identify specific pathways and mechanisms that promote cancer. A biomarker is a biological molecule found in blood, other body fluids, or tissues that may be a sign of a condition or disease.

**What is involved?**
Your samples and some related information may be stored in the NCI Biobank, along with samples and information from other people who take part. These are not additional samples that will be collected, but will consist of any material (blood, tissue, pancreatic fluid, and stool samples) that remains after the tests described for this study have been conducted. The samples will be kept until they are used up.

Qualified researchers can submit a request to use the materials stored in the NCI Biobank. A research committee at *(Insert institution name)* will review each request. There will also be an ethics review to ensure that the request is necessary and proper. You will not be notified if/when research is conducted using your samples.

**What are the possible risks?**
1) There is a risk that an unauthorized person could obtain the personal information in your medical records or other information we have stored about you.
2) There is a potential risk from collecting genetic information about you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) There are laws against the misuse of genetic information, but they may not give full protection. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

A new Federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums.

Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment. All health insurance companies and group health plans must follow this law by May 21, 2010. All employers with 15 or more employees must follow this law as of November 21, 2009.

Be aware that this new Federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

**How will information about me be kept private?**
Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name or birth date) will be sent. Samples will be identified by a unique study code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any NCI Biobank and *(Insert institution name)* staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom *(Insert institution name)* sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) The results from research on your samples will not be put in your medical record.
6) If research results are published, your name and other personal information will not be used.

**What are the possible benefits?**
You will not benefit from taking part. The study of your samples and data will help us to learn about the biological markers and mechanisms that influence an individual's risk of pancreatitis, cancer, and other diseases. We hope that studying the samples and data may, in the future, help to prevent or cure these diseases and result in new treatments.

**Are there any costs or payments?**
There will be no cost to you or your insurance company for storage of your samples. Your blood, tissue, pancreatic fluid, and stool samples will be used only for research and will not be sold. You will not be paid for allowing your leftover samples to be used in research. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any

profits.

**What if I change my mind?**
If you decide you no longer want your samples to be used, you can call *(insert name and phone number)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

**What if I have more questions?**
If you have questions about the use of your samples for research, contact the principal investigator, Dr. Marc T. Goodman, at 310-423-6188.

**Samples for future research studies**
My samples and related information may be kept in the NCI Biobank for use in future health research.

*Please circle one:* YES NO

I agree that my study doctor, or their representative, may contact me or my physician to see if I wish to participate in other research in the future.

*Please circle one:* YES NO

This is the end of the section about optional studies.

**Consent Summary**
I have read this consent form and the research study has been explained to me. I have been given time to ask questions, and have been told whom to contact if I have more questions. I agree to be in the research study described above. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

| | |
|---|---|
| Name (printed) and Signature of Research Participant | Date of Signature |
| Name (printed) and Signature of Person Obtaining Consent | Date of Signature |

# APPENDIX A

## Clinical Laboratory Minimum Test Requirements

Clinical labs must include at least the following tests. It is acceptable to do additional tests if they are included in the blood panels at your institution.

| **Blood Hematology: Complete Blood Count and Differential** | **Blood Chemistry: Comprehensive Metabolic Panel** | **Lipid Panel *** | **Other Blood Tests** |
|---|---|---|---|
| Hemoglobin<br>Platelet count<br>White blood cell count (WBC, leukocytes), total<br>Neutrophil count, absolute | Alanine aminotransferase (ALT (SGPT))<br>Aspartate aminotransferase (AST (SGOT))<br>Alkaline phosphatase (ALP)<br>Bilirubin, total<br>Creatinine<br>Glucose | Total cholesterol<br>High density lipoprotein (HDL) cholesterol<br>Low density lipoprotein (LDL) cholesterol<br>Triglycerides | Hemoglobin A1C (HbA1C) †<br>Creatine phosphokinase (CPK) § |
| * Lipid panels will be done at Study Visits 1, 2, and 3.<br>† Hemoglobin A1C will be measured at Study Visits 1 and 3.<br>§ Creatine phosphokinase (CPK) will be measured at Study Visit 1 to establish a patient-specific reference for this indicator of muscle toxicity. If the patient reports unexplained muscle pain or weakness during the trial, CPK will be tested again to check for elevation. | | | |

# APPENDIX B

## Performance Status Criteria

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| **Grade** | **Descriptions** | **Percent** | **Description** |
| 0 | Normal activity. Fully active, able to carry on all pre-disease performance without restriction. | 100 | Normal, no complaints, no evidence of disease. |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease. |
| 1 | Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g*., light housework, office work). | 80 | Normal activity with effort; some signs or symptoms of disease. |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work. |
| 2 | In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. | 60 | Requires occasional assistance, but is able to care for most of his/her needs. |
| | | 50 | Requires considerable assistance and frequent medical care. |
| 3 | In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. | 40 | Disabled, requires special care and assistance. |
| | | 30 | Severely disabled, hospitalization indicated. Death not imminent. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. | 20 | Very sick, hospitalization indicated. Death not imminent. |
| | | 10 | Moribund, fatal processes progressing rapidly. |
| 5 | Dead. | 0 | Dead. |

# APPENDIX C
## Study Diary
## Statin Therapy to Reduce the Risk of Recurrent Pancreatitis

*Please bring your completed diary and your study drug supply, including empty bottles, with you to every study visit. This will help us keep track of your study drug and how well you are tolerating it.*

**Protocol Number: NWU2014-04-01** **Site:** _____

**Participant Study ID:** _____ **Participant Name:** _____

**Date Study Drug Dispensed:** _____ **Participant Signature:** _____

### Instructions

*Complete one line in the table for each day you take the study drug.*

- Take your study drug once per day at bedtime or with an evening meal. Take the capsule at the same time every day. Please swallow the capsule whole and do not chew, crush, or open it.
- Record the date and time of day you took the study drug.
- If you notice any side effects such as headache, abdominal pain, constipation, nausea or vomiting, respiratory infection, or mild skin rash, or if you have any comments please record them in the Side Effects/Comments column and tell the study staff when they call you.
- If you miss a dose of the study drug, take it as soon as you remember. Do not take the drug if it has been more than 12 hours since you missed your last dose. Wait and take the next dose at your regular time. Do not take 2 doses of the study drug at the same time. Please write the reason for missing a dose in the Side Effects/Comments column.
- Using this pain scale, write a number for the amount of pain you feel **today** in the Pain Level column.

