STUDY NUMBER: CASE6220

ClinicalTrials.gov NCT #: NCT05289830

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STUDY TITLE: A Phase II, Randomized, Double-Blind Trial Comparing Escitalopram to Placebo in Patients with Localized Pancreatic Cancer

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SPONSOR: Case Comprehensive Cancer Center

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AGENT: Escitalopram and placebo

IND #: Exempt

Title: A Phase II, Randomized, Double-Blind Trial Comparing Escitalopram to Placebo in Patients with Localized Pancreatic Cancer

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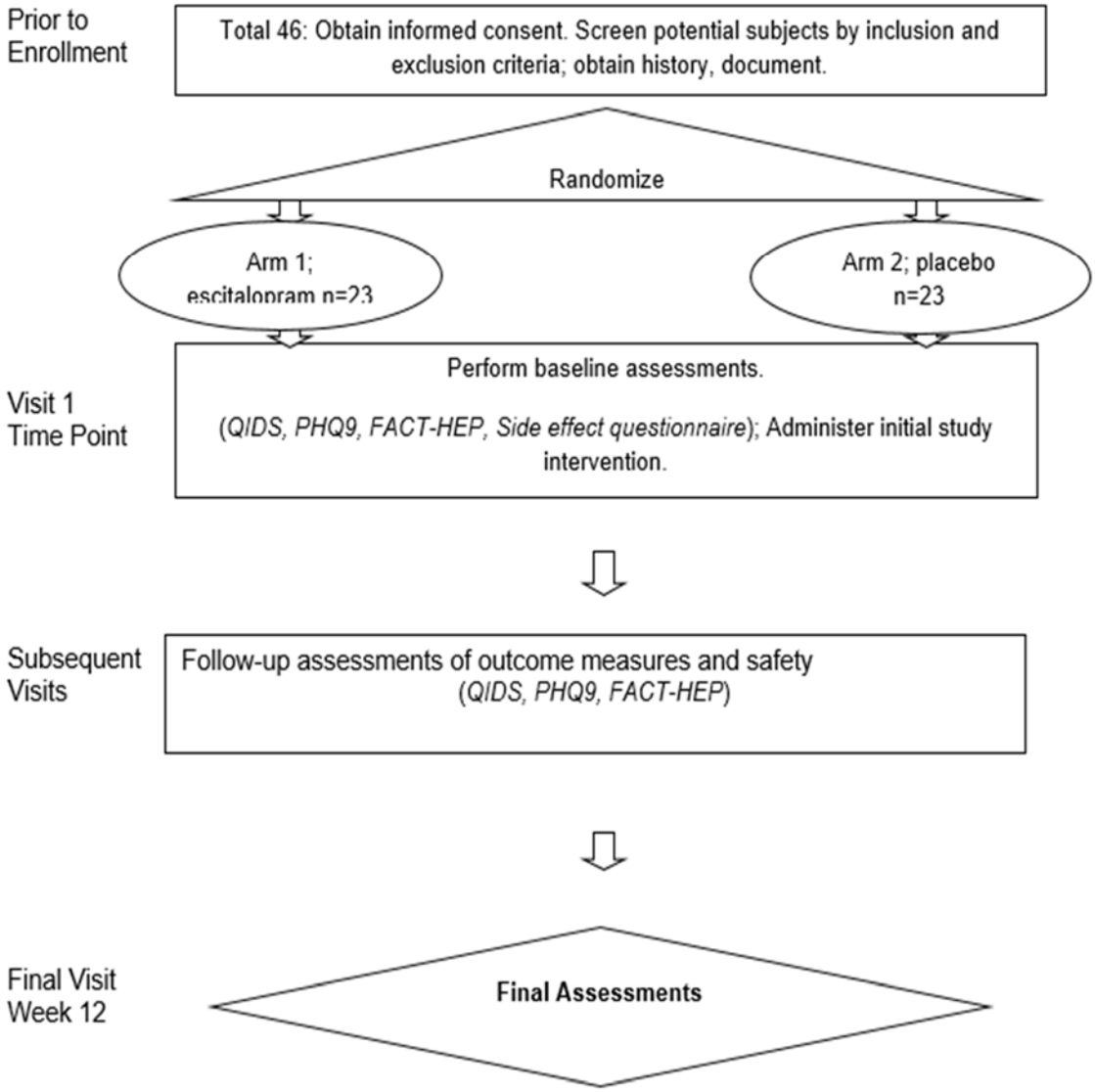
SUMMARY OF CHANGES

Protocol Date	Section	Change
1/12/2022		Initial IRB approval
4/14/2022 v.2	Cover page	Addition of Co-Investigators Jennifer Brandstetter, MD, Kristy Rostocil, CNP Removal of Co-Investigators Richard Lee, MD, Susan Padrino, MD. Corrections to Funding and Agent information
	Protocol Summary	Added pancreatic cancer to objectives for clarity
	Abbreviations	Added IDS
	3.1	Updated blinding procedures
	3.4	Revised to align criteria for patient removal from study with Table 7.1
	6.1	Clarified that research blood draw is to take place before first dose of escitablopram/placebo. Corrected days FACT-Hep is completed Revised unblinding criteria to include Gr. 4 hyponatremia. Added: Patients who are unblinded before they complete all study visits will be asked to continue to have study-related phone calls with study staff and complete all study-related questionnaires.
	6.2	Added to second bullet: or patient inability to swallow escitalopram/placebo capsules,
	6.3	Clarified that long-term survival follow-up starts after Week 25
	7.1	Corrected name and email for Psycho-Oncology Provider
	Table 7.1	Added hyponatremia
	9.1	Revised to reflect new drug supplier information and changes to drug packaging
	11.1.1	Screening visit updated to include ECOG performance status. Week 1, Day 1 updated to include toxicity assessment.
	14.2	Correction made – added word “treatment”.
	Appendix II	Small revision to Pill Diaries made for clarity.

Protocol Date	Section	Change
8/31/2022 V2.1	Cover page	Updated version date. Updated study staff and made corrections to add staff who were erroneously not included or not removed when they left UH: Added Mukesh Bhatt, MD, Sakti Chakrabarti, MD, Amit Mahipol, MD., Gordon Goolamier, CNP Removed: Richard Chang, MD, Katherine Daunov CNP and Jennifer Dorth, MD
10/21/2022 V3.0	Cover page	Update version date to 10/21/2022
	Section 6.1	The following line has been removed: "and the patient is being treated at UH Main campus". This line no longer relevant as study procedures will take place at satellites.
	Study Calendar	Updated to remove the following footnote as this amendment allows patients to be enrolled and have study procedures at satellites: *Patients who receive chemotherapy at satellites sites are required to come to Main campus for D1, 15, 71 and End of Treatment visits to receive pills/return unused pills and to collect/return their pill diary.
11/07/2022 v4.0	Cover page	Updated version date to 11/07/2022
	Section 7	**Table 7.1**: The CTCAE grading reference ranges for hyponatremia have been corrected.
	Section 8	Revisions are being made to clarify that only study related SAEs and AESI are to be recorded and reported. SAEs related to chemo are not entered into the Oncore database or reported on a MedWatch form. The following revision have been made to this section: **8.2.3 Adverse Event Evaluation** changed: From: The investigator or designee is responsible for ensuring that adverse events of interest (both serious and non-serious as defined in previous sections) observed by the study staff or reported by the subject that are determined to be related to escitalopram/placebo which occur after the initiation of escitalopram/placebo are fully recorded in the subject's medical record. Source documentation must be available to support all adverse events. To: The investigator or designee is responsible for ensuring that ***all*** adverse events, (both serious and non-serious as defined in previous sections) observed by the study staff or reported by the subject that are determined to be related or possibly related to escitalopram/placebo which occur after the initiation of escitalopram/placebo are fully recorded in the subject's medical record ***and reported according to AE reporting policies of the IRB of record. Adverse events attributed to chemotherapy and/or underlying disease will not be recorded for this study.*** Source documentation must be available to support all adverse events. **8.4 Reporting Procedures for Serious Adverse Events** changed

Protocol Date	Section	Change
		From: For the purposes of safety reporting, all adverse events of interest will be reported that occur from the initiation of escitalopram/placebo on Day 1 until the Week 25 study visit. Adverse events of interest, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization. To: For the purposes of safety reporting, all adverse events ***determined to be related or possibly related to escitalopram/placebo*** will be reported that occur from the initiation of escitalopram/placebo on Day 1 until the Week 25 study visit. Adverse events both serious and non-serious, and deaths that occur during this period will be recorded in the source documents ***and reported according to AE reporting policies of the IRB of record.*** All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization. **8.4.1 SAE Reporting Requirements** Language was added to clarify that only SAEs related to escitalopram/placebo are to be reported. **8.5 SAEs and OnCore** revised From: All SAEs will be entered into OnCore. To: All SAEs ***related or possibly related to escitalopram/placebo*** will be entered into OnCore.
	Section 8.3	Revised to state that the SAE Report Form to be used for this study is the FDA Form 3500A (MedWatch for Industry Form FDA 3500A – Mandatory Reporting) This form can be found at the following link: https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting.

