A Phase II Trial of Lanreotide for the Prevention of Postoperative Pancreatic Fistula

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Conference on Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the NIDCR Clinical Terms of Award. All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CRO	Contract Research Organization
CSOC	Clinical Study Oversight Committee
DCC	Data Coordinating Center
DHHS	Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FFR	Federal Financial Report
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IDE	Investigational Device Exemption
IND	Investigational New Drug Application
IRB	Institutional Review Board
ISM	Independent Safety Monitor
MedDRA®	Medical Dictionary for Regulatory Activities
MOP	Manual of Procedures
N	Number (typically refers to subjects)
NDA	New Drug Application
NIH	National Institutes of Health
OCTOM	Office of Clinical Trials Operations and Management, NIDCR, NIH
OHRP	Office for Human Research Protections
PHI	Protected Health Information
PI	Principal Investigator

QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event/Serious Adverse Experience
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
WHO	World Health Organization

PROTOCOL SUMMARY

Title:

A phase II trial of lanreotide (SOMATULINE DEPOT) for the prevention of postoperative pancreatic fistula

Précis:

This is a single arm investigator-initiated study designed to test the feasibility and potential efficacy of preoperative lanreotide to reduce the risk of postoperative abscess or pancreatic leak and fistula. All consenting patients undergoing planned elective pancreaticoduodenectomy or distal pancreatectomy for malignancy or suspected malignancy will be treated with a single deep subcutaneous dose of lanreotide prior to planned resection on the day of surgery. Following this intervention, care will be based on standard treatment protocols. Sixty-day mortality and morbidity will be collected for all patients.

Objectives:

Primary: To determine if preoperative lanreotide reduces the incidence of intraabdominal abscess or clinically significant (grade B or C) postoperative pancreatic fistula, as compared with published literature and historical controls.

Secondary:

1. To determine if preoperative lanreotide reduces the incidence of grade A postoperative pancreatic fistula, as compared with published literature and historical controls.
2. To determine if preoperative lanreotide reduces the incidence of postoperative surgical site infection, as compared with published literature and historical controls.
3. To determine if preoperative lanreotide reduces the incidence of overall postoperative morbidity, as compared with published literature and historical controls.
4. To determine if preoperative lanreotide reduces drain amylase levels on days 1 & 3 postoperatively, as compared with published literature and historical controls
5. To determine if preoperative lanreotide reduces duration of drainage required for patients with pancreatic fistulae, as compared with published literature and historical controls.

Population:	Patients undergoing planned elective pancreaticoduodenectomy or distal pancreatectomy for malignancy or suspected malignancy will be enrolled into this study
Phase:	II
Number of Sites:	1 – University of Washington Medical Center
Description of Intervention:	A single deep subcutaneous dose of 120 mg of an extended-release aqueous-gel formulation of lanreotide (SOMATULINE DEPOT) will be administered preoperatively on the day of planned surgical resection. All subsequent care and interventions will follow established standard care pathways. Outcome data will be gathered during hospital-based, and clinical follow up appointments, as well as through scheduled phone calls and chart reviews.
Study Duration:	36 months
Subject Participation Duration:	60 days
Estimated Time to Complete Enrollment:	36 months

1 KEY ROLES AND CONTACT INFORMATION

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2 BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

Pancreatic surgery is highly complex and is associated with 90-day mortality rates of up to 8%, depending upon the level of experience of the surgeon and the hospital.(1) Even in the best of hands, perioperative morbidity of pancreatic surgery is quite common, affecting nearly half of patients undergoing pancreatic resections.(2) Among the causes of major morbidity and mortality following pancreatic resections, the most important one is postoperative pancreatic fistula (POPF).(3)

POPFs result from leakage of pancreatic juice from the cut edge of the gland. Following distal pancreatectomy, which accounts for approximately 20% of pancreatic resections, the cut edge is typically closed with surgical staples or sutures, and leakage can occur from inadequate sealing of the main pancreatic duct or from small ducts. In contrast, the cut edge of the pancreas in a pancreaticoduodenectomy – the most commonly performed pancreatic resection – is anastomosed to a segment of small intestine or, less often, the stomach. POPF from this anastomosis is associated with even greater risks than leaks following distal pancreatectomy, as the pancreatic enzymes in this situation may be in a more activated state due to contact with intestinal contents. In order to facilitate cross-institutional study of this major problem, the International Study Group of Pancreatic Surgery (ISGPS) developed a uniform method for grading POPF (Table 1).(4) POPF which alter the patient's clinical course or require intervention are classified as grade B or C, while grade A fistula have no major clinical significance. Methods to reduce the incidence of clinically significant POPF are highly sought after and have the potential to dramatically improve patient outcomes and reduce the cost of care.

Table 2.1: ISGPS Grading of POPF

Grade	*A*	*B*	*C*
Clinical conditions	Well	Often well	Ill appearing/ bad
Specific teatment*	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/ positive	Positive
Persistent drainage (after 3 weeks)†	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

US, Ultrasonography; *CT,* computed tomographic scan; *POPF,* postoperative pancreatic fistula.
*Partial (peripheral) or total parenteral nutrition, antibiotics, enteral nutrition, somatostatin analogue and/or minimal invasive drainage.
†With or without a drain in situ.

The International Study Group of Pancreatic Surgery (ISGPS) developed this classification scheme for grading POPF that has been widely used to standardize reporting. Bassi et al., 20052

Although multiple methods for closure or anastomosis of the pancreatic cut edge have been studied, none have convincingly demonstrated superiority; therefore, POPF remains a common source of perioperative morbidity.(5,6) Natural somatostatin and its analogues, especially octreotide, have been extensively studied as a potential method to reduce pancreatic exocrine secretion and can be used to treat enterocutaneous fistulae. Somatostatin analogues have also

been used to reduce the incidence of POPF, and subcutaneously (SC) injected octreotide is indicated for this purpose in some countries, but not the United States.(7)

2.2 Overview of Lanreotide autogel (SOMATULINE DEPOT)

Lanreotide is an injectable synthetic somatostatin analogue. Its chemical name is 3-(2 naphthyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-L-threoninamide (2->7)-disulfide. Lanreotide binds with high specificity to type 2 and 5 somatostatin receptors (SSTR), and has lower affinity to SSTR 1, 3, and 4. Through its agonist activity, lanreotide reduces endocrine secretion of such hormones as insulin, glucagon, and growth hormone, while also reducing exocrine secretion of enzymes involved in digestion. The extended release, SC delivered formulation, lanreotide autogel (Somatuline Depot; herein referred to as lanreotide) will be used in this study.