| 0 | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| No pain | Very mild pain | Mild pain | Moderate pain | Severe pain | Very severe pain |

| Day | Date | Time Study Drug Taken | Pain Level | Side Effects/Comments |
|---|---|---|---|---|
| 1 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 2 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 3 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 4 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 5 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 6 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 7 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 8 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 9 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 10 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 11 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 12 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 13 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 14 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 15 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 16 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 17 | | ____:____ ☐ a.m. / ☐ p.m. | | |

| Day | Date | Time Study Drug Taken | Pain Level | Side Effects/Comments |
|---|---|---|---|---|
| 18 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 19 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 20 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 21 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 22 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 23 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 24 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 25 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 26 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 27 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 28 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 29 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 30 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 31 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 32 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 33 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 34 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 35 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 36 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 37 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 38 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 39 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 40 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 41 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 42 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 43 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 44 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 45 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 46 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 47 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 48 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 49 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 50 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 51 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 52 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 53 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 54 | | ____:____ ☐ a.m. / ☐ p.m. | | |

| Day | Date | Time Study Drug Taken | Pain Level | Side Effects/Comments |
|---|---|---|---|---|
| 55 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 56 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 57 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 58 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 59 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 60 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 61 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 62 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 63 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 64 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 65 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 66 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 67 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 68 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 69 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 70 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 71 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 72 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 73 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 74 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 75 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 76 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 77 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 78 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 79 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 80 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 81 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 82 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 83 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 84 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 85 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 86 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 87 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 88 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 89 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 90 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 91 | | ____:____ ☐ a.m. / ☐ p.m. | | |

| Day | Date | Time Study Drug Taken | Pain Level | Side Effects/Comments |
|---|---|---|---|---|
| 92 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 93 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 94 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 95 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 96 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 97 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 98 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 99 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 100 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 101 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 102 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 103 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 104 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 105 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 106 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 107 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 108 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 109 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 110 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 111 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 112 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 113 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 114 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 115 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 116 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 117 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 118 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 119 | | ____:____ ☐ a.m. / ☐ p.m. | | |
| 120 | | ____:____ ☐ a.m. / ☐ p.m. | | |

| **FOR STUDY TEAM USE ONLY** | Staff Initials: |
|---|---|
| Date study drug dispensed: | Date study drug returned: |
| Number of pills/capsules dispensed: | Number of pills/capsules returned: |
| Number of pills/capsules that should have been taken: | |
| Discrepancy / Notes | |

**APPENDIX D**

**Participant ID:** _____

Date: _____

# Statin Therapy to Reduce the Risk of Recurrent Pancreatitis

## EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

| | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase? | 1 | 2 | 3 | 4 |
| 2. Do you have any trouble taking a long walk? | 1 | 2 | 3 | 4 |
| 3. Do you have any trouble taking a short walk outside of the house? | 1 | 2 | 3 | 4 |
| 4. Do you need to stay in bed or a chair during the day? | 1 | 2 | 3 | 4 |
| 5. Do you need help with eating, dressing, washing yourself or using the toilet? | 1 | 2 | 3 | 4 |

| **During the past week:** | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 6. Were you limited in doing either your work or other daily activities? | 1 | 2 | 3 | 4 |
| 7. Were you limited in pursuing your hobbies or other leisure time activities? | 1 | 2 | 3 | 4 |
| 8. Were you short of breath? | 1 | 2 | 3 | 4 |
| 9. Have you had pain? | 1 | 2 | 3 | 4 |
| 10. Did you need to rest? | 1 | 2 | 3 | 4 |
| 11. Have you had trouble sleeping? | 1 | 2 | 3 | 4 |
| 12. Have you felt weak? | 1 | 2 | 3 | 4 |
| 13. Have you lacked appetite? | 1 | 2 | 3 | 4 |
| 14. Have you felt nauseated? | 1 | 2 | 3 | 4 |
| 15. Have you vomited? | 1 | 2 | 3 | 4 |
| 16. Have you been constipated? | 1 | 2 | 3 | 4 |

Please go on to the next page

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 17. Have you had diarrhea? | 1 | 2 | 3 | 4 |
| 18. Were you tired? | 1 | 2 | 3 | 4 |
| 19. Did pain interfere with your daily activities? | 1 | 2 | 3 | 4 |
| 20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television? | 1 | 2 | 3 | 4 |
| 21. Did you feel tense? | 1 | 2 | 3 | 4 |
| 22. Did you worry? | 1 | 2 | 3 | 4 |
| 23. Did you feel irritable? | 1 | 2 | 3 | 4 |
| 24. Did you feel depressed? | 1 | 2 | 3 | 4 |
| 25. Have you had difficulty remembering things? | 1 | 2 | 3 | 4 |
| 26. Has your physical condition or medical treatment interfered with your family life? | 1 | 2 | 3 | 4 |
| 27. Has your physical condition or medical treatment interfered with your social activities? | 1 | 2 | 3 | 4 |
| 28. Has your physical condition or medical treatment caused you financial difficulties? | 1 | 2 | 3 | 4 |

**For the following questions please circle the number between 1 and 7 that best applies to you.**

29. How would you rate your overall health during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |

30. How would you rate your overall quality of life during the past week?

| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
|---|---|---|---|---|---|---|
| Very poor | | | | | | Excellent |