STUDY SCHEMA



PROTOCOL SUMMARY

Protocol Number/Title	CASE6220: A Phase II, Randomized, Double-blind, Trial Comparing Escitalopram to Placebo in Patients with Resectable Pancreatic Cancer
Study Phase	II
Brief Background/Rationale	Anti-depressants have been shown to be beneficial in cancer patients. They reduce depressive symptoms and improve quality of life. Randomized trials have shown that antidepressants can reduce the development of depression in non-depressed patients with breast, melanoma and head and neck cancers. In this trial, we will test the role of anti-depressants in patients with localized pancreatic and periampullary cancer receiving neoadjuvant therapy. It has been shown that treating depression can impact survival in cancer patients. Additionally, depressed pancreatic cancer patients have a worse survival. Therefore, anti-depressants may also have implications for cancer treatment.
Primary Objective	Primary Endpoint(s) To determine if patients with localized pancreatic and periampullary cancer have a decreased risk of depression with 12 weeks of escitalopram treatment.
Secondary Objective(s)	Secondary Endpoint(s) To determine if patients with localized pancreatic and periampullary cancer have improved quality of life with 12 weeks of escitalopram treatment.
Correlative Objective(s)	Correlative Endpoint(s) To collect serum, and tissue samples of metabolites related to serotonin metabolism, and determine if levels correlate with depression, quality of life, or benefit of escitalopram
Sample Size	46 patients including 23 patients in each arm (escitalopram and placebo)
Disease sites/Conditions	Localized pancreatic ductal adenocarcinoma or other periampullary adenocarcinoma (bile duct, duodenal, ampullary).
Interventions	Escitalopram or placebo for 12 weeks as follows: 2 weeks: 10 mg/day (1 capsule) 8 weeks: 20 mg/day (2 capsules) 2 weeks: 10 mg/day (1 capsule)

ABBREVIATIONS

AE	Adverse Event/Adverse Experience
CCCC	Case Comprehensive Cancer Center
CFR	Code of Federal Regulations
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSTC	Data, Safety and Toxicity Committee
DSMP	Data and Safety Monitoring Plan
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
IDS	Investigational Drug Services Pharmacy
IRB	Institutional Review Board
N	Number (typically refers to participants)
NCI	National Cancer Institute
NIH	National Institutes of Health
PDA	Pancreatic Ductal Adenocarcinoma
PHQ-9	Patient Health Questionnaire
PI	Principal Investigator
QA	Quality Assurance
QIDS	Quick Inventory of Depressive Symptoms
SAE	Serious Adverse Event/Serious Adverse Experience
SOC	Standard of Care
UH	University Hospitals

TABLE OF CONTENTS

1.0 INTRODUCTION
1.1 Background Information
1.2 Rationale for Proposed Study
1.3 Correlative Studies
1.4 Potential Risks and Benefits

2.0 OBJECTIVES
2.1 Primary Objective
2.2 Secondary Objective(s)
2.3 Exploratory Objectives(s)
2.4 Endpoints/Outcome Measures

3.0 STUDY DESIGN
3.1 Study Characteristics
3.2 Number of Subjects
3.3 Replacement of Subjects
3.4 Expected Duration of Treatment and Subject Participation

4.0 SUBJECT SELECTION
4.1 Inclusion Criteria
4.2 Exclusion Criteria
4.3 Inclusion of Women and Minorities

5.0 REGISTRATION

6.0 TREATMENT PLAN
6.1 Treatment Regimen Overview
6.2 Criteria for Removal from Study
6.3 Duration of Follow-Up

7.0 DOSE DELAYS / DOSE MODIFICATIONS

8.0 ADVERSE EVENTS AND POTENTIAL RISKS
8.1 Escitalopram Adverse events
8.2 Definitions
8.3 Serious Adverse Event Report Form
8.4 Reporting Procedures for Serious Adverse Event
8.5 Serious Adverse Events and OnCore™
8.6 Data Safety Toxicity Committee
8.7 Data and Safety Monitoring Plan

9.0 PHARMACEUTICAL INFORMATION
9.1 Investigational Agent(s)

10.0 EXPLORATORY/CORRELATIVE
10.1 Special Assays or Procedures
10.2 Specimen Preparations, Handling and Storage

11.0 STUDY PARAMETERS AND CALENDAR
11.1 Study Parameters
11.2 Calendar

12.0 MEASUREMENT OF EFFECT

13.0 RECORDS TO BE KEPT/REGULATORY CONSIDERATIONS
13.1 Data Reporting
13.2 Regulatory Considerations

14.0 STATISTICAL CONSIDERATIONS

REFERENCES

APPENDICES

APPENDIX I
ECOG / Karnofsky Performance Status Criteria

APPENDIX II
Subject Diary (pill, injectable, etc)

APPENDIX III
Clinical Medication Compliance Form for Investigational Studies

APPENDIX IV
QIDS-SR_{16}

APPENDIX V
Fact –Hep (Version 4)

APPENDIX VI
FIBSER Scale

APPENDIX VII
PHQ-9

APPENDIX VIII
Tumor Profile Assessment

1.0 Introduction

1.1 Background Information

The diagnosis of major depressive disorder (MDD) is typically made clinically according to the DSM-5 diagnostic criteria. The prevalence in the general United States population is 6% [1], and the lifetime risk is about 17% [2]. The risk is in fact lowest in older patients, with a point prevalence around 1% in individuals over 65 years [3]. Thus, the high rate of depression in patients with cancer is striking, particularly since it is so widely undertreated. The rate of depression in patients diagnosed with cancer is increased by 4-fold over the general population by some estimates, with a point-prevalence as high as 12% [4]. This has major implications for patients and their families. The comorbid incidence of depression in cancer patients leads to worse survival, longer and more frequent hospitalizations, decreased treatment compliance, and worse quality of life [5, 6]. In most instances, depressive symptoms develop within the first year of a cancer diagnosis[7], yet, unfortunately almost 73% of eligible patients do not receive appropriate therapy[8]. Other studies have demonstrated that almost all inpatients [9], and 50% of outpatients with cancer have undiagnosed depression [10]. There is a growing body of evidence that targeted interventions in cancer patients can improve depressive symptoms and quality of life, including behavioral therapy [11] and antidepressants[12-18]. Therefore, in light of the high risk of depression in cancer patients, the low risk of treatment, and the potential benefit of antidepressant treatment, there is a strong argument to be made in favor of broad depression screening. Even further, the evidence supports a line of investigation to examine the utility of anti-depression treatment as a new standard of care in patients with high-risk cancers. Herein, we propose testing the use of anti-depressants in all patients with localized pancreatic and related cancer, with the primary goal to prevent worsening depression at 12 weeks.

1.2 Rationale for Proposed Study

A recent randomized study of patients with head and neck cancer offers pioneering insights into the potential benefit of this approach. Lydiatt et al. randomized 148 patients with head and neck cancer of varying stages to escitalopram (Lexapro, an SSRI, 20 mg/day, except 10 mg/day during week 1) or placebo. Patients were included in the study if they were not depressed or had mild depression at the start of treatment, as indicated by a QIDS-SR score < 11. There were minimal adverse effects in both treatment groups. Depression was more common at later time points in the placebo group compared to the treatment group (24% vs. 10%), and the benefit persisted in a multivariable analysis. Thus, the number needed to treat to prevent a single case of depression was just 7 people. Additionally, there was better quality of life noted in patients in the treatment group at every time point in the study, and as early as after 1 month of treatment. Based on this study, we will administer the same dose of study drug. We will administer escitalopram at 10 mg/day for 2 weeks, 20 mg/day for 8 weeks, and 10 mg/day for the final 2 weeks (ramp up and ramp down periods) for a total of 12 weeks.

Due to the fact that depression is more common in pancreatic cancer than any other cancer type (40% of patients), depression symptoms overlap with presenting signs and symptoms of pancreatic cancer, and depression screening is currently not standard practice for patients undergoing treatment for pancreatic cancer, the QIDS survey (nor any other tool) has been validated in the

pancreatic cancer population, we will include all patients with localized pancreatic cancer in this trial, regardless of depression score. **Importantly, patients noted to have either severe depression per the QIDS screen or suicidal ideation will be referred to a study psychiatrist for a more thorough evaluation and care plan with consideration of starting a second pharmacologic agent. However, these patients will continue on study in a blinded fashion taking placebo or escitalopram.**

We will look at QIDS scores at 12 weeks as the primary study outcome. We hypothesize that patients receiving escitalopram will have a lower rate of moderate (or worse) depression, compared to patients receiving placebo.

QIDS (Quick inventory of depressive symptomatology)

QIDS is a 16-item survey that addresses each of the nine symptom domains covered in the DSM-V criteria for Major depressive disorder (depressed mood, loss of interest or pleasure, concentration/decision making, self-outlook, suicidal ideation, energy/fatigability, sleep, weight/appetite change, and psychomotor changes) [19]. The tool is used both for depression screening, and to measure depression severity, and has been heavily validated against established surveys. Its effectiveness is proven. The tool is straight forward, and is administered in either a self-reported form (SR), or a clinician-rated (CR) form, and requires minimal training. The QIDS scores range from 0-27. Scores are interpreted as follows [20]:

0-5	No depression
6-10	Mild depression
11-15	Moderate depression
16-20	**Severe depression**
21-27	**Very severe depression**

In this study, we will be using the QIDS to measure the rate of depression at each time point, with the incidence of worsening depression at 12 weeks as a primary outcome. Patients with a QIDS score ≥16 at any time point will be referred to a psychiatrist for a more thorough evaluation and consideration for additional therapy.

PHQ-9

This survey has just 9 questions with respect to the past 2 weeks of life, and each question is scored on a 4-point scale: not at all = 0; several days =1; more than half the days = 2; and nearly every day = 3. Scores are added up to determine if patients have depression. The 9th question asks about suicidal ideation. The tool mirrors the 9 criteria in DSM V and has been extensively validated [21].