Lanreotide is indicated for the long-term treatment of acromegalic patients with inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. The goal of treatment in acromegaly is to reduce growth hormone (GH) and insulin-like growth factor 1 (IGF-1) levels to normal. Importantly, Lanreotide 120 mg is also indicated for the treatment of patients with unresectable, well-or moderately-differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

2.3 Human Experience

As noted above, lanreotide is approved by the FDA for the long-term treatment both of acromegaly and advanced GEP-NETs. Overall, it is a well-tolerated drug at SC doses of 60, 90, or 120 mg every 4 to 8 weeks. Having been approved for the treatment of acromegaly in 2007, there is a great deal of evidence that lanreotide is a safe, well tolerated drug. In the recent PRIMARY treatment of macroadenomas in acromegaly with Somatuline (PRIMARYS) study, treatment-naïve patients with acromegaly were treated with 120 mg of lanreotide Autogel every 4 weeks for 1 year.(8) A majority of the achieved clinically significant tumor shrinkage and the drug was well tolerated, and no patients discontinued treatment due to gastrointestinal symptoms.

In the Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET) Trial, 204 patients were treated with 120 mg lanreotide (n=101) or placebo (n=103) every 4 weeks for 96 weeks, and total number of adverse events, most of which were mild or moderate, were similar between the two groups (88% vs. 90%, respectively).(9) Study treatment-related adverse events occurred in 50% of lanreotide-treated patients, while these

were seen in 28% of patients receiving placebo. The most common treatment-related adverse events in this long-term treatment study were mild (Table 2). Furthermore, serious adverse events were similar between groups (25% lanreotide vs. 31% placebo), as were serious adverse events related to study treatment (3% lanreotide vs. 1% placebo).

Table 2.2: Common treatment-related adverse events in the CLARINET trial

Adverse event	Lanreotide	Placebo
Diarrhea	26%	9%
Abdominal pain	14%	2%
Cholelithiasis	10%	3%
Flatulence	8%	5%
Injection site pain	7%	3%
Nausea	7%	2%
Vomiting	7%	0
Headache	5%	2%
Lethargy	5%	2%
Hyperglycemia	5%	0
Decreased level of pancreatic enzymes	5%	0

2.4 Study Rationale

The most important source of morbidity and mortality following pancreatic surgery is leakage of enzyme-rich digestive fluid from the major or minor ducts along the pancreatic parenchymal margin of resection. In the case of distal pancreatectomy, which involves removal of pancreatic tissue to the left of the portosplenic venous confluence, this leakage is typically along the parenchymal margin that has been stapled or sutured closed. In contrast, following pancreaticoduodenectomy, which is used to remove tumors involving the head or uncinate process of the pancreas, the leakage is usually from a connection made between the pancreatic duct and the small intestine.

While inherent characteristics of the patient, the texture of the pancreas (soft vs. firm), and the size of the pancreatic duct (small vs. dilated) impact the risk of pancreatic leak, surgical technique is an incredibly important factor. Perhaps due to improved training and concentration of surgical volume at specialized centers, patients undergoing pancreatic surgery today enjoy significantly better outcomes than did patients being treated as little as a decade ago. However, pancreatic resections continue to be plagued by high morbidity and mortality rates. The University of Washington Medical Center (UWMC) is an academic tertiary hospital with a high-volume pancreatic surgery program, and is a member of the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) Hepatopancreatobiliary (HPB) Collaborative. As evidenced by the NSQIP HPB Collaborative hospital report for UWMC, we performed a total of 91 pancreatectomies (25 distal pancreatectomies and 66 pancreaticoduodenectomies) in 2015 without any mortalities and with a serious morbidity rate under 20%, which is half the NSQIP average for these procedures.

As our field continues to improve techniques and perioperative management, we have also looked for methods to inhibit pancreatic enzyme secretion as way to reduce the incidence of pancreatic leak and subsequent POPF or abscess. Due to somatostatin's pleiotropic effects on endocrine and exocrine function, activating this axis has been heavily studied as a potential means to achieve the goal of reducing pancreatic leaks. The routine administration of somatostatin and its analogues to reduce POPF is supported by some data; however,

challenges remain with respect to medication dosing and administration, particularly for short half-life drugs. A recent, high-quality single-institution randomized controlled trial comparing one week of twice-daily administration of pasireotide vs. placebo demonstrated significantly reduced postoperative pancreatic fistula rate with pasireotide.(10) Although the results with pasireotide are compelling, its gastrointestinal side effect profile and the need for twice daily dosing make it a less than ideal perioperative pharmacologic intervention.

Lanreotide possesses many characteristics that provide a strong rationale for testing its efficacy in reducing POPF. First, its depot formulation that we will be testing rapidly achieves therapeutic blood levels that are stable for nearly the entire perioperative period, thus allowing for an extremely simple treatment strategy of one preoperative dose. Second, it has a well-established safety record and is FDA-approved for two separate indications. Third, the most common adverse events associated with lanreotide administration – diarrhea, abdominal pain, and flatulence – are likely at least partly due to its inhibition of pancreatic enzyme secretion. We therefore believe that a single preoperative dose of lanreotide will provide a similar reduction in postoperative pancreatic fistula rates to that seen with pasireotide.

2.5 Selection of Dose

The dose of 120 mg was selected based upon the pharmacokinetic data demonstrating rapid (peak reached by first day) and long-lasting (nearly 2 months) therapeutic blood concentrations of lanreotide. Furthermore, the standard dose for treatment of patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic GEP-NETs is 120 mg every 4 weeks. That patient population has significant overlap with the population planned to be treated in the present study, as a large proportion of our patients will be undergoing resection for pancreatic NETs.

2.6 Potential Risks and Benefits

2.6.1 *Potential Risks*

A single dose of SOMATULINE DEPOT 120 mg has been well tolerated with mostly mild, transient side effects reported. In the treatment of Acromegaly, the most common adverse events seen have been diarrhea, cholelithiasis, abdominal pain, nausea, and injection site reactions. In the treatment of GEP-NET, the most common adverse events seen have been abdominal pain, musculoskeletal pain, vomiting, headache, injection site reaction, hyperglycemia, hypertension, and cholelithiasis. For more information on SOMATULINE DEPOT please refer to Section 2.3 Human Experience or the SOMATULINE DEPOT Package Insert.