**Please continue to the next page**

**Participant ID:** _____

Date: _____

# Statin Therapy to Reduce the Risk of Recurrent Pancreatitis

## EORTC QLQ- PAN28(CP)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 31. Have you had abdominal discomfort? | 1 | 2 | 3 | 4 |
| 32. Did you have a bloated feeling in your abdomen? | 1 | 2 | 3 | 4 |
| 33. Have you had back pain? | 1 | 2 | 3 | 4 |
| 34. Did you have pain during the night? | 1 | 2 | 3 | 4 |
| 35. Did you find it uncomfortable in certain positions (e.g. lying down)? | 1 | 2 | 3 | 4 |
| 36. Were you restricted in the types of food you can eat as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 37. Were you restricted in the amounts of food you can eat as a result of your disease or treatment? | 1 | 2 | 3 | 4 |
| 38. Did food and drink taste different from usual? | 1 | 2 | 3 | 4 |
| 39. Have you had indigestion? | 1 | 2 | 3 | 4 |
| 40. Were you bothered by gas (flatulence)? | 1 | 2 | 3 | 4 |
| 41. Have you worried about your weight being too low? | 1 | 2 | 3 | 4 |
| 42. Did you feel weak in your arms and legs? | 1 | 2 | 3 | 4 |
| 43. Did you have a dry mouth? | 1 | 2 | 3 | 4 |
| 44. Have you had itching? | 1 | 2 | 3 | 4 |
| 45. To what extent was your skin yellow? | 1 | 2 | 3 | 4 |
| 46. Did you have frequent bowel movements? | 1 | 2 | 3 | 4 |
| 47. Did you feel the urge to move your bowels quickly? | 1 | 2 | 3 | 4 |
| 48. Have you felt physically less attractive as a result of your disease and treatment? | 1 | 2 | 3 | 4 |

**Please go on to the next page**

| During the past week: | Not at All | A Little | Quite a Bit | Very Much |
|---|---|---|---|---|
| 49. Have you found it difficult to avoid drinking alcohol? Not applicable | 1 | 2 | 3 | 4 |
| 50. Have you felt guilty or embarrassed about drinking alcohol? Not applicable | 1 | 2 | 3 | 4 |
| 51. Have you been dissatisfied with your body? | 1 | 2 | 3 | 4 |
| 52. To what extent have you been troubled with side effects from your treatment? | 1 | 2 | 3 | 4 |
| 53. Were you worried about your health in the future? | 1 | 2 | 3 | 4 |
| 54. Were you limited in planning activities, for example meeting friends, in advance? | 1 | 2 | 3 | 4 |
| 55. Have you received adequate support from your health care professionals? | 1 | 2 | 3 | 4 |
| 56. Has the information given about your physical condition and treatment been adequate? | 1 | 2 | 3 | 4 |
| 57. Have you felt less interest in sex? | 1 | 2 | 3 | 4 |
| 58. Have you felt less sexual enjoyment? | 1 | 2 | 3 | 4 |




Participant's Signature _____ Date _____

**APPENDIX E**

**Participant ID:** _____

Date: _____

# Statin Therapy to Reduce the Risk of Recurrent Pancreatitis

## Baseline Questionnaire

We appreciate the time you are taking to complete this questionnaire. Please try to answer each question as completely as you can, even if you are unsure about the answer. If you feel uncomfortable answering any question, you can choose not to answer it. All answers will be kept confidential.

## A. DEMOGRAPHICS

Thank you for answering the following questions. The first questions ask about your personal background. If you can't remember or aren't sure, please answer the best you can.

1. What is your sex? [1] ☐ Male [2] ☐ Female

2. What is your date of birth? Month _____ Day _____ Year _____ (*Current Age*: _____)

3. Were you born in the U.S.? [1] ☐ Yes [0] ☐ No
   IF YES: Which state were you born in? _____
   IF NO: Which country were you born in? _____

4. What is your racial background? *Check all boxes that apply.*
   [1] ☐ White or Caucasian
   [2] ☐ Black or African American
   [3] ☐ Asian
   [4] ☐ Hawaiian or Other Pacific Islander
   [5] ☐ Native American/American Indian
   [6] ☐ Other (please describe): _____

5. Do you consider yourself to be of Hispanic or Latino ancestry? [1] ☐ Yes [0] ☐ No

6. Do you consider yourself to be of Jewish ancestry? [1] ☐ Yes [0] ☐ No

7. What is your current marital status? *Check one box only.*
   [1] ☐ Single (never married)
   [2] ☐ Married
   [3] ☐ Living as married with partner
   [4] ☐ Separated
   [5] ☐ Divorced
   [6] ☐ Widowed

8. What is the highest grade or level of schooling you have completed? *Check one box only.*
   [1] ☐ No formal education
   [2] ☐ 8th grade or less
   [3] ☐ Some high school
   [4] ☐ High school graduate or GED
   [5] ☐ Technical or vocational school
   [6] ☐ Associate degree or some college
   [7] ☐ Bachelor's degree
   [8] ☐ Advanced degree (Master's degree or higher)

9. Are you covered by health insurance or a health care plan?
   [1] ☐ Yes [0] ☐ No → ***If NO Go to Section B. ANTHROPOMETRY***

10. What type of health insurance or health care plan are you enrolled in? *Check all boxes that apply.*
    [1] ☐ Insurance through my job (Employer group insurance)
    [2] ☐ Self-employed health plan
    [3] ☐ Private health insurance that I pay for myself
    [4] ☐ Medicaid/Medi-Cal
    [5] ☐ Medicare
    [6] ☐ Military health care
    [7] ☐ I have health insurance, but I don't know what type
    [8] ☐ Other health insurance plan (please describe): _____

## B. ANTHROPOMETRY

The following questions ask about your physical development. Please answer to the best of your ability.

1. What is your current height? _____ Feet _____ Inches

2. What is your current weight? _____ Pounds

3. Have you lost weight in the past 6 months? [1] ☐ Yes [0] ☐ No

   IF YES: What was your weight:

| 6 months ago? | 3 months ago? |
|---|---|
| _____ Pounds | _____ Pounds |

*Enter the subject's current age from question # 2 on the previous page:* _____.
*For question 4, only ask about weight for the past age categories relative to the current age, e.g., if subject is 55 years old now, ask about their weight at 30-39 years old, 40-49 years old, and 50-59 years old.*

4. (Excluding times when you were pregnant) what was your approximate **average** weight when you were:

| 30-39 years old | 40-49 years old | 50-59 years old | 60-69 years old | 70+ years old |
|---|---|---|---|---|
| _____ Pounds | _____ Pounds | _____ Pounds | _____ Pounds | _____ Pounds |

## C. MEDICAL CONDITIONS AND MEDICATIONS

The next questions ask about your medical history. If you can't remember, answer the best you can.