0-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Very severe depression

FACT-Hep (Quality of life survey)

The fact scales are quality of life surveys that can be administered by patients or by clinician/coordinators as an interview. The FACT-Hep has 27 general questions, and 18 questions that are specific to hepatopancreatobiliary cancer, for a total of 45 questions. The general questions span four domains: physical, social/family, emotional, and functional well-being [21]. It requires less than 10 minutes to complete and targets the 6th grade reading level. Answers are given in the form of a five-point Likert scale as follows: 0 (Not at all), 1 (A little bit), 2 (Somewhat), 3 (Quite a bit), and 4 (Very much). Points are re-calibrated and compiled, such that high scores indicate a higher quality of life (opposite to the grading scheme of QIDS or PHQ-9 where a high score reflects depression). The additional 18 questions in the FACT-Hep address a subscale to estimate hepatopancreatobiliary quality of life issues. From these 45 answers, several different scores can be computed, including a FACT-global score (G), a hepatobiliary cancer subscale (HCS) score, a FACT-Hep total score (a sum of the prior two scores), and a FACT-Hep Trial Outcome Score (TOI) which is a summary of the physical + functional + HCS scores. The FACT form has been validated for use in patients with advanced and localized pancreatic cancer [21-24].

1.3 Correlative Studies

The serotonin theory of depression is supported through clinical experience. Selective serotonin reuptake inhibitors (SSRIs) remain the most common class of medicines used to treat depression. Mechanistically, these drugs increase serotonin levels at brain synapses [25]. Tryptophan is the principal substrate for serotonin synthesis, and therefore, tryptophan breakdown may have biologic implications on clinical depression in patients with dysregulated tryptophan catabolism. We and others have demonstrated that the enzymes responsible for tryptophan metabolism are dysregulated in pancreatic cancer [26, 27]. Specifically, the enzymes that divert tryptophan into kynurenine and related metabolites are overexpressed, including IDO1, IDO2, and TDO (. This pathway effectively shunts tryptophan away from serotonin synthesis.

In this study, we will examine the expression of each of these tryptophan degrading enzymes in resected PDAs (25 of 46 patients in the trial are expected to have resected specimens for analysis). We will determine if a correlation exists between expression levels of these enzymes in the tumor and 1) depression at baseline, and 2) the development of depression in patients on trial. Additionally, plasma levels of specific tryptophan metabolites will be measured in patients at the start of treatment. Patients undergoing resection will have repeat levels taken 1-2 months after resection to determine how tumor burden impacts metabolite levels.

1.4 Potential Risks and Benefits

The study drug, escitalopram, is FDA approved for the treatment of depression. It is safe and well tolerated.

Potential Risks

Adverse side effects include:[44]
Nausea (15%)

Ejaculatory disorder (9%)
Insomnia (9%)
Diarrhea (8%)
Dry mouth (6%)
Somnolence (6%)
Dizziness (5%)
Hyperhidrosis (5%)
Fatigue (5%)
Rhinitis (5%)
Influenza-like symptoms (5%)

Benefits

Potential benefits of the study for the patient include prevention of depression, improved quality of life, and improved cancer survival. For the field, the study may demonstrate that prophylactic anti-depressant use is beneficial and provide a justification for a larger, phase III trial.

2.0 Objectives

Anti-depressants have been shown in multiple studies to be beneficial in cancer patients [29-33]. They reduce depressive symptoms and improve quality of life. Moreover, anti-depressants have been shown in randomized trials of breast cancer, melanoma, and head and neck cancer to reduce the development of depression in non-depressed cancer patients [34-36]. In this trial, we will test the role of anti-depressants in patients with localized pancreatic and periampullary cancer receiving neoadjuvant therapy. It has also been shown that treating depression can impact survival in cancer patients [37, 38]. Additionally, depressed pancreatic cancer patients have a worse survival [39]. Therefore, anti-depressants may also have implications for cancer treatment.

2.1 Primary Objective

To obtain preliminary evidence of the efficacy of daily escitalopram in reducing depression in patients with localized pancreatic or periampullary cancer receiving neoadjuvant therapy. The primary endpoint will be a reduction in the rate of depression at 12 weeks using a QIDS survey.

2.2 Secondary Objectives

- To determine depression rates in patients with resected pancreatic cancer at baseline and at 12 weeks.
- To determine if daily escitalopram improves the quality of life in patients with localized pancreatic and periampullary cancer.
    - To determine if daily escitalopram improves survival in patients with resected pancreatic cancer.
    - Study tissues and serum to determine if molecular markers of the serotonin-tryptophan-kynurenine pathway are associated with depression scores.
    - Study tissues and serum to determine if molecular markers of the serotonin-tryptophan-kynurenine pathway are associated with the efficacy of anti-depressants in patients with pancreatic cancer.

- Test for an association between tryptophan intermediates and immune profile in tumors and blood of patients with pancreatic cancer.

2.3 Exploratory Objective

We will also examine the impact of IDO2 polymorphisms in depression rates and response to anti-depressants.

2.4 Endpoints/Outcome Measures

Endpoints will include depression, quality of life, survival endpoints, and biomarkers.

Primary:

The primary outcome measure will be depression rates, based on answers from the QIDS form. Depression is reflected by a score ≥ 11 (moderate depression or worse).

Secondary:

The secondary outcome measures will include:

- Quality of life, as measured by the FACT-Hep total score, and FACT-Hep subscores.
- Measurements of overall survival

Exploratory:

Exploratory endpoints include:

- genetic biomarkers
- tissue biomarkers of resected specimens
- tissue biomarkers in the plasma or blood
- early PDA recurrence or clinical evidence of disease after resection or radiographic progression in patients who have not yet had surgery (early recurrence is defined as progression of disease within 8 months after the start of systemic chemotherapy)

3.0 Study Design

This trial is a phase II, prospective, randomized, placebo controlled trial, evaluating escitalopram (vs. placebo) in patients with localized pancreatic or periampullary cancer.

3.1 Study Characteristics

Patients may be non-depressed or depressed. Those who are severely depressed according to the Quick Inventory of Depression Survey (QIDS ≥16 points) will be referred to a psychiatrist for further evaluation and possibly additional therapy, based on clinical judgement. The study will be started at University Hospitals Cleveland Medical Center with the possibility that it can be opened at alternative sites if needed for patient accrual.

At the time of study enrollment, the treating physician must have the intent to treat the patient with 12 weeks of neoadjuvant chemotherapy as standard of care cancer treatment. For this study, patients will be randomized in a 1:1 ratio to receive escitalopram or placebo using a randomization table prepared by the study statistician. This randomization table will be shared by the statistician only with the Investigational Drug Services Pharmacy (IDS) personnel and will detail for all 55 patients/study IDs whether that patient is to receive escitalopram or placebo. Each patient will be

assigned a study number, in sequential order, only after all eligibility criteria have been confirmed by the study coordinator, treating physician (Investigator or Co-investigator) involved in the case, and by a member of the Clinical Trials Unit's Quality Assurance department.

It is possible that burden of disease could influence mood. Therefore, patients will also be stratified according to whether they have resectable disease or locally advanced disease (borderline resectable or unresectable) according to NCCN criteria. A pancreatic surgeon (PI or Co-Investigator) will determine this status using the Tumor Profile Assessment (see Appendix VIII). The Tumor Profile Assessment is to be filled out by the PI or by the Co-investigator prior to randomization.

3.2 Number of Subjects

The clinical trial is powered for 46 patients, including 23 patients in each arm (escitalopram and placebo). However, 55 patients will be enrolled, in order to achieve the desired number due to expected attrition both before and after initiation of therapy or due to removal from study due to reasons noted in Section 6.2.

3.3 Replacement of Subjects

Patients will not be replaced.

3.4 Expected Duration of Treatment and Subject Participation

Patients will be treated with escitalopram or placebo for 12 weeks. An end of treatment visit and assessment will be conducted at Week 13 and another at Week 25. After Week 25, patients will be followed every three months for three years for treatment details and to document disease and survival status.

The typical course of neoadjuvant therapy for resectable or unresectable patients is virtually always ≥ 12 weeks. Patients whose cancer progresses during that time will remain on study unless the patient meets criteria for removal from study as noted in Table 7.1 or if the patient becomes unable to swallow oral medications.

The first day of medication will be considered day = zero with respect to the depression (QIDS-SR, PHQ-9) and QOL (FACT-Hep) survey time points (Survival analyses however will be dated back to the date of consent). Surveys will be performed biweekly for 12 weeks. The FACT-Hep will be administered at a slightly less frequent interval (once per month). In the follow-up phase, beginning after Week 25, subjects will be followed for up to 3 years, for recurrence, treatment details, and survival information. Follow-up information will be obtained every 3 months.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

Subject's Name _____

Medical Record # _____

Research Nurse / Study Coordinator Signature:

_____

Date _____

Treating Physician [Print] _____

Treating Physician Signature: _____

Date _____

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment:

___ 4.1.1 Patients must have histologically or cytologically confirmed localized or locally advanced pancreatic ductal adenocarcinoma or other periampullary adenocarcinoma (bile duct, duodenal, ampullary)

___ 4.1.2 Patients must not currently be on an antidepressant, anti-anxiety, anti-bipolar, or anti-psychotic medicine

___ 4.1.3 Aged 18-80 years.

___ 4.1.4 ECOG PS score of 0-2

___ 4.1.5 Planned to have at least 12 weeks of neoadjuvant chemotherapy as standard of care cancer treatment

___ 4.1.6 No diagnosis of bipolar disease

___ 4.1.7 Willing to comply with all study procedures and be available for the duration of the study

___ 4.1.8 Patient must be mentally competent and must have the ability to understand and the willingness to sign a written informed consent document

___ 4.1.9 Patients must be able to speak English

4.2 Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment.

___ 4.2.1 Patients under the age of 18 or over age of 80

___ 4.2.2 Metastatic pancreatic or other periampullary cancer

___ 4.2.3 Resection of pancreatic cancer within the past year prior to study enrollment or planned surgery within the next 12 weeks

___ 4.2.4 Currently on an antidepressant, anti-anxiety, anti-bipolar or anti-psychotic medicine. Patients who have taken MAOI inhibitors within the past 6 months are excluded.