Natural somatostatin and somatostatin analogues (octreotide and pasireotide) have been extensively studied in the perioperative setting to reduce the risk of POPF. Although there have been mixed results with regards to efficacy, these drug treatments have proven to be quite safe.

Long-term somatostatin analogue therapy has been associated with cholelithiasis and cholecystitis; however, treatment in this study is by-definition short-term. Additionally, the risk in our study is further reduced because approximately two-thirds of the patients (all of those undergoing pancreaticoduodenectomy) will have a cholecystectomy performed as part of their operation.

Overall, our study design, which is based on drug treatment on the day of surgery further limits risk by having the patient in a highly monitored setting immediately following drug administration. Therefore, study drug-associated pain, nausea, vomiting, hypertension, and hyperglycemia, which are all commonly expected adverse events in the perioperative period for pancreatic surgery will be readily managed.

2.6.2 *Potential Benefits*

Although the operative mortality following pancreatectomy has decreased to approximately 2% at high-volume institutions the morbidity of this procedure remains significant. The most important complications of pancreatic resection arise from leakage of enzyme-rich pancreatic fluid from the cut edge of pancreas. The physical and emotional burden these complications place upon patients, as well as the financial cost to the health care system, cannot be overestimated. Currently no preoperative or intraoperative technique has demonstrated the ability to decrease the risk of these complications. Preoperative lanreotide may prove to reduce the rates of pancreatic fistulas, intraabdominal abscesses, surgical site infections, and overall morbidity.

3 OBJECTIVES

3.1 Primary objectives

To determine if preoperative lanreotide reduces the incidence of intraabdominal abscess or clinically significant (grade B or C) postoperative pancreatic fistula, as compared with published literature and historical controls.

3.2 Secondary Objectives

1. To determine if preoperative lanreotide reduces the incidence of grade A postoperative pancreatic fistula, as compared with published literature and historical controls.
2. To determine if preoperative lanreotide reduces the incidence of postoperative surgical site infection, as compared with published literature and historical controls.
3. To determine if preoperative lanreotide reduces the incidence of overall postoperative morbidity, as compared with published literature and historical controls.

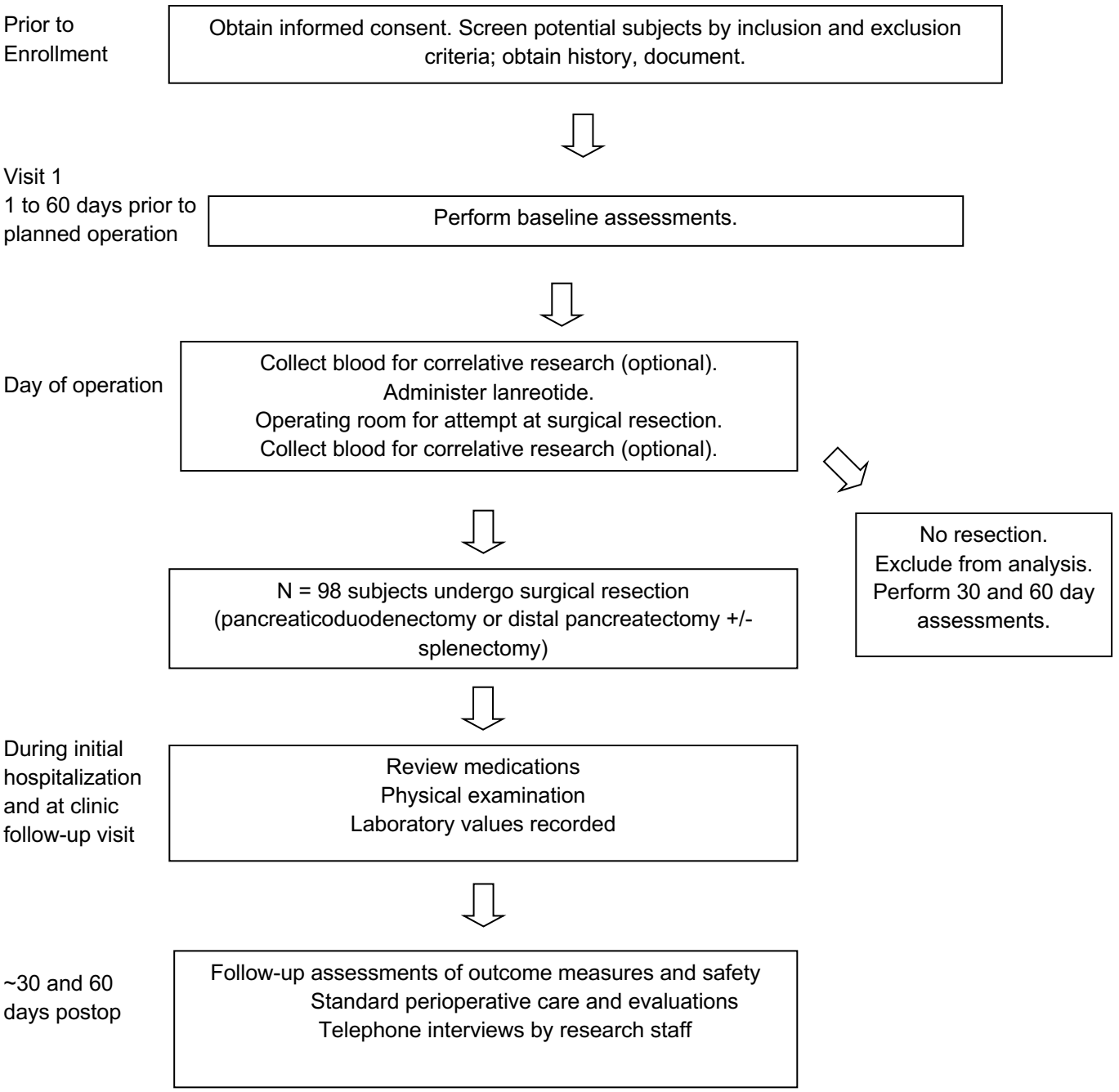
4. To determine if preoperative lanreotide reduces drain amylase levels on days 1 & 3 postoperatively, as compared with published literature and historical controls
5. To determine if preoperative lanreotide reduces duration of drainage required for patients with pancreatic fistulae, as compared with published literature and historical controls.