| 1. Has a doctor or health care provider ever told you that you had the following medical condition? *Repeat for each condition. If Yes, ask question about age when first told.* | Yes | No | How old were you when a doctor **first told** you that you had (condition)? |
|---|---|---|---|
| a. High blood pressure, or hypertension | 1 ☐ | 0 ☐ | _____ |
| b. High cholesterol | 1 ☐ | 0 ☐ | _____ |
| c. Stroke or Transient Ischemic Attack (TIA) | 1 ☐ | 0 ☐ | _____ |
| d. Heart disease or heart attack | 1 ☐ | 0 ☐ | _____ |
| e. Alcoholism | 1 ☐ | 0 ☐ | _____ |
| f. Pernicious anemia or lack of vitamin B-12 | 1 ☐ | 0 ☐ | _____ |
| g. Pancreatitis | 1 ☐ | 0 ☐ | _____ |
| h. Pancreatic pseudocyst | 1 ☐ | 0 ☐ | _____ |
| i. Celiac disease, gluten sensitivity, sclerosing cholangitis | 1 ☐ | 0 ☐ | _____ |
| j. Gallstones | 1 ☐ | 0 ☐ | _____ |
| k. Stomach ulcers | 1 ☐ | 0 ☐ | _____ |
| l. Ulcer in your small intestine or duodenum | 1 ☐ | 0 ☐ | _____ |
| m. Barrett's Esophagus | 1 ☐ | 0 ☐ | _____ |
| n. Inflammatory bowel disease | 1 ☐ | 0 ☐ | _____ |
| o. Ulcerative colitis | 1 ☐ | 0 ☐ | _____ |
| p. Liver cirrhosis | 1 ☐ | 0 ☐ | _____ |
| q. Hepatitis B | 1 ☐ | 0 ☐ | _____ |
| r. Hepatitis C | 1 ☐ | 0 ☐ | _____ |
| s. Cancer | 1 ☐ | 0 ☐ | _____ |
| If had cancer, specify type(s): _____ _____ | | | |

| 2. Have you ever had surgery to remove your (type of tissue)? *Repeat for each type of tissue. If Yes, ask question about age when had surgery.* | Yes | No | How old were you when you had this surgery? |
|---|---|---|---|
| a. Appendix | 1 ☐ | 0 ☐ | _____ |
| b. Gall Bladder | 1 ☐ | 0 ☐ | _____ |
| c. Gall Stones | 1 ☐ | 0 ☐ | _____ |
| d. Stomach or part of your stomach | 1 ☐ | 0 ☐ | _____ |
| e. Colon or rectum | 1 ☐ | 0 ☐ | _____ |
| **WOMEN ONLY:** | | | |
| f. Breast (mastectomy) | 1 ☐ | 0 ☐ | _____ |
| g. Uterus (hysterectomy) | 1 ☐ | 0 ☐ | _____ |
| h. Ovaries (oophorectomy) | 1 ☐ | 0 ☐ | _____ |

3. Has a doctor or health care provider ever told you that you had diabetes?
   1 ☐ Yes  0 ☐ No → *If NO Go to Question # 7*

4. How old were you when a doctor **first told** you that you had diabetes? _____ years old

5. Did you do any of the following to monitor or treat your diabetes?

| *Check Yes or No for each item.* | Yes | No |
|---|---|---|
| a. Use a home glucose test to monitor your insulin level? | 1 ☐ | 0 ☐ |
| b. Change your diet? | 1 ☐ | 0 ☐ |
| c. Take medication by mouth?* | 1 ☐ | 0 ☐ |
| d. Take insulin by injection?* | 1 ☐ | 0 ☐ |

*IF RESPONDENT TOOK MEDICATION BY MOUTH OR INSULIN BY INJECTION, ASK:

| 6. Have you ever taken (type of drug) for **one year or longer**? *Repeat for each drug. If Yes, ask additional details. Use continuation sheet if needed.* | Yes | No | What was the name of the medication? *Show Hand Card* | How old were you when you **first** took (drug)? | How old were you when you **last** took (drug)? | Was there a period of **one month or more** when you did not take (drug)? *If Yes, ask*: How many months? Yes | No | |
|---|---|---|---|---|---|---|---|---|
| a. Oral agent for diabetes | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| b. 2nd oral agent for diabetes | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| c. Insulin injection agent | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| d. 2nd insulin injection agent | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| e. Other injectable for diabetes | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| f. 2nd injectable for diabetes | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| g. Inhalable powder for diabetes | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |

| 7. Have you ever taken (type of drug) for **one year or longer**? *Repeat for each drug. If Yes, ask additional details. Use continuation sheet if needed.* | Yes | No | What was the name of the medication? *Show Hand Card* | How old were you when you **first** took (drug)? | How old were you when you **last** took (drug)? | Was there a period of **one month or more** when you did not take (drug)? *If Yes, ask*: How many months? Yes | No | |
|---|---|---|---|---|---|---|---|---|
| a. A prescription drug to control high blood pressure | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| b. 2nd drug to control high blood pressure | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| c. Anti-depressant | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |
| d. 2nd anti-depressant | 1 ☐ | 0 ☐ | _____ | _____ | _____ | 1 ☐ | 0 ☐ | _____ |

8. Over the **past year**, have you taken an antibiotic for any reason?
   [1] ☐ Yes [0] ☐ No → *If NO Go to Question # 9*
   a. What was the name of the antibiotic(s) you took? _____
   b. When was the **last time** you took antibiotics? _____/_____ (Month/Year)
   c. Over the **past year**, how many courses of antibiotics have you taken? A course usually lasts about one week, and does not count refills. _____ courses of antibiotics

9. Have you ever used over-the-counter probiotic supplements such as Acidophilus, Accuflora, Align, Culturelle, Spirulina, or Phillips' Colon Health?
   [1] ☐ Yes [0] ☐ No → *If NO Go to Question # 10*
   a. What was the name of the probiotic supplement(s)? _____
   b. How old were you the **last time** you took probiotics? _____ years old