___ 4.2.5 Patients with a diagnosis of bipolar disease

___ 4.2.6 Patients with a history of seizure disorder

___ 4.2.7 Patients with a recent medical history of myocardial infarction or unstable heart disease

___ 4.2.8 Patients with a history of QTc prolongation or torsade de points, a baseline QTc interval of > 500ms, a history of drug-induced QTc prolongation or congenital long QT syndrome

___ 4.2.9 Patients with Child-Pugh score of B or C

___ 4.2.10 Patients with moderate to severe renal disease with a GFR < 45.

___ 4.2.11 Patients who cannot ingest oral medication

___ 4.2.12 Patients with any history of mania

___ 4.2.13 Patients with known allergy to escitalopram

___ 4.2.14 Patients who are pregnant or lactating

___ l.2.15 Patients who do not speak English

4.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for participation in this trial. Children (under 18) will be excluded. Note that escitalopram is safe and effective in the elderly [40].

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.
All subjects will be registered through University Hospitals Cleveland Medical Center and will be provided a study number by contacting the study coordinator listed on the cover page.

6.0 Treatment Plan

6.1 Treatment Regimen Overview

This interventional trial involves the administration of a safe and well-tolerated oral antidepressant. Patients will take escitalopram or placebo, at the standard dose, with a ramp-up and ramp-down interval, as previously described in a similar trial in head and neck cancer [18].

The schedule is as follows:

2 weeks: 10 mg/day (1 capsule)

8 weeks: 20 mg/day (2 capsules)

2 weeks: 10 mg/day (1 capsule)

Patients will come to the clinic on Day 1 and will be given a pill diary and enough blinded escitalopram/placebo for the first 2 weeks of the study. The patient will taught how/when to take the pills and how to complete the pill diary. The patients will be given pill bottles for Weeks 1-2. Patients will take their first dose of escitalopram/placebo and have blood drawn for serum metabolites at this visit (prior to dosing). The QIDS-SR depression survey, PHQ-9, FACT-Hep QOL and FIBSER Side Effect Questionnaires (see Appendices IV, V, VI and VII) will be completed. A member of the study staff will give the questionnaires to the patient to complete in a private area. The study staff member will remain with the patient during completion of the questionnaires to assist, if necessary, and to ensure that the patient is answering all questions on their own.

There will be study-related clinic visits scheduled for Days 15 and 71. On Day 15, patients will be given pill bottles for Weeks 3-10. On Day 71, patients will be given pill bottles for Weeks 11-12. The Week 11-12 pill diary along with any unused pills will be collected at the end of treatment clinic visit (Week 13, Day 85). All other visits will be conducted via phone call from the study staff every two weeks beginning on Day 8. Phone visits will be conducted on Days 8, 22, 36, 50, 64 and 78 (+/- 7 days). However, if a patient's scheduled chemotherapy-related visit, clinic visit or hospital visit for any other reason happens to fall on (or within the 7 day window of) a planned study visit, the visit may be conducted in person with study staff. During these visits (phone or in-person), the study staff will perform a toxicity assessment and ask questions to determine if the patient is being compliant with taking the pills and completing the pill diary. The study staff member will verbally conduct the QIDS-SR, PHQ-9, and FIBSER with the patient and record the patient's answers and the FACT-Hep will be given directly to the patient to complete (if not done over the phone). The FACT-Hep will be performed monthly on Days 1, 22, 50 78, and 85.

<u>Unblinding Procedures:</u>

- Patients will be unblinded if study drug is discontinued for the Adverse Events of Special Interest (hemorrhage, suicidal ideation and mania) as described in Table 7.1.
- Patients will be unblinded if study drug is discontinued due to Grade 4 hyponatremia as described in Table 7.1.

- Patients will be unblinded if they meet the criteria for removal from study as defined in Section 6.2.
- Patients will be unblinded at the time of their Day 85 (Week 13) end of treatment visit.

Patients will be unblinded by IDS staff as outlined in the Unblinding Manual. Patients who are unblinded before they complete all study visits will be asked to continue to have study-related phone calls with study staff and complete all study-related questionnaires. Patients who are unblinded prior to the end of treatment visit and undergo tumor resection will be required to have the research tissue sample and post-surgery research blood samples taken.

An assessment of depression will be made by the treating physician. Based on the assessment, patients who received escitalopram may be given the option of continuing the medication either under the supervision of their medical oncologist or primary care provider. If this occurs, the patient will obtain escitalopram from commercial supply at the dose prescribed by the patient's medical oncologist, primary care physician or other provider.

6.2 Criteria for Removal from Study

Withdrawal Visit/Discontinuation of Therapy
In the absence of treatment delays due to adverse events, treatment may continue for 12 weeks or until one of the following criteria applies:

- Patient misses more than four consecutive weeks of escitalopram.
- Intercurrent illness that prevents further administration of treatment or patient inability to swallow escitalopram/placebo capsules,
- The investigator considers it, for safety reasons, to be in the best interest of the patient.
- Unacceptable adverse event(s):

  -NCI CTCAE version 5.0 Grade 2 or higher hemorrhage that occurs within the first four weeks of treatment
  -NCI CTCAE version 5.0 Grade 4 suicidal ideation
  -NCI CTCAE version 5.0 Grade 3 or higher mania
  -NCI CTCAE version 5.0 Grade 4 hyponatremia

  Patients who experience severe depression will be referred to a psychiatrist. They will also continue, if agreeable, on the study and with scheduled surveys according to the defined schedule (QIDS, PHQ-9, FACT-Hep, FIBSER).

  Patients will be withdrawn if they are deemed at high risk for suicide or if they wish to voluntarily withdraw from the study.

- Patient decision to withdraw from treatment (partial consent) or from the study (full consent),
- Pregnancy during the course of the study
- Death

- The Principal Investigator and/or the Case Comprehensive Cancer Center Data Safety Toxicity Committee (DSTC) reserve the right to temporarily suspend or prematurely discontinue this study if unacceptable study-related risks are identified. The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

Handling of Participant Withdrawals and Participant Discontinuation of Study Intervention

Patients who withdraw from treatment will have an end of study visit as described in Section 6.3. They will continue to be followed with surveys at the scheduled intervals and for cancer-specific outcomes, unless patients refuse this follow-up by withdrawal of consent.

6.3 Duration of Follow-Up

End of Treatment Study Procedures

An end of treatment visit will be conducted on Day 85 (Week 13). This will be a clinic visit and will include a physical exam, collection of pill diary and any unused pills, toxicity assessment, QIDS-SR, PHQ-9, Fact-Hep and FIBSER. The patient's disease and treatment status will also be assessed.

During Week 25 (12 weeks after the end of treatment), a phone visit will be conducted which will include a toxicity assessment, QIDS-SR, PHQ-9, Fact-Hep and FIBSER. Patients who screen above 11 on the QIDS-SR or above 9 on the PHQ-9 will be referred by the study team to a social worker, who will then conduct their own assessment and make appropriate referrals to psychiatry if necessary. Patients who give an affirmative reply to Question 12 on the QIDS-SR or 9 on the PHQ-9 indicating thoughts of suicide, will be referred to Seidman Psychiatry Service for evaluation (please see Section 7.0).

Post-treatment/Follow-Up

Patients will call the research coordinator, their doctor, or the study PI if they experience depression-related symptoms.

Long Term/Survival Follow-up

After the Week 25 visit, cancer-specific information will be obtained for three years to assess disease and survival status. The information will be obtained every three months either by a review of the patients' medical record or by phone. Patients who undergo tumor resection after completion of the study will have tumor and blood samples collected for research studies.

7.0 Dose Delays/Dose Modifications

The starting dose will be one pill (10mg of escitalopram/placebo) during Weeks 1 and 2 followed by two pills daily (20mg of escitalopram/placebo) during Weeks 3-10 then one pill (10mg of escitalopram/placebo) during Weeks 11-12. Drug toxicities will be assessed based upon responses to questionnaires and from entries on pill diaries every two weeks by the clinical staff during the scheduled phone calls or in-person visits. There will be no dose reductions. Drug will be discontinued for the Adverse Events of Special Interest (hemorrhage, suicidal ideation and mania)

and for Grade 4 hyponatremia as described in Table 7.1. Drug may also be discontinued, at the discretion of the treating physician, for other adverse events determined by the PI to be related to escitalopram/placebo. If the event takes place in the first four weeks of starting treatment, the patient will be removed from study and will not be followed.

Patients who discontinue drug for any reason will continue to complete all questionnaires as outlined on the Study Calendar. The study team will make every effort to ensure that patients stay on schedule.

Table 7.1 Criteria for dosing delays and re-initiation of treatment due to study drug-related toxicity

CTCAE Grade* *Patient report or from any assessment scale*		**Dose Discontinuation Guidelines**
Hemorrhage (any site)	Grade 1: Mild symptoms; intervention not indicated Grade 2: Moderate symptoms; intervention indicated Grade 3: Transfusion indicated; invasive intervention indicated; hospitalization Grade 4: Life-threatening consequences; urgent intervention indicated	Grade 2 or greater: Discontinue drug, inform treating physician and PI immediately upon discovery. (if this happens within first 4 weeks remove patient from study)
Suicidal ideation**	Grade 1: Increased thoughts of death but no wish to kill oneself Grade 2: Suicidal ideation with no specific plan or intent Grade 3: Specific plan to commit suicide without serious intent to die which may not require hospitalization Grade 4: Specific plan to commit suicide with serious intent to die which requires hospitalization	Grade 1-3: inform treating physician immediately upon discovery Grade 4: discontinue drug and remove from study. See Table 7.2
Mania	Grade 1: Mild manic symptoms (e.g., elevated mood, rapid thoughts, rapid speech, decreased need for sleep) Grade 2: Moderate manic symptoms (e.g., relationship and work difficulties; poor hygiene)	Grade 3-4: discontinue drug and remove from study, notify treating physician and PI immediately.