4 STUDY DESIGN

4.1 Study Design

This is a single arm phase II trial of preoperative lanreotide in patients undergoing planned elective pancreaticoduodenectomy or distal pancreatectomy for malignancy or suspected malignancy at the University of Washington Medical Center. All patients will receive a single deep subcutaneous dose of 120 mg of an extended-release aqueous-gel formulation of lanreotide (SOMATULINE DEPOT) administered immediately prior to the planned surgical resection. Our goal accrual is 98 evaluable patients who receive the study drug and undergo the planned surgical resection. These subjects will be followed at 30, and 60 days postoperatively for data collection purposes. We anticipate 3 years for the completion of the study.

The study design of a single arm phase II trial was chosen because, although there are many data on the use of somatostatin analogues for the prevention of postoperative pancreatic fistulae, there is currently no consensus on their use and there have been no prior trials using lanreotide for this purpose. A clinical or biological signal in this study would potentially provide justification for a large-scale multicenter randomized controlled trial of lanreotide to prevent pancreatic fistulae. Below is a schema of the study design:


Prior to Enrollment
Obtain informed consent. Screen potential subjects by inclusion and exclusion criteria; obtain history, document.
Visit 1
1 to 60 days prior to planned operation
Perform baseline assessments.
Day of operation
Collect blood for correlative research (optional).
Administer lanreotide.
Operating room for attempt at surgical resection.
Collect blood for correlative research (optional).
No resection.
Exclude from analysis.
Perform 30 and 60 day assessments.
N = 98 subjects undergo surgical resection (pancreaticoduodenectomy or distal pancreatectomy +/- splenectomy)
During initial hospitalization and at clinic follow-up visit
Review medications
Physical examination
Laboratory values recorded
~30 and 60 days postop
Follow-up assessments of outcome measures and safety
Standard perioperative care and evaluations
Telephone interviews by research staff

5 SUBJECT SELECTION

5.1 Subject Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

- Male or female patients age ≥ 18 years
- Candidate for planned elective pancreaticoduodenectomy or distal pancreatectomy for malignancy or suspected malignancy
- Able to provide informed consent
- Able to adhere to dose and schedule of visits
- Female subject of childbearing potential should have a negative clinical urine or serum pregnancy test within 72 hours prior to study drug administration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Female subjects who are at risk of becoming pregnant must agree to use an effective method of contraception such as double barrier contraception, an injectable, combined oral contraceptive or an intra-uterine device (IUD). The subject must agree to use the contraception during the whole period of the study and for three months after the study drug administration. Non childbearing potential is defined as being postmenopausal for at least 1 year, or permanently sterilized at least 3 months before study entry.

5.2 Subject Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

- Use of disallowed concomitant medications
- Has been treated with an SSA at any time prior to planned study drug administration, except if that treatment was for less than 15 days of short acting SSA or one dose of long acting SSA and the treatment was received more than 6 weeks prior to randomization
- Planned tumor enucleation or total pancreatectomy
- Pregnancy or breastfeeding
- Malabsorption syndrome, short bowel, or chologenic diarrhea uncontrolled by specific therapeutic interventions
- NYHA Class III or IV congestive heart failure, unstable angina, sustained ventricular arrhythmia, advanced heart block, clinically significant bradycardia, or acute myocardial infarction within six months before enrollment; patients with asymptomatic sinus

bradycardia will not be excluded, but will be intensively monitored on telemetry for at least 6 hours following drug administration, even in the event that complete surgical resection is not performed.

- Severe renal insufficiency as defined by a calculated creatinine clearance <30 mL/min
- Moderate to severe hepatic impairment as defined by liver enzyme elevation more than 5 times the upper limit of normal (either AST >190 U/L or ALT >320 U/L); patients with normalization of their liver enzymes to below these levels prior to study enrollment will not be excluded
- Known allergic reactions to components of the study drug
- Has been treated with Peptide Receptor Radionuclide Therapy (PRRT) at any time prior to randomization
- Treatment with systemic immunosuppressive medications, such as cyclosporine, tacrolimus, or prednisone (≥10 mg daily) within 3 months prior to dosing of study drug
- Treatment with another investigational drug within 10 days prior to dosing of study drug
- Anything that would place the individual at increased risk or preclude the individual's full compliance with or completion of the study.

6 RECRUITMENT PLAN

Patients will be recruited from the University of Washington Medical Center and the Seattle Cancer Care Alliance. Patient records will be assessed to determine eligibility. Prior to enrollment, patients will be told about all potential risks and benefits associated with the study. Informed consent will be obtained from all subjects prior to participation in the study. Subjects will not receive any compensation for participation in the study. In addition, subjects will not incur any additional costs as a result of participation in the study.

7 STUDY INTERVENTION

All patients enrolled in this study will receive SOMATULINE DEPOT 120 mg immediately prior to going to the operating room for planned pancreatic resection. The pharmacist will dispense loaded syringes of the study drug. The single preoperative dose will be given in the pre-surgical center at the University of Washington by a trained health care professional. The study drug will be injected via the deep subcutaneous route in the superior external quadrant of the buttock.

Safety and efficacy will be assessed throughout the study period. Assessment for pancreatic and non-pancreatic complications will be made at the time of discharge and in follow-up by the attending surgeon. Patients will be evaluated in clinic postoperatively within 21 days of discharge for evaluation of the primary endpoint. The research team will perform long term follow-up by phone or in person with patients at 30 and 60 days (+/- 10 days at each time point).

8 INVESTIGATIONAL PLAN

8.1 Duration of Study

Once enrolled, subjects will receive a SOMATULINE DEPOT 120 mg immediately prior to planned pancreatic resection. Subjects will be followed for 60 days. The proposed enrollment period and study duration will be 36 months.

8.2 Screening and Enrollment

Subjects undergoing planned elective pancreaticoduodenectomy or distal pancreatectomy for malignancy or suspected malignancy will be identified and screened for eligibility. Eligible patients who agree to participate will sign a written consent form at this time. At the initial visit, eligibility will be confirmed and documented in the study records.

8.3 Informed Consent

Informed consent will be obtained prior to enrollment utilizing the consent form found in Appendix A.

8.4 Study Drug

Lanreotide (SOMATULINE DEPOT) is formulated as a solution for injection in prefilled syringes at the dosage for this study of 120 mg/0.5mL.

8.4.1 *Acquisition*

Lanreotide (120 mg/0.5 mL) will be labeled and provided in a single, sterile, prefilled, ready-to-use polypropylene syringe (fitted with an automatic needle guard) by Ipsen Biopharmaceuticals, Inc.