10. Have you ever taken aspirin (Bayer, Bufferin, Excedrin, etc.) at least **4 days per week** for **3 months** or longer? This doesn't include acetaminophen (Tylenol), ibuprofen (Advil, Motrin) or naproxen (Aleve).
    [1] ☐ Yes [0] ☐ No → ***If NO Go to Section D. PHYSICAL ACTIVITY***

11. For what reason do/did you take aspirin? *Check all boxes that apply.*
    [1] ☐ To treat an existing condition such as arthritis, heart disease, or stroke
    [2] ☐ To prevent heart attacks, stroke, or cancer
    [3] ☐ To treat chronic pain or headaches
    [4] ☐ Other reason (please describe): _____

12. How old were you when you **started** taking aspirin at least **4 days per week**? _____ years old

13. Do you take aspirin at least **4 days per week** now? [1] ☐ Yes [0] ☐ No

| 14. Please tell me about the type(s) of aspirin you have used. *Repeat for each type. If Yes, ask additional details.* | How often do/did you take (type of aspirin)? | How many tablets did you take at a time? | Over your lifetime, about how long did you take (aspirin type)? *Write in a number and check one box.* | |
|---|---|---|---|---|
| a. Low-dose or baby aspirin (81 mg per tablet)<br>[0] ☐ I don't use it | [1] ☐ Every day<br>[2] ☐ 4-6 days a week<br>[3] ☐ 2-3 days a week<br>[4] ☐ Once a week or less | [1] ☐ 1<br>[2] ☐ 2<br>[3] ☐ 3 or more | _____ | [2] ☐ Weeks<br>[3] ☐ Months<br>[4] ☐ Years |
| b. Regular strength aspirin (325 mg per tablet)<br>[0] ☐ I don't use it | [1] ☐ Every day<br>[2] ☐ 4-6 days a week<br>[3] ☐ 2-3 days a week<br>[4] ☐ Once a week or less | [1] ☐ 1<br>[2] ☐ 2<br>[3] ☐ 3 or more | _____ | [2] ☐ Weeks<br>[3] ☐ Months<br>[4] ☐ Years |
| c. Extra strength aspirin (500 mg per tablet)<br>[0] ☐ I don't use it | [1] ☐ Every day<br>[2] ☐ 4-6 days a week<br>[3] ☐ 2-3 days a week<br>[4] ☐ Once a week or less | [1] ☐ 1<br>[2] ☐ 2<br>[3] ☐ 3 or more | _____ | [2] ☐ Weeks<br>[3] ☐ Months<br>[4] ☐ Years |
| d. Other type of aspirin<br>_____<br>Dose: ____ mg per tablet | [1] ☐ Every day<br>[2] ☐ 4-6 days a week<br>[3] ☐ 2-3 days a week<br>[4] ☐ Once a week or less | [1] ☐ 1<br>[2] ☐ 2<br>[3] ☐ 3 or more | _____ | [2] ☐ Weeks<br>[3] ☐ Months<br>[4] ☐ Years |

## D. PHYSICAL ACTIVITY

The following questions ask about your physical activity and exercise during the past year.

1. During the **past year**, did you WALK for exercise? Include walking to work, walking the dog, walking for fun, and walking on a treadmill.

   [1] ☐ Yes [0] ☐ No → *If NO Go to Question # 2*

   a. How many months in the past year? [1] ☐ 1-3 [2] ☐ 4-6 [3] ☐ 7-9 [4] ☐ 10-11 [5] ☐ 12

   b. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

   c. How many minutes per day? [1] ☐ 10-25 [2] ☐ 30-40 [3] ☐ 45-55 [4] ☐ 60+ minutes

   d. What was your usual pace?

   [1] ☐ Casual (each mile takes 30 minutes or more)
   [2] ☐ Moderate (each mile takes 20-29 minutes)
   [3] ☐ Fast (each mile takes 19 minutes or less)

2. During the **past year**, did you do MILD exercise such as golf, slow dancing, or bowling?

   [1] ☐ Yes [0] ☐ No → *If NO Go to Question # 3*

   a. How many months in the past year? [1] ☐ 1-3 [2] ☐ 4-6 [3] ☐ 7-9 [4] ☐ 10-11 [5] ☐ 12

   b. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

   c. How many hours per day? [1] ☐ <1 hour [2] ☐ 1-2 [3] ☐ 3-4 [4] ☐ 4+ hours

3. During the **past year**, did you do MODERATE exercise such as doubles tennis, ballroom dancing, folk dancing, slow cycling, leisurely swimming, softball, or low impact or water aerobics?

   [1] ☐ Yes [0] ☐ No → *If NO Go to Question # 4*

   a. How many months in the past year? [1] ☐ 1-3 [2] ☐ 4-6 [3] ☐ 7-9 [4] ☐ 10-11 [5] ☐ 12

   b. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

   c. How many minutes per day? [1] ☐ 10-25 [2] ☐ 30-40 [3] ☐ 45-55 [4] ☐ 60+ minutes

4. During the **past year**, did you do STRENUOUS exercise such as singles tennis, jogging, swimming laps, basketball, soccer, fast cycling, aerobic dance, or ZUMBA?

   [1] ☐ Yes [0] ☐ No → *If NO Go to Question # 5*

   a. How many months in the past year? [1] ☐ 1-3 [2] ☐ 4-6 [3] ☐ 7-9 [4] ☐ 10-11 [5] ☐ 12

   b. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

   c. How many minutes per day? [1] ☐ 10-25 [2] ☐ 30-40 [3] ☐ 45-55 [4] ☐ 60+ minutes

5. During the **past year**, did you do exercises to increase muscle strength and endurance, such as lifting weights, using weight machines, or pushups?

   [1] ☐ Yes [0] ☐ No → *If NO Go to Question # 6*

   a. How many months in the past year? [1] ☐ 1-3 [2] ☐ 4-6 [3] ☐ 7-9 [4] ☐ 10-11 [5] ☐ 12

   b. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

   c. How many minutes per day? [1] ☐ 10-25 [2] ☐ 30-40 [3] ☐ 45-55 [4] ☐ 60+ minutes

6. During the **past month**, how often did you participate in sitting activities such as using a computer, watching TV, reading, or doing handcrafts?

   a. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

   b. How many hours per day? [1] ☐ <1 hour [2] ☐ 1-2 [3] ☐ 3-4 [4] ☐ 4+ hours

## E. SMOKING

The next questions ask about tobacco use. Please answer to the best of your ability.