	Grade 3: Severe manic symptoms (e.g., hypomania; major sexual or financial indiscretions); hospitalization not indicated; new onset Grade 4: Life-threatening consequences, threats of harm to self or others; hospitalization indicated	
Hyponatremia	Grade 1: <LLN - 130.0 mmo/L Grade 2: 125-129 mmol/L and asymptomatic Grade 3: 125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms Grade 4: <120 mmo/L; life-threatening consequences	Grade 4: discontinue drug and remove from study.
*CTCAE Version 5.0 **Please see safety guidelines section below regarding patients exhibiting suicidal ideation		

Safety Assessment

Patients will not be allowed to participate or will be withdrawn if at any point in the trial they are found to be at high risk for suicide. Patients who provide an affirmative response (checks 1, 2 or 3) on Question 12 of QIDS will be referred and evaluated by a UH/Seidman Psychiatrist to assess whether high risk for suicide is present. Patients who are severely or moderately severely depressed by QIDS (≥16) or PHQ-9 greater than 14 will be referred and evaluated by a UH/Seidman psychiatrist. They will not be discontinued from the trial, but may be offered additional therapy as part of standard of care, according to the judgement of the evaluating psychiatrist.

For a referral to a Psycho-Oncology Provider call [redacted] or email [redacted], [redacted]

Table 7.2 Suicidal Ideation Safety Guidelines

Response to Question 12 on QIDS-SR*	**Response to Question 9 on the PHQ-9**	**Action to be taken**
0	0	No action
1	1	Immediately inform treating physician and PI*

2	2	Immediately inform social worker to perform assessment or send patient to ED (also inform treating physician and PI)*
3	3	Immediately inform social worker to perform assessment or send patient to ED (also inform treating physician and PI)*

***** If positive response discovered via phone assessment, clinical team must be informed within 4 hours. If a patient is at acute risk for self-harm, hospital/system suicide safety plan will be followed.

8.0 Adverse Events and Potential Risks

8.1 Escitalopram

Adverse side effects include:[44]
Nausea (15%)
Ejaculatory disorder (9%)
Insomnia (9%)
Diarrhea (8%)
Dry mouth (6%)
Somnolence (6%)
Dizziness (5%)
Hyperhidrosis (5%)
Fatigue (5%)
Rhinitis (5%)
Influenza-like symptoms (5%)

Please refer to the escitalopram package insert for a comprehensive list of adverse events.

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

The measurement of side effects of escitalopram in not an endpoint of this study and escitalopram has been studied extensively in patients [28, 41-43]. This drug has also been studied as prophylactic antidepressant in the cancer populations[18]. All patients enrolled to this study will be receiving chemotherapy at the time of treatment and will be under clinical care during this interval. Adverse events attributed to chemotherapy and/or underlying disease will not be recorded for this study.

Akathisia, or restlessness, is a serious but uncommon side effect, which patients will be alerted to report. Other common side effects typically go away on their own. Patients will be educated on possible symptoms, as is routinely done when patients are started on an anti-depressant off-of trial. They will contact the PI if the symptom becomes debilitating and referred to psychiatry for consideration of removal from the study.

Suicidal ideation will be queried every 2 weeks and prompt an immediate referral to psychiatry.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. 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.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  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.

- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic

bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events, (both serious and non-serious as defined in previous sections) observed by the study staff or reported by the subject that are determined to be related or possibly related to escitalopram/placebo which occur after the initiation of escitalopram/placebo are fully recorded in the subject's medical record and reported according to AE reporting policies of the IRB of record. Adverse events attributed to chemotherapy and/or underlying disease will not be recorded for this study. Source documentation must be available to support all adverse events.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **5.0** will be utilized for AE reporting.

An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.

- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.2.4 Adverse Events of Special Interest

The following adverse events must be recorded, evaluated, and reported according to reporting policies of the IRB of record. Procedures related to these events will be followed as noted in Tables 7.1 and 7.2. Events are graded using CTCAE v5.0.

- Serious bleeding event (Grade 2 or greater). Will prompt discontinuation of escitalopram or placebo and removal from study.
- Mania. Symptoms consistent with mania will prompt referral to psychiatry.
- Suicidal ideation. Patients will be evaluated for suicidal ideation every 2 weeks using the QIDS and referred to psychiatry if present.

8.3 SAE Report Form

SAEs (including AEs of special interest, as applicable) related or at least possibly related to escitalopram/placebo will be recorded on the FDA Form 3500A (MedWatch for Industry Form FDA 3500A –Mandatory Reporting) but should only be reported as instructed below. This form can be found at the following link: https://www.fda.gov/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting

The electronic FDA SAE reporting forms should not be used.

The PI will evaluate all SAEs for relationship to study participation and report to IRB of record per applicable reporting policies.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events determined to be related or possibly related to escitalopram/placebo will be reported that occur from the initiation of escitalopram/placebo on Day 1 until the Week 25 study visit. Adverse events both serious and non-serious, and deaths that occur during this period will be recorded in the source documents and reported according to AE reporting policies of the IRB of record. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.4.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events related to escitalopram/placebo to the Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - Jordan Winter, MD, Jordan.winter@uhhospitals.org

- The Lead Site Principal Investigator will review the SAE and report the event to external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events related to escitalopram/placebo that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

8.5 SAEs and OnCore

- All SAEs related or possibly related to escitalopram/placebo will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that all SAEs related to escitalopram occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.

9.1 Investigational Agents

9.1.1 Name of Agent Escitalopram

Other Names: Lexapro

Product description: Escitalopram and placebo will be supplied as 10 mg capsules

Formulation, Packaging and Labeling: All aspects of drug and placebo manufacturing, preparation, packaging, and labeling will be managed by Buderer Drug Co. Escitalopram will be supplied as a 10mg oblong white tablet, commercially manufactured pharmaceutical by Aurobindo, supplied by Buderer Drug, over-encapsulation in a #1 dark blue capsule. Twenty (20) capsules placed into a labeled child resistant prescription vial. Eight (8) bottles will be supplied for each patient. Placebo is a white capsule containing microcrystalline cellulose, compounded (to match the weight of the escitalopram 10mg tablet) over-encapsulation into a #1 dark blue capsule. Twenty capsules placed into a labeled child resistant prescription vial. Eight (8) bottles will be

supplied for each patient. A batch will be prepared every 180 days or sooner as required. Bottles will be labeled with the patient's study number, blinded ID (B or D) and drug storage information.

Storage requirements and stability: Stability will be for six months duration, and stable at room temperature 15°-30°C (59°-86°F).

Route of administration: There will be no mixing or added preparation by pharmacists, technicians or nurses once the finished clinical supply is received from Budrer. Patients will take escitalopram or placebo at the standard dose, with a ramp up and ramp down interval as follows:

2 weeks: 10 mg (1 capsule)

8 weeks: 20 mg (2 capsules)

2 weeks: 10 mg (1 capsule)

Drug Procurement: Escitalopram and placebo for this study will be obtained from Buderer Drug Co.

Drug Accountability: Orders will be placed by study staff and product shipped by Buderer and stored at University Hospital's Investigational Drug Services Pharmacy at room temperature for the duration of the trial. Patients will be given one bottle of escitalopran/placebo upon study initiation for the first two weeks on study. At Day 15 patients will be given six bottles for the next eight weeks and at Day 71 patients will be given one bottle for the remainder of the study.

Investigational Drug Services Pharmacy is responsible for maintaining accurate dispensing records of the study drug.

Drug Destruction:
At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to destruction of unused study drug. All unused investigational product/placebo will be destroyed at the site per institutional policy. Drug destroyed on site will be documented in the study files.

10.0 EXPLORATORY or CORRELATIVE STUDIES

10.1 Serum Metabolites
10.1.1 Background

Tryptophan is the principal substrate for serotonin synthesis, and therefore, tryptophan breakdown may have biologic implications on clinical depression in patients with dysregulated tryptophan catabolism. We and others have demonstrated that the enzymes responsible for tryptophan metabolism are dysregulated in pancreatic cancer [26, 27]. Specifically, the enzymes that divert tryptophan into kynurenine and related metabolites are overexpressed, including IDO1, IDO2, and TDO. This pathway effectively shunts tryptophan away from serotonin synthesis.

10.1.2 Rationale
We will determine if a correlation exists between expression levels of these enzymes in the tumor and 1) depression at baseline, and 2) the development of depression in patients on trial. Additionally, serum levels (or plasma levels are a suitable alternative) of specific tryptophan metabolites will be measured in patients at the start of treatment. Patients undergoing resection will have repeat levels taken 1-2 months after resection to determine how tumor burden impacts metabolite levels.

10.1.3 Collection of Specimens
Blood samples will be collected on Day 1. For patients who undergo resection, samples will also be collected between one and three months after surgery to account for half-life of metabolites and determine if tumor burden influences metabolite levels. Approximately 30 ml blood will be collected into three red top tubes from each patient via venipuncture or port.

10.1.4 Handling of Specimens
Samples will be left at room temperature for two hours to coagulate. Samples will then be centrifuged at 1000 g for 15-20 minutes and serum collected.

All specimens will be handled according to universal precautions. They will be stored in the Winter lab. Samples will be labeled with the patient's study number and will not contain any patient identifiers.

10.1.5 Analytical Laboratory
Once samples are collected, contact [redacted] to inform her that samples are ready for pick-up and delivery to the Winter lab.

[redacted]

Wolstein Research Building (WRB [redacted])
Lab phone #: [redacted]

10.1.6 Methods
- ELISA kits should be brought to room temperature prior to assays (at least 30 minutes)
- All samples will be run fresh
- ELISAs will be carried out according to kit protocol. All necessary reagents are provided within kits.
    - Kynurenine ELISA - Biovision (E4629-100)
    - Melatonin ELISA - Biovision (E4630-100)
    - Serotonin ELISA - Biovision (E4294-100)

  (ELISA kits are suited for either plasma or serum).