8.4.2 *Formulation, Packaging, and Labeling*

Lanreotide will be formulated as a solution for injection at 120 mg/0.5mL in single-use prefilled syringes fitted with an automatic needle guard (SOMATULINE DEPOT). The prefilled syringes contain a white to pale yellow, semi-solid formulation. Each prefilled syringe is sealed in a laminated pouch and packed in a carton.

8.4.3 *Drug Storage and Stability*

Lanreotide must be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) and protected from light in its original package. Keep pouch sealed until injection. Each syringe is intended for single use, and will not be used beyond the expiration date on the packaging.

8.4.4 *Study Drug Accountability*

SOMATULINE DEPOT 120 mg will be shipped from Ipsen Pharma Biotech to the University of Washington Medical Center, Investigational Drug Service (IDS) Pharmacy. The IDS Pharmacist will maintain accurate records (including dates) of all supplies received. Current dispensing records will be maintained, including the date and amount of medication dispensed per subject. If a subject is enrolled but does not receive the study drug because he/she becomes ineligible, the unused study drug will be returned to the Investigational Drug Pharmacy. All unused and returned study medication not required by applicable federal and state regulations to be held by the clinical facility must be destroyed in accordance with applicable federal and state regulations or be returned as directed immediately after the study is completed.

8.5 Concomitant Medications/Treatments

A complete list of all medications being taken by subjects will be evaluated during screening, prior to enrollment, and on the day of study drug administration. A history of current or previous natural somatostatin or somatostatin analog therapy will be specifically elicited, as this would lead to exclusion from the study.

Insulin and oral hypoglycemic medications will be specifically noted, as effects of lanreotide on insulin and glucagon secretion may require adjustment of antidiabetic treatments. For patients who undergo planned resection, routine aggressive blood glucose monitoring (every 1-2 hours for the first day) and administration of intravenous glucose and insulin solutions as needed will be performed.

As noted above (5.2 Subject Exclusion Criteria), patients having taken cyclosporine, tacrolimus, or prednisone (≥10 mg daily), or similar immunosuppressive medications, within 3 months of study drug dosing are excluded from this study.

8.6 Study Drug Administration

All patients enrolled in this study will receive SOMATULINE DEPOT 120 mg on the day of surgery, prior to planned surgical resection. The single preoperative dose will be administered by a healthcare professional in the pre-surgical center at the University of Washington Medical Center. The study drug will be injected via the deep subcutaneous route in the superior external quadrant of the buttock. Approximately thirty (30) minutes prior to injection, the sealed pouch of SOMATULINE DEPOT will be removed from refrigerator and allowed to come to room temperature. The pouch will be kept sealed until injection.

9 VISIT SCHEDULE AND ASSESSMENTS

Table 9 lists all of the assessments and the visits at which they are to be performed with an “X”. All data obtained from these assessments must be supported in the patient’s source documentation.

Table 9.1: Visit Schedule and Assessments

Visits	**Screening visit**	**Day of surgery to Discharge**			**Follow-up post-discharge**		
	Day -60 to -1	Pre-op	Intra-op	*Post-op	Clinic follow-up days 1-21	Day 30 post-op	Day 60 post-op
Informed consent	**X**						
Medical history/current medical conditions from subject and/or chart	**X**	**X**		**X**	**X**	**X**	**X**
Medication review	**X**	**X**		**X**	**X**	**X**	**X**
Inclusion/exclusion criteria	**X**	**X**					
Physical exam (Use clinical results if available)	**X**			**X**	**X**		
Pregnancy test for women of childbearing potential (Use clinical test if available)	**X**	**X**					
Basic metabolic panel from chart	**X**			**X**			
CBC from chart	**X**			**X**			
PT, PTT from chart as available	**X**			**X**			
AST & ALT from chart	**X**			**X**			
Blood glucose from chart	**X**	**X**	**X**	**X**	**X**		
Review intensive blood glucose monitoring and management per clinical protocol			**X**	**X**			
Draw blood for correlative research (optional)		**X**	**X**				
Administer study drug		**X**					
Record pain assessments from chart		**X**		**X**	**X**		
Administer Symptoms Questionnaire		**X**		**X**	**X**	**X**	**X**
Review vital signs(clinical results)	**X**			**X**	**X**		
If surgical drain present:							
Record drain amylase levels from chart				**X**	**X**	**X**	**X**
Record drain output in ml from chart				**X**	**X**	**X**	**X**
Determine day of drain removal from chart				**X**	**X**	**X**	**X**
Review for adverse events			**X**	**X**	**X**	**X**	**X**

*Hospital length of stay varies

9.1 Screening Visit (Day -60 to -1)

Eligible patients will be identified at the SCCA and UWMC SSC surgical oncology clinics. At the screening visit, the Research Coordinator (RC) or one of the investigators will obtain signed

informed consent. This will take place prior to any procedures being performed. Subjects will not receive any compensation for participation in the study. In addition, subjects will not incur any additional costs as a result of participation in the study.

- Obtain and document consent from potential subject on study consent form
- Review medical history to determine eligibility based on inclusion/exclusion criteria
- Review medications history to determine eligibility based on inclusion/exclusion criteria
- Perform physical examination: vital signs, weight, height (use clinical results if available)
- Collect, or obtain from routine care records, the following laboratory studies within 30 days prior to treatment:
    - Complete blood count with white blood cell differential and platelet counts;
    - Prothrombin time and activated partial thromboplastin time (PT&PTT)
    - Basic metabolic panel, including blood glucose level
    - AST and ALT
    - Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to study drug administration performed for routine care. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required for entry into the study.

9.2 Day of Surgery to Discharge

9.2.1 *Preoperative: Baseline (Day 0)*

The baseline visit will take place on the day of surgery, prior to the patient's operation and administration of the study drug. Some subjects initially consented into the study may be deemed ineligible on the day of surgery prior to drug administration. The study team will assess inclusion/exclusion criteria prior to drug administration.

- Verify inclusion/exclusion criteria
- Obtain demographic information, medical history/current condition, medication list from subject and/or chart
- Review results of clinical serum pregnancy test for women of childbearing potential prior to drug administration, unless testing negative within prior 72 hours (for example, if testing was performed at Screening Visit within the previous 3 days)
- Review preoperative blood glucose level as part of standard perioperative care
- Draw blood for correlative research (Up to 30 ml ml)) prior to study drug administration (optional research)

9.2.2 *Preoperative: Drug Administration (Day 0)*

The study drug will be administered and other study procedures performed after baseline procedures are conducted; prior to the surgery.