1. Have you ever smoked at least **one cigarette a day** for **6 months or longer**?
   [1] ☐ Yes [0] ☐ No → ***If NO Go to Section F. ALCOHOL***

2. How old were you when you **first** started smoking cigarettes daily?
   _____ years old [Age 1]

3. How old were you when you **last smoked** cigarettes daily? *If still smoking enter current age.*
   _____ years old [Age 2]

4. During the time you smoked, how many cigarettes did you usually smoke **each day**?
   _____ cigarettes per day

5. Do you smoke cigarettes now? *If NO Continue to Question # 6; If YES Skip to Question # 8.*
   [1] ☐ Yes [0] ☐ No

6. How long has it been since you quit smoking cigarettes? *Fill in the blank and check one box.*
   How many _____ [1] ☐ Days [2] ☐ Weeks [3] ☐ Months [4] ☐ Years

7. At that time (when you quit smoking) how many cigarettes did you usually smoke **each day**?
   _____ cigarettes per day

8. Between [Age 1] and [Age 2, or now if still smoking] did you ever quit smoking for **at least 1 year**?
   [1] ☐ Yes [0] ☐ No → ***If NO Go to Section F. ALCOHOL***

9. How many years between [Age 1] and [Age 2, or now if still smoking] did you **not** smoke daily?
   _____ years

## F. ALCOHOL

The last questions ask about consumption of alcohol. Please answer each question the best you can.

1. Did you ever drink alcohol **at least once a week** for **6 months or longer**?
   [1] ☐ Yes [0] ☐ No → ***If NO the Questionnaire is Completed***

2. How old were you when you **first** started drinking alcohol at least once a week?
   _____ years old

3. How many drinks of alcohol did you usually have **per week** at each of the following ages? One drink is a 12-ounce bottle or can of beer, an 8-ounce bottle or can of malt liquor, a 12-ounce wine cooler, a 5-ounce glass of wine, a 1½ ounce shot of liquor, or a mixed drink containing 1½ ounces of liquor.

| | **Number of drinks of alcohol per week** ***Check one box for each age where applicable.*** | | | | | |
|---|---|---|---|---|---|---|
| | < 1 drink per week | 1-6 drinks (< 1 per day) | 7-13 drinks (1-2 per day) | 14-20 drinks (2-3 per day) | 21-27 drinks (3-4 per day) | 28+drinks (4+ per day) |
| Age 18 | [0] ☐ | [1] ☐ | [2] ☐ | [3] ☐ | [4] ☐ | [5] ☐ |
| Age 30 | [0] ☐ | [1] ☐ | [2] ☐ | [3] ☐ | [4] ☐ | [5] ☐ |
| Age 45 | [0] ☐ | [1] ☐ | [2] ☐ | [3] ☐ | [4] ☐ | [5] ☐ |
| Age 60 | [0] ☐ | [1] ☐ | [2] ☐ | [3] ☐ | [4] ☐ | [5] ☐ |

4. During the **past 6 months** about how many times have you had **5 or more drinks** of alcohol in one day (that includes in the evening)? *If none enter 0.*
   _____ times

5. About how many years did you drink alcohol at least once a week?
   _____ years

6. Do you drink alcohol at least once a week now?
   [1] ☐ Yes [0] ☐ No → *If NO Continue to Question # 7; If YES Skip to Question # 8.*

7. How long has it been since you stopped drinking alcohol at least once a week? *Fill in the blank and check one box.* How many _____ [1] ☐ Days [2] ☐ Weeks [3] ☐ Months [4] ☐ Years

8. *IF **still drinking** ask:* How many drinks of alcohol do you usually have **per week** now?
   *IF **stopped drinking** ask:* At that time (when you stopped drinking) how many drinks of alcohol did you usually have **per week**? *Check one box only.*
   [0] ☐ < 1 drink per week
   [1] ☐ 1-6 drinks per week (less than 1 per day)
   [2] ☐ 7-13 drinks per week (1-2 per day)
   [3] ☐ 14-20 drinks per week (2-3 per day)
   [4] ☐ 21-27 drinks per week (3-4 per day)
   [5] ☐ 28 or more drinks per week (4+ per day)

**YOU HAVE COMPLETED THE QUESTIONNAIRE. THANK YOU VERY MUCH FOR YOUR HELP!**

**INTERVIEWER'S REMARKS**

1. Participant ID _____

2. Visit Number [1] ☐ First

3. Interviewer ___ ___ (Initials)

4. Date of Interview Month _____ Day _____ Year _____

5. Interview Start Time ___ ___ : ___ ___ (Hour: Minutes [24-hour time])

6. Interview End Time ___ ___ : ___ ___ (Hour: Minutes [24-hour time])

7. The interview included: *(Check all boxes that apply.)*
   [1] ☐ The participant only
   [2] ☐ A spouse or partner
   [3] ☐ Another family member
   [4] ☐ Another person (please specify) _____

8. The participant's cooperation was: *(Check one box only.)*
   [1] ☐ Excellent [2] ☐ Very Good [3] ☐ Good [4] ☐ Fair [5] ☐ Poor

9. The quality of the interview is: *(Check one box only.)*
   [1] ☐ Excellent [2] ☐ Generally reliable [3] ☐ Questionable [4] ☐ Unreliable

_____ _____
Signature of Clinical Research Staff who administered questionnaire Date

**APPENDIX F**

**Participant ID:** _____

Date: _____

# Statin Therapy to Reduce the Risk of Recurrent Pancreatitis

## Follow-Up Questionnaire – Study Visit 3 (6-Month Visit)

Thank you for continuing to participate in our study. We appreciate the time you are taking to complete this questionnaire. This questionnaire focuses on any changes that may have occurred since your first research visit for this study on _____ (date of baseline visit). Please try to answer each question as completely as you can, even if you are unsure about the answer. If you feel uncomfortable answering any question, you can choose not to answer it. All answers will be kept confidential.

## A. DEMOGRAPHICS

The first questions ask about changes to your personal information since your first research visit for this study on _____ (date of baseline visit). Please answer each question the best you can.