- Standards should be run in triplicate
- Optimal dilution factor should be determined for human subjects (1:10 for mice)
- Samples are analyzed using a microplate reader, absorbance (450 nm)

10.2 Tissue Specimen Assays

10.2.1 Background

The serotonin theory *of depression* is supported through clinical experience. Selective serotonin reuptake inhibitors (SSRIs) remain the most common class of medicines used to treat depression. Mechanistically, these drugs increase serotonin levels at brain synapsis [25]. Tryptophan is the principal substrate for serotonin synthesis, and therefore, tryptophan breakdown may have biologic implications on clinical depression in patients with dysregulated tryptophan catabolism. We and others have demonstrated that the enzymes responsible for tryptophan metabolism are dysregulated in pancreatic cancer [26, 27]. Specifically, the enzymes that divert tryptophan into kynurenine and related metabolites are overexpressed, including IDO1, IDO2, and TDO. This pathway effectively shunts tryptophan away from serotonin synthesis.

10.2.2 Rationale

In this study, we will examine the expression of each of these tryptophan degrading enzymes in resected PDAs (25 of 46 patients in the trial are expected to have resected specimens for analysis). We will determine if a correlation exists between expression levels of these enzymes in the tumor and 1) depression at baseline, and 2) the development of depression in patients on trial.

10.2.3 Collection of Specimens

Patients undergoing resection after completion of the study will have tumors collected and assayed for IDO1, IDO2, and TDO2 expression. This will be performed on sections prepared from resected specimens. Blocks will be requested from pathology and pulled for each patient and immunohistochemical staining will be performed.

10.2.4 Handling of Specimens

All specimens will be handled according to universal precautions. They will be stored in paraffin embedded blocks in the Winter lab. Samples will labeled with the patient's study number and will not contain any patient identifiers. Samples will be stored for up to two years.

10.2.5 Analytical Laboratory

Once samples are collected, contact [redacted] to inform her that samples are ready for pick-up and delivery to the Winter lab.

[redacted]

Wolstein Research Building (WRB [redacted])
Lab phone #: [redacted]

10.2.6 Methods

Collected tumors will be assayed for ID01, ID02 and TD02 expression. We will test to see if expression of these enzymes correlate with depression scores or response to treatment.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 Study Parameters

11.1.1 Screening Evaluation:

The following must be completed within 28 days of initiating treatment:

- Informed consent
- Medical history
- Review of current medications
- Physical exam to include head and neck, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, cognitive and cutaneous systems
- Electrocardiogram
- Pregnancy test for patients of child-bearing potential (ie. women who are pre-menopausal or not surgically sterile)
- ECOG

The following must be completed Week 1, Day 1 (clinic visit):

- ECOG performance status
- Blood collection for plasma metabolites
- FIBSER Side effect questionnaire
- QIDS-SR baseline survey for depression
- PHQ-9 Patient Health Questionnaire
- FACT-Hep quality of life survey
- Provide supply of blinded escitalopram/placebo and pill diary to patient
- Explain study procedures including dosing, completion of pill diary and questionnaires
- Toxicity assessment

11.1.2 Treatment Period (these visits have window of +/- 7 days)

Daily:

- Escitalopram (Lexapro) is an SSRI (1 capsule) 10mg/ day for 2 weeks followed by Escitalopram (Lexapro) is an SSRI (2 capsules) 20mg/ day for 8 weeks followed by Escitalopram (Lexapro) is an SSRI (1 capsule) 10mg/ day for 2 weeks
- Patients randomized to the placebo arm will receive the same dose schedule but no active drug.
- Pill diary.

Every 2 weeks (phone call or clinic visit):

- QIDS-SR
- PHQ-9
- FIBSER
- Toxicity assessment
- Review drug diary compliance

Weeks 3 and 11 (clinic visit)

- Turn in unused pills and pick up new supply

- Review pill diary and pick up new diary

Once per month (phone call or clinic visit):

- FACT-Hep

Week 13 (end of treatment clinic visit):

- Collect pill diary
- Medical History
- Physical exam
- ECOG Performance Status
- QIDS-SR (via phone or mail)
- PHQ-9
- FIBSER (via phone or mail)
- FACT-Hep
- Toxicity Assessment

Week 25 (phone call or clinic visit)

- QIDS-SR (via phone or mail)
- PHQ-9
- FIBSER (via phone or mail)
- FACT-Hep
- Toxicity Assessment

Follow-up (every 12 weeks, via EMR review, patient visit or phone call)

- Assessment of disease and survival status, treatment details
- Tissue will be obtained from patients who undergo resection and stored in paraffin embedded blocks
- Patients who undergo tumor resection will have blood samples drawn for plasma metabolites 1-3 month after surgery

11.1.2 Study Calendar

Assessments	**Screening** (within 28 days before treatment)	**D1**	**D8[5] Wk2**	**D15 Wk 3** (increase to 20mg)	**D22[5] Wk4**	**D36[5] Wk6**	**D50[5] Wk8**	**D64[5] Wk 10**	**D71 Wk11** (decrease to 10mg)	**D78[5] Wk12**	**D85[5] Wk13** (end of treatment)	**Wk 25**	**Follow-up: every 3 mos x 3 years[7]**	**1-3 mos after surgery** (if applicable)
Informed consent	√													
Medical history /physical[1]	√										√			
ECOG performance status	√	√									√			
ECG	√													
Pregnancy test	√													
Study visits*		√ clinic	√ phone	√ clinic	√ phone	√ phone	√ phone	√ phone	√ clinic	√ phone	√ clinic	√ phone		
Serum metabolites[2]		√												√[8]
Treatment escitalopram vs. placebo (10mg or 20mg) per day[3]		√	√	√	√	√	√	√	√	√				
Pill diary[4]		√	√	√	√	√	√	√	√	√	√			
Toxicity assessment		√	√[6]		√[6]	√[6]	√[6]	√[6]		√[6]	√	√[6]		
QIDS-SR (Depression)		√	√[6]		√[6]	√[6]	√[6]	√[6]		√[6]	√	√[6]		
PHQ-9 Health Questionnaire		√	√[6]		√[6]	√[6]	√[6]	√[6]		√[6]	√	√[6]		
FACT-Hep (Quality of Life)		√			√[,6]		√[,6]			√[6]	√[,]	√[6]		

FIBSER side effect questionnaire)		√	√,[6]		√[6]	√[6]	√[6]	√[6]		√[6]	√,	√[6]		
Tissue obtained if resection done													√	
Disease/ survival status/treatment details											√	√	√	

[1]History must include a review of current medications. Physical must include head and neck, pulmonary, cardiovascular, gastrointestinal, musculoskeletal, cognitive and cutaneous systems

[2]Collect 30ml in three 10ml red top tubes prior to dosing.

[3]Blinded escitalopram vs placebo is to be taken daily days 1 through 84 (10mg wks 1-2., 20mg wks 3-10, 10mg wks 11-12) unless dose reduction/drug discontinuation is required.

[4]Diary is to be completed daily by patients and reviewed with clinical study staff during study visits to confirm compliance. Patients are required to come to the clinic on Days 15 and 71 to pick up drug supply and new pill diary. Unused pills and final pill diary will be returned at the end of treatment visit (Day 85).

[5] +/- 7 days

[6]QoL assessments and Toxicity assessment will be completed with clinical study staff over the phone or in person if the patient's regular chemotherapy visit coincides with a study visit.

[7]Patients will continue to be followed for survival for three years or until deceased (whichever occurs first).

[8]Patients who undergo tumor resection will have repeat correlative plasma samples collected one to three months after surgery.

12.0 MEASUREMENT OF EFFECT

Efficacy will be defined as the prevention of incidents of moderate or greater depression defined as a QIDS-SR score greater than 11 at 12 weeks.

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore™ and Forte EDC Databases will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for accrual entry. OnCore™ is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. OnCore™ has the capability to facilitate study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification.

The investigators are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents must be completed in a neat, legible manner to ensure accurate interpretation of data. The investigators will maintain adequate case histories of study participants, including accurate case report forms (CRFs), and source documentation.

Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

Data Capture Methods

The University Hospitals Research Information System (REDCap) database will be used for this study to record clinical data and toxicity-related data.

Types of Data

Data will be maintained on paper source documents and entered into REDCap for data analysis. Captured data include patient medical history, laboratory values, treatment data and compliance, toxicity data, survival and outcome data, survey data, and radiographic data.

Study Records Retention

Data will be maintained for at least two years after closure of the study and final data analysis.

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the

subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

The study subjects will be assigned a unique study identification number that will be used on all study data forms, and other study records. Patient names, initials and/or hospital IDs will not be used as protocol identifiers. Randomization records will be maintained by the Seidman Cancer Center, Clinical Trials Unit Quality Assurance Team at a secure location at 6700 Euclid Ave. Cleveland, OH 44106.

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Hypotheses

The primary hypothesis is that the incidence of depression in patients with localized pancreatic and related cancer will be lower with treatment with escitalopram compared to placebo at 12 weeks.

14.2 Analysis Plans

The primary endpoint of the study is depression by QIDS at 12 weeks.

Depression

The primary outcome is moderate or greater depression defined as a QIDS-SR score greater than 11. All patients will have localized disease, but be stratified by extent of disease: resectable vs. unresectable, based on imaging and as determined by the PI Based on the Tumor Profile Assessment. Under Generalized Linear Model (GLM) framework, a modified Poisson model can be constructed as the working model to directly estimate the relative risk of depression at each measurement time through 12 weeks (Zou and Donner 2013). Measurement time will be treated as a categorical/ordinal variable to allow for differing risk of depression in controls at each time point. The model will adjust for baseline QIDS-SR score as a continuous covariate and the stratification variable. Generalized Estimating Equation (GEE) will be used to account for correlation among the 6 repeated post-randomization measurements through month 3 for each participant. A time by randomization assignment interaction variable will be included to allow for estimation of the relative risk at each measurement time. The primary interest is to compare the two treatment groups at 12 weeks. This comparison will be performed at the one-sided alpha=0.10 level.