- Administer the study drug
- Administer Symptoms Questionnaire
- Review vital signs from chart
- Record results of pain scale from chart

9.2.3 *Intraoperative (Day 0)*

- Draw blood for correlative research (Up to 30 ml) intraoperatively immediately following resection (optional research)
- Review results of clinical intensive blood glucose management consisting of approximately hourly blood glucose level checks and insulin infusion per standard perioperative care protocol

9.2.4 *Hospital Stay (Postoperative Days 0-7)*

Subjects who receive the study drug and have a clinical resection will be followed postoperatively for 60 days. The initial postoperative assessment will occur during the subject's hospital stay. Hospital stays will vary widely by patient, but are expected to range from 3-7 days. The study team will periodically review the patient chart for safety and outcomes as available for individual subjects during this timeframe.

- Record adverse events as reported by subject or observed by clinical team and/or investigator. See section 10.2 for list of information to be reviewed for adverse event monitoring
- Obtain medical history/current condition, medication list from subject's chart
- Record results of physical examination from subject's chart
- Review results of clinical intensive blood glucose management per standard perioperative care protocol.
- Collect the following laboratory studies, as available from routine care records:
    - Complete blood count with white blood cell differential and platelet counts;
    - Prothrombin time and activated partial thromboplastin time (PT&PTT)
    - Basic metabolic panel
    - AST and ALT
- Review vital signs from chart
- Record results of pain scale from chart

- Administer Symptoms Questionnaire
- Record drain amylase levels from chart, as available
- Record drain output in ml from chart, as available
- Evaluate for day of drain removal from chart, as available

For subjects who receive the study drug but do not have a clinical resection performed during their surgery, the study team will review adverse events related to the study drug during the immediate postoperative hospital stay, and contact them by phone at 30 and 60 days to ask about their symptoms. No other procedures will be performed.

9.3 Follow-up Post Discharge

9.3.1 *Clinic Follow-up Visit (Post discharge Days 1-21)*

Subjects will typically have a clinical follow-up appointment with their UW Medicine surgical provider or an external provider within 1 – 21 days following discharge. There may be more than one clinical appointment during this timeframe. The study team will review patient charts and collect information on individual subjects as available from their clinical care. Subjects who are seen at UW Medicine will receive an in-person symptoms questionnaire to complete. Subjects who have their follow-up care performed external to UW Medicine will receive a phone call from the research coordinator (RC) between 1 and 21 after discharge to complete the symptoms questionnaire by phone. Records from external institutions will be obtained and reviewed for the timeframe.

- Record adverse events as reported by subject or observed by clinical team and/or investigator
- Obtain medical history/current condition, medication list from subject and/or chart
- Record results of clinical physical examination
- Collect from routine care records the following laboratory studies, as available:
    - Complete blood count with white blood cell differential and platelet counts;
    - Comprehensive profile; prothrombin time and activated partial thromboplastin time (PT&PTT)
- Review vital signs from chart
- Record results of pain scale from chart
- Administer Symptoms Questionnaire

9.3.2 *Follow-up Phone Call (Postoperative Days 30 & 60)*

The RC will follow-up with all subjects by phone at approximately 30 and 60 days postoperatively to identify missed complications. If the RC identifies a missed complication by phone, the Principal Investigator or Co-Investigator will then contact the subject with a second phone call to discuss the reported complications in more detail.

Patient charts will be reviewed throughout 60 days postoperatively. Some subjects may receive their follow-up care outside of UW Medicine. In this case, records from external institutions will be obtained and reviewed for the timeframe.

- Record adverse events as reported by subject or observed by investigator.
- Obtain medical history/current condition, medication list
- Administer Symptoms Questionnaire
- Review clinical charts for complications, as available

10 ASSESSMENT OF SAFETY

Adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events—Version 4.03. A copy of the CTCAE v4.03 can be downloaded from the NIH at https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

10.1 Adverse Event Overview

An adverse event in this protocol is the appearance of, or worsening of preexisting, undesirable sign, symptom, or medical condition, after signing the informed consent, that is **not considered to be a postoperative complication,** whether or not the event is considered to be related to the study drug. Common postoperative complications that will not considered be an adverse event of the study drug are presented in Table 10.1.

An adverse event is any untoward medical occurrence in a clinical investigation in which a subject has been administered a pharmaceutical product. The adverse event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not

Table 10.1: The most frequent complications following 351 pancreatic resections performed at the University of Washington Medical Center from 2011 through 2016, based upon data from the National Surgical Quality Improvement Program.

Complication	**n (%)**
Hemorrhage requiring blood transfusion	37 (11%)
Intra-abdominal infection/abscess	25 (7%)
Sepsis or septic shock	22 (6%)
Wound Infection	18 (5%)
Delayed gastric emptying†	4 (5%)
Pneumonia or unplanned intubation or mechanically ventilated >48 hours	13 (4%)
Anastomotic leak, biliary or pancreas*	5 (3%)
Fistula, pancreatic or biliary	8 (2%)
Urinary tract infection, acute renal failure or progressive renal insufficiency	6 (2%)
Pulmonary embolus or DVT requiring therapy	6 (1%)

†Data only available for last 87 cases
*Data only available for last 164 cases

considered related to the medicinal product. Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An adverse event occurring in the course of the use of a drug product in professional practice.
- An adverse event occurring from drug withdrawal.
- An adverse event where there is a reasonable possibility that the event occurred purely as a result of the subject's participation in the study

The clinical manifestation of any failure of expected pharmacological action is not recorded as an adverse event if it is already reflected as a data point captured in the case report form and source documents. If, however, the event fulfills any of the criteria for a "serious" adverse event, it must be recorded and reported as such.

Separate instructions will be provided on how to complete the adverse events and SAE forms.

If grading does not exist for a particular adverse event, the severity of mild, moderate, severe, life threatening, and leading to death, **or** grades 1 - 5, will be used. Adverse event monitoring will be continued for approximately 60 days following the administration of the study drug. Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form will be recorded. Abnormal laboratory values or test results constitute adverse events and will be recorded only if they induce clinical signs or symptoms and are considered clinically significant or require therapy.