1. What is your current marital status? *Check one box only.*

[1] ☐ Single (never married) [2] ☐ Married [3] ☐ Living as married with partner
[4] ☐ Separated [5] ☐ Divorced [6] ☐ Widowed

## B. ANTHROPOMETRY

2. What is your current height? _____ Feet _____ Inches

3. What is your current weight? _____ Pounds

## C. MEDICAL CONDITIONS AND MEDICATIONS

The next questions ask about your medical history and medication use since your first study visit.

| 4. Since your first research visit for this study on _____ (date of baseline visit), has a doctor or healthcare provider told that you have developed the following medical condition that you had **not reported previously**? *Repeat for each condition. If Yes, ask about date when told.* | Yes | No | When did a doctor tell you that you had (condition)? *Month/Day/Year* |
|---|---|---|---|
| a. High blood pressure, or hypertension | [1] ☐ | [0] ☐ | ___/___/____ |
| b. High cholesterol | [1] ☐ | [0] ☐ | ___/___/____ |
| c. Stroke or Transient Ischemic Attack (TIA) | [1] ☐ | [0] ☐ | ___/___/____ |
| d. Heart disease or heart attack | [1] ☐ | [0] ☐ | ___/___/____ |
| e. Alcoholism | [1] ☐ | [0] ☐ | ___/___/____ |
| f. Pernicious anemia or lack of vitamin B-12 | [1] ☐ | [0] ☐ | ___/___/____ |
| g. Diabetes | [1] ☐ | [0] ☐ | ___/___/____ |
| h. Pancreatic pseudocyst | [1] ☐ | [0] ☐ | ___/___/____ |
| i. Celiac disease, gluten sensitivity, sclerosing cholangitis | [1] ☐ | [0] ☐ | ___/___/____ |
| j. Gallstones | [1] ☐ | [0] ☐ | ___/___/____ |
| k. Stomach ulcers | [1] ☐ | [0] ☐ | ___/___/____ |
| l. Ulcer in your small intestine or duodenum | [1] ☐ | [0] ☐ | ___/___/____ |
| m. Barrett's Esophagus | [1] ☐ | [0] ☐ | ___/___/____ |
| n. Inflammatory bowel disease | [1] ☐ | [0] ☐ | ___/___/____ |
| o. Ulcerative colitis | [1] ☐ | [0] ☐ | ___/___/____ |
| p. Liver cirrhosis | [1] ☐ | [0] ☐ | ___/___/____ |
| q. Hepatitis B | [1] ☐ | [0] ☐ | ___/___/____ |
| r. Hepatitis C | [1] ☐ | [0] ☐ | ___/___/____ |
| s. Cancer (Type): _____ | [1] ☐ | [0] ☐ | ___/___/____ |

| 5. Since your first research visit for this study on _____ (date of baseline visit), have you had surgery to remove your (type of tissue)? *Repeat for each type of tissue. If Yes, ask question about surgery date.* | Yes | No | When did you have this surgery? *Month/Day/Year* |
|---|---|---|---|
| a. Appendix | 1 ☐ | 0 ☐ | ___/___/____ |
| b. Gall Bladder | 1 ☐ | 0 ☐ | ___/___/____ |
| c. Gall Stones | 1 ☐ | 0 ☐ | ___/___/____ |
| d. Stomach or part of your stomach | 1 ☐ | 0 ☐ | ___/___/____ |
| e. Colon or rectum | 1 ☐ | 0 ☐ | ___/___/____ |
| **WOMEN ONLY:** | | | |
| f. Breast (mastectomy) | 1 ☐ | 0 ☐ | ___/___/____ |
| g. Uterus (hysterectomy) | 1 ☐ | 0 ☐ | ___/___/____ |
| h. Ovaries (oophorectomy) | 1 ☐ | 0 ☐ | ___/___/____ |

| 6. Since your first research visit for this study on _____ (date of baseline visit), have you taken (type of drug)? *Repeat for each drug. If Yes, ask additional details. Use continuation sheet if needed.* | Yes | No | What was the name of the medication? *Show Hand Card* | When did you **last take** (drug)? |
|---|---|---|---|---|
| a. Oral agent for diabetes | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| b. 2nd oral agent for diabetes | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| c. Insulin injection agent | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| d. 2nd insulin injection agent | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| e. Other injectable for diabetes | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| f. 2nd injectable for diabetes | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| g. Inhalable powder for diabetes | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| h. A prescription drug to control high blood pressure | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| i. 2nd drug to control high blood pressure | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| j. Anti-depressant | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| k. 2nd anti-depressant | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| l. Antibiotic | 1 ☐ | 0 ☐ | _____ | ___/___/____ |
| m. 2nd antibiotic | 1 ☐ | 0 ☐ | _____ | ___/___/____ |

| 7. Since your first visit for this study on _____ (date of baseline visit), have you taken (type of aspirin) **at least 4 days a week**? *If Yes, ask additional details.* | Yes | No | How often do you take (aspirin type)? | How many tablets did you take at a time? | When did you **last take** (aspirin type)? |
|---|---|---|---|---|---|
| a. Low-dose or baby aspirin (81 mg per tablet) | 1 ☐ | 0 ☐ | 1 ☐ Every day<br>2 ☐ 4-6 days a week<br>3 ☐ 2-3 days a week | 1 ☐ 1<br>2 ☐ 2<br>3 ☐ 3 or more | ___/___/____ |
| b. Regular strength aspirin (325 mg per tablet) | 1 ☐ | 0 ☐ | 1 ☐ Every day<br>2 ☐ 4-6 days a week<br>3 ☐ 2-3 days a week | 1 ☐ 1<br>2 ☐ 2<br>3 ☐ 3 or more | ___/___/____ |
| c. Extra strength aspirin (500 mg per tablet) | 1 ☐ | 0 ☐ | 1 ☐ Every day<br>2 ☐ 4-6 days a week<br>3 ☐ 2-3 days a week | 1 ☐ 1<br>2 ☐ 2<br>3 ☐ 3 or more | ___/___/____ |
| d. Other type of aspirin<br>Type: _____<br>Dose: ____ mg per tablet | 1 ☐ | 0 ☐ | 1 ☐ Every day<br>2 ☐ 4-6 days a week<br>3 ☐ 2-3 days a week | 1 ☐ 1<br>2 ☐ 2<br>3 ☐ 3 or more | ___/___/____ |

## D. PHYSICAL ACTIVITY

The following questions ask about your physical activity and exercise since your first study visit.