Since the GEE estimates are only valid under the Missing At Random (MAR) assumption if the working correlation structure is correctly specified, missing dichotomous outcomes will be imputed using Multiple Imputation (MI) prior to analysis (Li et al 2006). Estimates using this method are consistent under the MAR assumption (Beunckens et al 2008).

Analytical Plan for PHQ-9 Outcome

PHQ-9 outcomes can be summarized into ordinal statistics or dichotomized variables, thus the same analytical procedure for QIDS outcomes can be adapted here. We expect the same statistical power for data analysis using a similar Generalized Linear Model (GLM) framework for depression risk estimation and correlation control using Generalized Estimating Equation (GEE). Therefore, detailed statistical power justification is omitted.

Equivalence of Results

Analyses using QIDS and PHQ-9 will be conducted separately. The results from them will be compared for equivalence of results purpose. The comparison will include directions of effective size, level of significance of the potential changes, and biological dispersion of estimations from both metrics.

Quality of life

The FACT-Hep will be utilized to assess quality of life at the pre-determined time intervals specified above. Longitudinal measurements of FACT-Hep scores will be modeled using mixed effects linear regression. Randomization assignment, time, and randomization by time interaction terms will be included in the model as fixed effects. An appropriate

correlation structure will be assumed for the residual covariance matrix to account for within-subject correlation. Groups will be compared with respect to average scores at 12 weeks using a linear contrast of model parameters. Missing data will not be imputed for this analysis.

Survival
Overall survival will be measured from the date of randomization to date of death or last follow-up, and adjusted for staging. The distribution of survival time will be estimated using the Kaplan-Meier method, and randomization groups will be compared using a stratified log-rank test.

The primary and secondary analyses will be performed on all randomized patients. Patients will be analyzed according to randomization assignment, regardless of the treatment actually received.

Treatment failures
Patients with high risk for suicide, suicide attempts, or a score of ≥ 16 points on the QIDS-SR at 12 weeks will be considered "treatment failures" and will be provided referrals for more optimal depression treatment throughout the duration of the study. Patient scores and adverse events will be reviewed by clinical study staff (RN or MD) within 24 hours of collecting information from patients to determine if additional action is needed per Section 7. Cases of suspected suicidal ideation will be reviewed within four hours as noted in Section 7, and study staff will immediately take action as appropriate upon review.

14.3 Sample Size Considerations

The primary objective of this study is to obtain preliminary evidence of efficacy of the treatment in preventing incident moderate or greater depression defined as a QIDS-SR score greater than 11 at 12 weeks. Assuming 23 subjects per arm and a true rate of depression in the control arm of 40%, we have 80% power to detect a difference if the true rate in treatment arm is 13.8% using a one-sided alpha of 0.10. Assuming an observed rate of 40% in the control arm, the upper limit of the 80% confidence interval for the risk ratio ranges from 0.56 when the observed treatment arm rate is 10% to 1.09 when the observed treatment arm rate is 25%. Any patient who has less than 65% compliance rate after four weeks of escitalopram/placebo (as determined during bi-weekly pill diary review) will be considered not evaluable and will be replaced. Any patient who experiences a serious adverse event that requires discontinuation of study drug within the first four weeks of treatment will be considered not evaluable and will be replaced.

To achieve a final sample size of 46 (23 per arm) at 12 weeks we will randomize 55 patients allowing for up to 15% attrition**.**

Replacement Policy
Patients will not be replaced. Based on prior experience, we anticipate that we can comfortably accrue 36 patients per year and complete the study within 2 years.

14.4 Evaluation of Safety

In light of the well reported safety of escitalopram, there will be no statistical aspect to safety review. We will closely measure side effects as part of this clinical trial, but will not specifically have this as a secondary endpoint, since escitalopram has been studied extensively in patients [28, 41-43], and even as a prophylactic antidepressant in the cancer population[18]. Standard toxicity recording will be performed through phone interviews at monthly intervals at a minimum, using the CTCAE 5.0 grading system.

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APPENDIX I

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Description	Percent	Description
0	Normal activity. Full 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% if 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 II

SUBJECT PILL DIARY

Subject Name _____Protocol # CASE6220 **Subject Study ID _____**

Weeks #: 1 and 2 ***(Days 1-14)***

INSTRUCTIONS FOR THE SUBJECT:

1. You will take one 10mg capsule of escitalopram/placebo each day. You should take your pill in the morning or evening. You may take the pill with or without food, as you wish.
2. Record the date, the number of tablets you took, and what time you took them.
3. If you have any comments or side effects please record them in the "Comments" column below.
4. If you have bleeding, please record in the "Bleeding" column below.
5. Please bring your pill bottle and this form to your physician when you come for your next appointment.
6. Please sign your name at the bottom of the diary.

Date	Day	# of 10mg pills and time taken	Comments	Bleeding **Type of bleeding**: nose bleed, cut that won't stop bleeding, bruising, blood in urine, red or black stool, Other (please describe) **State if:** Mild, Moderate, Severe
	(Wk 1) 1			
	2			
	3			
	4			
	5			
	6			
	7			
	(Wk 2) 8			
	9			
	10			
	11			
	12			
	13			
	14			

Subject's Signature: _____ Date: _____

SUBJECT PILL DIARY

Subject Name _____Protocol # CASE6220__ **Subject Study ID _____**

Weeks #: 3 through 10 ***(Days 15 through 70) Page 1***

INSTRUCTIONS FOR THE SUBJECT:

1. You will take two 10mg capsules of escitalopram/placebo each day. You should take your pill in the morning or evening. You may take the pill with or without food, as you wish.
2. Record the date, the number of tablets you took, and what time you took them.
3. If you have any comments please record them in the "Comments" column below.
4. If you have bleeding, please record in the "Bleeding" column below.
5. Please bring your pill bottle and this form to your physician when you come for your next appointment.
6. Please sign your name at the bottom of the diary.

Date	Day	# of 10 mg pills and time taken	Comments	Bleeding **Type of bleeding**: nose bleed, cut that won't stop bleeding, bruising, blood in urine, red or black stool, Other (please describe) **State if:** Mild, Moderate, Severe
	(Wk 3) 15			
	16			
	17			
	18			
	19			
	20			
	21			
	(Wk 4) 22			
	23			
	24			
	25			
	26			
	27			
	28			
	(Wk 5) 29			
	30			
	31			
	32			
	33			
	34			
	35			
	(Wk 6) 36			
	37			
	38			
	39			
	40			
	41			
	42			

Subject's Signature: _____ Date: _____

SUBJECT PILL DIARY

Subject Name _____Protocol # CASE6220__ **Subject Study ID _____**

Weeks #: 3 through 10 ***(Days 15 through 70) Page 2***

INSTRUCTIONS FOR THE SUBJECT:

1. You will take two 10mg capsules of escitalopram/placebo each day. You should take your pill in the morning or evening. You may take the pill with or without food, as you wish.
2. Record the date, the number of tablets you took, and what time you took them.
3. If you have any comments please record them in the "Comments" column below.
4. If you have bleeding, please record in the "Bleeding" column below.
5. Please bring your pill bottle and this form to your physician when you come for your next appointment.
6. Please sign your name at the bottom of the diary.

Date	Day	# of 10 mg pills and time taken	Comments	Bleeding **Type of bleeding**: nose bleed, cut that won't stop bleeding, bruising, blood in urine, red or black stool, Other (please describe) **State if:** Mild, Moderate, Severe
	(Wk 7) 43			
	44			
	45			
	46			
	47			
	48			
	49			
	(Wk 8) 50			
	51			
	52			
	53			
	54			
	55			
	56			
	(Wk 9) 57			
	58			
	59			
	60			
	61			
	62			
	63			
	(Wk 10) 64			
	65			
	66			
	67			
	68			
	69			
	70			

Subject's Signature: _____ Date: _____

SUBJECT PILL DIARY

Subject Name _____Protocol # CASE6220 **Subject Study ID _____**

Weeks #: 11 and 12 ***(Days 71-84)***

INSTRUCTIONS FOR THE SUBJECT:

1. You will take one 10mg capsule of escitalopram/placebo each day. You should take your pill in the morning or evening. You may take the pill with or without food, as you wish.
2. Record the date, the number of tablets you took, and what time you took them.
3. If you have any comments or side effects please record them in the "Comments" column below.
4. If you have bleeding, please record in the "Bleeding" column below.
5. Please bring your pill bottle and this form to your physician when you come for your next appointment.
6. Please sign your name at the bottom of the diary.

Date	Day	# of 10mg pills and time taken	Comments	Bleeding **Type of bleeding**: nose bleed, cut that won't stop bleeding, bruising, blood in urine, red or black stool, Other (please describe) **State if:** Mild, Moderate, Severe
	(Wk 11) 71			
	72			
	73			
	74			
	75			
	76			
	77			
	(Wk 12) 78			
	79			
	80			
	81			
	82			
	83			
	84			

Subject's Signature: _____ Date: _____

APPENDIX III

Clinical Medication Compliance Form for Investigational Studies

UH Seidman Cancer Center
Clinical Trials Unit
IDS Provided Agent Compliance form

Pt Name: _____
Pt MRN: _____
(or place patient label here)

Protocol ID:	Inv Product:	Study ID:	Date Initiated:	Date Discontinued:

Dose/ Kit #	Cycle Start Date	Cycle Stop Date	Date Dispensed	# IP Dispensed per script	Date IP returned by subject	# IP Returned by Subject	Did subject complete and sign IP diary?	Were any missed doses reported?	# IP taken this cycle per diary	# IP doses to be taken per prot calendar	Date Returned to IDS	Compliance Rate*	RN Signature:

* Calculate by: (# taken /# prescribed to take) X 100 = Comp

Note: If need to document any discrepancies or issues with dosing, etc. use NTF or other clinical source documents

V2 2/27/2014

APPENDIX IV

QIDS-SR16

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SR16)

Name or ID: _____ Date: _____

CHECK THE ONE RESPONSE TO EACH ITEM THAT BEST DESCRIBES YOU FOR THE PAST SEVEN DAYS.