Subjects will be carefully monitored for adverse events. An adverse event will be evaluated to determine:

1. Its severity grade
2. Its relationship to study drug (suspected/not suspected)
3. Its duration (start and end dates or if continuing at final exam)
4. If action was taken (no action taken; medication administered; non-drug therapy given; subject hospitalized or hospitalization prolonged)
5. Whether it is serious

10.2 Data Collection for AE Review

The study team will review patient charts to assess safety for this study throughout 60 days postoperative. If a clinical complication is identified, the following variables will be reviewed for adverse event monitoring:

- Readmission
- Admission to ICU
- Pain scale
- Drain placement
- Reoperation
- Institution of antimicrobial therapy
- Vital signs

- WBC
- Presence or absence of abscess on CT scan
- Drain amylase level
- Drain output in ml per day

10.3 Serious Adverse Event (SAE)

A serious adverse event is an undesirable sign, symptom or medical condition that is not felt to be a postoperative complication and has one or more of the following characteristics:

- Results in death.
- Is life threatening.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event

Life threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event, which hypothetically might have caused death if it were more severe.

Re-admission to the hospital is common following pancreatic resection (~20%) and will not be reported as an SAE nor will it be reported in an expedited manor, unless probably or definitely related to study drug administration. The planned admission to the hospital will not be reported. However, it should be noted that invasive treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability: a substantial disruption of a person's ability to conduct normal life functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the health of the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction Terminology-Critical Terms List." These terms either refer to or might be indicative of a serious disease state. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.
SAEs will be reported to the study medical monitor within 24 hours of learning of the event and followed up until resolution, in accordance with the guidelines set forth by federal agencies. Listings of adverse events will be generated quarterly to assess for trends or unexpected events, and examined for possible patterns between the groups and over time. If potential trends or unexpected events are noted, a summary will be provided to the medical monitor for review and evaluation.

10.4 Unexpected Adverse Event

An unexpected adverse event is any adverse drug event, which is not consistent with the current package insert. Also, if a report adds information, which is more specific or severe than the documented adverse event, this constitutes an unexpected adverse event. For example, an event more specific or more severe than described in the Investigator Brochure would be considered "unexpected."

10.5 Relationship of Adverse Event to Investigational Drug

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of 'No' would include:

- The existence of a clear alternative explanation

  OR

- Non-plausibility (e.g., The subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the drug administration).

An assessment of 'Yes' indicates that there is a reasonable suspicion that the adverse event is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the adverse event to the study drug include:

- The temporal sequence from drug administration: the event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: the other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might be suspected to cause the event in question.
- The pharmacology and pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of the test drug, coupled with the individual subject's pharmacodynamics should be considered.

10.6 Severity of the Adverse Event

The severity of adverse events should be graded as follows:

1 – Mild - usually transient in nature and generally not interfering with normal activities
2 – Moderate – sufficiently discomforting to interfere with normal activities
3 – Severe – prevent normal activities
4 – Life-threatening – leads to severe disability
5 – Death

10.7 Adverse Event Documentation

All adverse events occurring after the subject has signed the informed consent up through the 60-day follow up period, must be fully recorded in the subject's case report form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

10.8 Reporting of Serious Adverse Events

SAE's including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. A SAE form must also be completed within 24 hours of the investigator awareness and forwarded to the designated person as detailed in the study file. Each serious adverse event must be followed up until resolution or stabilization by submission of updated reports to the designated person.

When required, and according to local law and regulations, serious adverse events must be reported to the Institutional Review Board at each trial site where the SAE occurs. SAEs will also be reported to the coordinating center at the University of Washington.

10.9 Stopping Rules

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the FDA. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.

11 OUTCOME ASSESSMENT

11.1 Primary Endpoints

The primary outcome variable is reduction in the incidence of intraabdominal abscess or development of clinically significant (grade B or C) pancreatic fistula before 60 days postoperatively. These complications are being considered together, as they represent a common etiology (pancreatic leak), clinical presentation (systemic signs of infection or sepsis), and treatment (antimicrobial therapy with or without percutaneous or operative drainage).

Assessment for the diagnosis of intraabdominal abscess or the development of grade B or C pancreatic fistula will be made at the time of discharge and in follow-up by the attending surgeon in clinic postoperatively within 21 days of operation. The clinical findings used in Grading POPF noted in Table 1 (clinical condition, specific treatment, imaging results, persistence of drainage after 21 days, reoperation, death related to POPF, signs of infection, sepsis, and readmission) will be gathered during inpatient admission(s), at postoperative visit(s), and at planned 30- and 60-day follow up phone calls.

11.2 Secondary Endpoints

The secondary endpoints include the following:

1. Grade A pancreatic fistula will be defined based on principles noted in evaluation of Primary endpoint.
2. Surgical site infection is defined as purulent drainage from a surgical wound, requiring intervention including, but not limited to, institution of antimicrobial therapy or opening of the wound.
3. Overall morbidity will be an aggregate of all perioperative complications.
4. Drain amylase levels on day 1 & 3 postoperatively will be collected on a routine basis, as part of our standardized care pathway. Mean and median drain amylase levels at each time point will be calculated.
5. Duration of drainage for patients with pancreatic fistulae will be defined based upon the date of drain removal subtracted from the date of drain placement.

12 SUBJECT WITHDRAWL

Patients may voluntarily withdraw from the study or be dropped from it at the discretion of the investigator at any time. Patients may be withdrawn from the study if any of the following occur:

- Pregnancy discovered after enrollment, but prior to study drug treatment
- Protocol violation
- Subject withdrawal of consent
- Lost to follow-up
- Do not have clinical resection performed post drug administration
- Death

12.1 Replacement of Subjects

Subjects withdrawn from the study prior to administration of the study drug will be replaced. Subjects withdrawn from the study after administration of the study drug and who do not have a clinical resection performed will not be replaced. Other subjects withdrawn prior to complete 60-day follow up will not be replaced. If subjects do not respond to phone follow-up at 30 or 60 days, three repeated attempts will be made over the 10 days following each of these time points. Subjects who have incomplete follow up will be included with limited follow up.

13 BIOSTATISTICS

13.1 Sample Size and Power

We estimate the final target sample size will be 98 patients. We aim to screen 154 patients and enroll n=123 patients into this single-arm study to test whether treatment with lanreotide reduces the risk of postoperative pancreatic fistula. Based upon a 20% probability of not proceeding with surgical resection after drug treatment due to findings of metastatic or unresectable disease at surgery, we anticipate that 123 treated patients will yield 98 evaluable patients.

13.2 Analysis Plan

As a primary method analysis, we will use a one-sample t-test to compare the rate of postoperative pancreatic fistula among the n=98 patients who were treated with lanreotide and underwent surgical resection against a published rate of 21% for patients treated with a placebo in another study, while 9% of patients treated with pasireotide experienced postoperative pancreatic fistula. The present study has 80% power (one-sided alpha = 0.05) to detect pancreatic fistula rates smaller than 11.5%, the approximate upper estimate of an 80% confidence interval of the pancreatic fistula rate of 9% in the study of pasireotide.