8. Since your first research visit for this study on _____ (date of baseline visit), did you WALK for exercise? Include walking to work, walking the dog, walking for fun, and walking on a treadmill.

1 ☐ Yes 0 ☐ No → *If NO Go to Question # 9*

a. How many days per week? 1 ☐ 1-2 2 ☐ 3-4 3 ☐ 5-6 4 ☐ 7

b. How many minutes per day? 1 ☐ 10-25 2 ☐ 30-40 3 ☐ 45-55 4 ☐ 60+ minutes

c. What was your usual pace?

1 ☐ Casual (each mile takes 30 minutes or more)
2 ☐ Moderate (each mile takes 20-29 minutes)
3 ☐ Fast (each mile takes 19 minutes or less)

9. Since your first study visit, did you do MILD exercise such as golf, slow dancing, or bowling?

1 ☐ Yes 0 ☐ No → *If NO Go to Question # 10*

a. How many days per week? 1 ☐ 1-2 2 ☐ 3-4 3 ☐ 5-6 4 ☐ 7

b. How many hours per day? 1 ☐ <1 hour 2 ☐ 1-2 3 ☐ 3-4 4 ☐ 4+ hours

10. Since your first study visit, did you do MODERATE exercise such as doubles tennis, ballroom dancing, folk dancing, slow cycling, leisurely swimming, softball, or low impact or water aerobics?

1 ☐ Yes 0 ☐ No → *If NO Go to Question # 11*

a. How many days per week? 1 ☐ 1-2 2 ☐ 3-4 3 ☐ 5-6 4 ☐ 7

b. How many minutes per day? 1 ☐ 10-25 2 ☐ 30-40 3 ☐ 45-55 4 ☐ 60+ minutes

11. Since your first study visit, did you do STRENUOUS exercise such as singles tennis, jogging, swimming laps, basketball, soccer, fast cycling, aerobic dance, or ZUMBA?

1 ☐ Yes 0 ☐ No → *If NO Go to Question # 12*

a. How many days per week? 1 ☐ 1-2 2 ☐ 3-4 3 ☐ 5-6 4 ☐ 7

b. How many minutes per day? 1 ☐ 10-25 2 ☐ 30-40 3 ☐ 45-55 4 ☐ 60+ minutes

12. Since your first study visit, did you do exercises to increase muscle strength and endurance, such as lifting weights, using weight machines, or pushups?

[1] ☐ Yes [0] ☐ No → *If NO Go to Question # 13*

a. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

b. How many minutes per day? [1] ☐ 10-25 [2] ☐ 30-40 [3] ☐ 45-55 [4] ☐ 60+ minutes

13. Since your first study visit on _____ (date of baseline visit), how often did you participate in sitting activities such as using a computer, watching TV, reading, or doing handcrafts?

a. How many days per week? [1] ☐ 1-2 [2] ☐ 3-4 [3] ☐ 5-6 [4] ☐ 7

b. How many hours per day? [1] ☐ <1 hour [2] ☐ 1-2 [3] ☐ 3-4 [4] ☐ 4+ hours

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The last questions ask about your use of tobacco and alcohol since your first research visit for this study on _____ (date of baseline visit). Please answer to the best of your ability.

## E. SMOKING

14. Since your first research visit for this study on _____ (date of baseline visit), have you smoked cigarettes?

[1] ☐ Yes [0] ☐ No → *If NO Go to Question # 17*

15. When did you **last smoke** a cigarette? _____ (Month/Day/Year)

16. How many cigarettes do you usually smoke **each day**? _____ cigarettes per day

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## F. ALCOHOL

17. Since your first research visit for this study on _____ (date of baseline visit), have you had a drink of alcohol? One drink is a 12-ounce bottle or can of beer, an 8-ounce bottle or can of malt liquor, a 12-ounce wine cooler, a 5-ounce glass of wine, a 1½ ounce shot of liquor, or a mixed drink containing 1½ ounces of liquor.

[1] ☐ Yes [0] ☐ No → ***If NO the Questionnaire is Completed***

18. When did you **last have a drink** of alcohol? _____ (Month/Day/Year)

19. How many drinks of alcohol do you usually have **per week**? *Check one box only.*

[0] ☐ < 1 drink per week
[1] ☐ 1-6 drinks per week (less than 1 per day)
[2] ☐ 7-13 drinks per week (1-2 per day)
[3] ☐ 14-20 drinks per week (2-3 per day)
[4] ☐ 21-27 drinks per week (3-4 per day)
[5] ☐ 28 or more drinks per week (4+ per day)

**YOU HAVE COMPLETED THE QUESTIONNAIRE. THANK YOU VERY MUCH FOR YOUR HELP!**

**INTERVIEWER'S REMARKS**

1. Participant ID _____

2. Visit Number [3] ☐ Third

3. Interviewer ___ ___ (Initials)

4. Date of This Visit Month _____ Day _____ Year _____

5. Date of Baseline Visit Month _____ Day _____ Year _____

6. Interview Start Time ___ ___ : ___ ___ (Hour: Minutes [24-hour time])

7. Interview End Time ___ ___ : ___ ___ (Hour: Minutes [24-hour time])

8. The interview included: *(Check all boxes that apply.)*
   [1] ☐ The participant only
   [2] ☐ A spouse or partner
   [3] ☐ Another family member
   [4] ☐ Another person (please specify) _____

9. The participant's cooperation was: *(Check one box only.)*
   [1] ☐ Excellent [2] ☐ Very Good [3] ☐ Good [4] ☐ Fair [5] ☐ Poor

10. The quality of the interview is: *(Check one box only.)*
    [1] ☐ Excellent [2] ☐ Generally reliable [3] ☐ Questionable [4] ☐ Unreliable

_____ _____
Signature of Clinical Research Staff who administered questionnaire Date