During the past seven days...

1. Falling Asleep:

- ☐ 0 I never take longer than 30 minutes to fall asleep.
- ☐ 1 I take at least 30 minutes to fall asleep, less than half the time.
- ☐ 2 I take at least 30 minutes to fall asleep, more than half the time.
- ☐ 3 I take more than 60 minutes to fall asleep, more than half the time.

2. Sleep During the Night:

- ☐ 0 I do not wake up at night.
- ☐ 1 I have a restless, light sleep with a few brief awakenings each night.
- ☐ 2 I wake up at least once a night, but I go back to sleep easily.
- ☐ 3 I awaken more than once a night and stay awake for 20 minutes or more, more than half the time.

3. Waking Up Too Early:

- ☐ 0 Most of the time, I awaken no more than 30 minutes before I need to get up.
- ☐ 1 More than half the time, I awaken more than 30 minutes before I need to get up.
- ☐ 2 I almost always awaken at least one hour or so before I need to, but I go back to sleep eventually.
- ☐ 3 I awaken at least one hour before I need to, and can't go back to sleep.

4. Sleeping Too Much:

- ☐ 0 I sleep no longer than 7-8 hours/night, without napping during the day.
- ☐ 1 I sleep no longer than 10 hours in a 24-hour period including naps.
- ☐ 2 I sleep no longer than 12 hours in a 24-hour period including naps.
- ☐ 3 I sleep longer than 12 hours in a 24-hour period including naps.

During the past seven days...

5. Feeling Sad:

- ☐ 0 I do not feel sad.
- ☐ 1 I feel sad less than half the time.
- ☐ 2 I feel sad more than half the time.
- ☐ 3 I feel sad nearly all of the time.

Please complete either 6 or 7 (not both)

6. Decreased Appetite:

- ☐ 0 There is no change in my usual appetite.
- ☐ 1 I eat somewhat less often or lesser amounts of food than usual.
- ☐ 2 I eat much less than usual and only with personal effort.
- ☐ 3 I rarely eat within a 24-hour period, and only with extreme personal effort or when others persuade me to eat.

- OR -

7. Increased Appetite:

- ☐ 0 There is no change from my usual appetite.
- ☐ 1 I feel a need to eat more frequently than usual.
- ☐ 2 I regularly eat more often and/or greater amounts of food than usual.
- ☐ 3 I feel driven to overeat both at mealtime and between meals.

Please complete either 8 or 9 (not both)

8. Decreased Weight (Within the Last Two Weeks):

- ☐ 0 I have not had a change in my weight.
- ☐ 1 I feel as if I have had a slight weight loss.
- ☐ 2 I have lost 2 pounds or more.
- ☐ 3 I have lost 5 pounds or more.

- OR -

9. Increased Weight (Within the Last Two Weeks):

- ☐ 0 I have not had a change in my weight.
- ☐ 1 I feel as if I have had a slight weight gain.
- ☐ 2 I have gained 2 pounds or more.
- ☐ 3 I have gained 5 pounds or more.

Pg. 1 of 2

The Quick Inventory of Depressive Symptomatology (16-Item) (Self-Report) (QIDS-SRn)

During the past seven days...

10. Concentration / Decision Making:

☐ 0 There is no change in my usual capacity to concentrate or make decisions.

☐ 1 I occasionally feel indecisive or find that my attention wanders.

☐ 2 Most of the time, I struggle to focus my attention or to make decisions.

☐ 3 I cannot concentrate well enough to read or cannot make even minor decisions.

11. View of Myself:

☐ 0 I see myself as equally worthwhile and deserving as other people.

☐ 1 I am more self-blaming than usual.

☐ 2 I largely believe that I cause problems for others.

☐ 3 I think almost constantly about major and minor defects in myself.

12. Thoughts of Death or Suicide:

☐ 0 I do not think of suicide or death.

☐ 1 I feel that life is empty or wonder if it's worth living.

☐ 2 I think of suicide or death several times a week for several minutes.

☐ 3 I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried to take my life.

13. General Interest

☐ 0 There is no change from usual in how interested I am in other people or activities.

☐ 1 I notice that I am less interested in people or activities.

☐ 2 I find I have interest in only one or two of my formerly pursued activities.

☐ 3 I have virtually no interest in formerly pursued activities.

During the past seven days...

14. Energy Level:

☐ 0 There is no change in my usual level of energy.

☐ 1 I get tired more easily than usual.

☐ 2 I have to make a big effort to start or finish my usual daily activities (for example, shopping, homework, cooking, or going to work).

☐ 3 I really cannot carry out most of my usual daily activities because I just don't have the energy.

15. Feeling Slowed Down:

☐ 0 I think, speak, and move at my usual rate of speed.

☐ 1 I find that my thinking is slowed down or my voice sounds dull or flat.

☐ 2 It takes me several seconds to respond to most questions and I'm sure my thinking is slowed.

☐ 3 I am often unable to respond to questions without extreme effort.

16. Feeling Restless:

☐ 0 I do not feel restless.

☐ 1 I'm often fidgety, wringing my hands, or need to shift how I am sitting.

☐ 2 I have impulses to move about and am quite restless.

☐ 3 At times, I am unable to stay seated and need to pace around.

APPENDIX V

Fact –Hep (Version 4)

FACT-Hep (Version 4)

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Hep (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
Hep 1	I am unhappy about a change in my appearance	0	1	2	3	4
CNS 7	I have pain in my back	0	1	2	3	4
Cn5	I am bothered by constipation	0	1	2	3	4
H17	I feel fatigued	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Hep 2	I am bothered by jaundice or yellow color to my skin	0	1	2	3	4
Hep 3	I have had fevers (episodes of high body temperature)	0	1	2	3	4
Hep 4	I have had itching	0	1	2	3	4
Hep 5	I have had a change in the way food tastes	0	1	2	3	4
Hep 6	I have had chills	0	1	2	3	4
HN 2	My mouth is dry	0	1	2	3	4
Hep 8	I have discomfort or pain in my stomach area	0	1	2	3	4

APPENDIX VI

FIBSER Scale

FIBSER Scale

Please choose and circle your response based on side effects that you believe are caused by medications for depression **IN THE PAST WEEK**.

Do **NOT** rate side effects if you believe they are caused by medications for medical conditions other than depression.

1. IN THE PAST WEEK, how **much of the time** did you experience side effects caused by medications for depression?

0	1	2	3	4	5	6
None of the time (no side effects)	10% of the time	25% of the time	50% of the time	75% of the time	90% of the time	All the time

2. IN THE PAST WEEK, how **severe** were the side effects to your medications for depression?

0	1	2	3	4	5	6
None (no side effects)	Minimal severity	Mild severity	Moderate severity	Marked severity	Severe severity	Intolerable severity

3. IN THE PAST WEEK, how much have the side effects to your medications for depression **interfered** with your day-to-day activities?

0	1	2	3	4	5	6
No interference with activities	Minimal interference with activities	Mild interference with activities	Moderate interference with activities	Marked interference with activities	Severe interference with activities	Unable to function

Clinical Relevance: Question 3	
0 – 2	No changes needed.
3 – 4	Side effect should be addressed.
5 – 6	Change treatment.

Adapted by Dr. Raymond W. Lam (r.lam@ubc.ca)
with permission from Wisniewski SR et al, J Psychiatr Prac 2006;12:71-9.

APPENDIX VII

PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

NAME:_____ DATE:_____

Over the last 2 *weeks*, how often have you been bothered by any of the following problems?
(use "✓" to indicate your answer)

	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself—or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite — being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3
		add columns	+	+

(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card). TOTAL:

10. If you checked off *any problems*, how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

A2663B 10-04-2005

PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1;
More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

A2662B 10-04-2005

APPENDIX VIII

Tumor Profile Assessment

Patient Name: _____Patient Study ID #: _____

Protocol: _____ Date of Assessment: _____

Completed by/Signature:

_____

(must be completed by PI, Co-Investigator, or Radiologist)

Study Coordinator/Pager: _____

Complete the following table, indicating involvement type with a X in the appropriate box:

VESSEL	NO INVOLVEMENT	ABUTMENT (0-180)	ENCASEMENT (180+)
Superior Mesenteric Vein			
Portal Vein			
Common Hepatic Artery			
Superior Mesenteric Artery			
Celiac Trunk			

Borderline? (indicate YES or NO): -

_____

Unresectable? (indicate YES or NO): -

_____

(please see table below: NCCN Guidelines Version 2.2018, Pancreatic Adenocarcinoma, page 25, [Criteria Defining Resectability Status])

CRITERIA DEFINING RESECTABILITY STATUS[a]

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	<u>Pancreatic head/uncinate process</u>: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. <u>Pancreatic body/tail</u>: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some panel members prefer these criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).
Unresectable[b]	• Distant metastasis (including non-regional lymph node metastasis) <u>Head/uncinate process</u>: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° <u>Body and tail</u>: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	<u>Head/uncinate process</u>: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV <u>Body and tail</u>: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

[a]Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the Society of Abdominal Radiology and the American Pancreatic Association. Radiology 2014 Jan; 270(1):248-260.

[b]Solid tumor contact may be replaced with increased hazy density/stranding of the fat surrounding the peri-pancreatic vessels (typically seen following neoadjuvant therapy); this finding should be reported on the staging and follow-up scans. Decision on resectability status should be made in these patients, in consensus at multidisciplinary meetings/discussions.