As a secondary exploratory analysis, we will use McNemar's test to compare the pancreatic fistula rate in the present study to that of historical controls at the same institution matched on pancreatic firmness and duct size.

14 DATA MANAGEMENT, MONITORING, AND RETENTION

A RC will be assigned to the study. The responsibilities of the RC include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record.

14.1 Data Management

All data procedures will be conducted using good computing practices for the handling and analysis of data for clinical trials. Study personnel will enter data from source documents corresponding to a participant's day on study onto the CRF when the information corresponding to that day is available. The data collected for this study will be entered into a secure database. Source documentation will be available to support the computerized patient record. Study participants will not be identified by name on any study documents to be collected by the Sponsor or authorized designee, but will be identified by an identification number and participant initials.

All clinical information requested in this protocol will be entered on the CRFs. CRF corrections will be made without obliterating the original entry.

The Principal Investigator is responsible for all information collected on participants enrolled in this study. All data collected will be reviewed by the PI throughout the course of the study for completeness and accuracy.

14.2 Data and Safety Monitoring

This study will be monitored for subject safety, protocol compliance, and data integrity. In addition to the PI's responsibility for oversight, a medical monitor will provide objective review of the protocol and protect the safety of the subjects. The medical monitor will be independent of the study team; with expertise in surgery. The medical monitor will assess for safety and efficacy data (if applicable), study progress, and data integrity for the study. The medical monitor will review the study data after the first 15 subjects have completed the 60 day study period. Thereafter, the medical monitor will review the study data after 50 subjects and 123 subjects have completed study procedures. The medical monitor can recommend early termination of the trial at any time for safety concerns. The medical monitor will be informed of all serious adverse events at the reviews, and at other times if substantial numbers or unusual kinds of serious adverse events occur.

Serious adverse events (as defined in 21 CFR 312.32) will be reported to the study medical monitor and Ipsen within 24 hours of learning of the event and followed up until resolution, in accordance with the guidelines set forth by federal agencies. Listings of adverse events will be generated at the end of enrollment to assess for trends or unexpected events, and examined for

possible patterns between the groups and over time. If potential trends or unexpected events are noted, a summary will be provided to the medical monitor for further review and evaluation.

In addition, all SAEs will be emailed to Ipsen at ***drugsafety@propharmagroup.com***

14.3 Availability and Retention of Investigational Records

The Sponsor or authorized designee must make study data accessible to regulatory authorities upon request. A file for each participant must be maintained that includes the signed Informed Consent and copies of all source documentation related to that participant. The Investigators must ensure the reliability and availability of source documents from which the information on the CRF was derived.

14.4 Archiving of Data

At all times, appropriate backup copies of the database and related software files will be maintained and the information will be appropriately protected from illegitimate access. Databases will be backed up by the database administrator in conjunction with any updates or changes to the database. Tape or cartridge backup copies will be maintained at an off-site safe storage location. When the structure of the database is changed, a permanent archive of the database will be made to protect against loss of data in the changeover. When each backup is made, the media will be checked for usability and the integrity of the database will be verified.

At completion of data verification, a permanent archive of the database will be made. Archived versions of the database will be saved for at least three years after the end of the study.

14.5 Participant Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations will not be made publicly available.

To maintain participant confidentiality, only an identification number, and participant initials will identify all study participants in reports and on specimens. Only the subject number will be recorded in the case report form, and if the subject name (or initials) appears on any other source document, (e.g. lab work), it must be obliterated before a copy of the document is included in the case report form.

All records identifying the subject, including contact information, will be kept confidential and in a location, separate from the case report form. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that the IRB or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential. The investigator will maintain a list to enable subjects' records to be identified.

15 ADMINISTRATIVE, ETHICAL, AND REGULATORY CONSIDERATIONS

15.1 Institutional Review Board

Documented approval from the IRB will be obtained prior to the start of the study from the University of Washington Human Subjects Division. The written approval of the IRB together with the approved ICF will be stored in the study files. When necessary, an extension, amendment or renewal of the IRB approval will be obtained.

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigators abide by good clinical practice guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by Regulatory Authority representatives at any time. The investigator must agree to the inspection or study-related records by the Regulatory Authority representative, and must allow direct access to source documents to the Regulatory Authority representatives.

15.2 Protocol Modifications

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment. Some modifications also require approval by the IRB. These requirements for approval should in no way prevent any immediate action from being taken by the investigator in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons, the IRB must be notified immediately. Any deviations from the protocol must be fully explained and documented by the investigator.

15.3 Informed Consent

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to UW IRB guidelines. An Informed Consent Form (ICF) will be provided to eligible subjects. The ICF will document the study-specific information the Investigator provides to the participant and the participant's agreement to participate. Among other things, the Investigator will fully explain in layman's terms the nature of the study, along with the aims, methods, anticipated benefits, potential risks, and discomforts. The ICF must be signed and dated by both patient and investigator before any study-related procedures are performed. The original and any amended signed and dated ICFs must be retained in the participant's file; one copy will be returned to the patient, and one will be placed in the patient's medical record.

15.4 Research Authorization

In addition to signing the ICF, all patients must sign the Research HIPAA Authorization Form. This contains information about the Health Insurance Portability & Accountability Act (HIPAA) that protects the participant's individually identifiable health information (protected health information) and authorization (or agreement) for researchers to be able to use or disclose the participant's protected health information for research purposes. The Research HIPAA Authorization requires a separate set of signatures from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents.

15.5 Quality Control and Quality Assurance

The PI or authorized designee will conduct audits. Study site audits will include review of regulatory documents, including study drug and device accountability records and medical source documents. Data and information will be disclosed to the regulatory authorities in full compliance with applicable regulations.

15.6 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/notifications, where required, must be in place and fully documented prior to study start.

15.7 Investigator Responsibilities

The Investigators agree to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the PI (or authorized designee), except when to protect the safety, rights, or welfare of subjects/participants.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the PI/Medical Monitor any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments and are listed on the appropriate study documents.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the PI or authorized designee.
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. To promptly report to the IRB and the PI or authorized designee all changes in the research activity and all unanticipated problems involving risks to subjects/participants or others.

9. Not make any changes in the research study without IRB approval, except when necessary to eliminate hazards to the subjects/participants.
10. To comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

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APPENDIX A: CONSENT FORM