Phase II Study of Pasireotide LAR in Patients with Metastatic Neuroendocrine Carcinomas

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Phase II Study of Pasireotide LAR in Patients with Metastatic Neuroendocrine Carcinomas

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List of abbreviations

5-HIAA	Urinary 5-hydroxyindole acetic acid
AE	Adverse Event
ALT	Alanine aminotransferase/glutamic pyruvic transaminase/SGPT
AST	Aspartate aminotransferase/glutamic oxaloacetic transaminase/SGOT
BG	Blood Glucose
CPO	Clinical Pharma Organization
CRF	Case Report/Record Form
CRO	Contract Research Organization
CT	Computer Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
DM	Diabetes Mellitus
ECG	Electrocardiogram
GCP	Good Clinical Practices
GEP	Gastroenteropancreatic
GI	Gastrointestinal
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IM	Intramuscular
ITT	Intent to Treat
i.v.	intravenous(ly)
IRB	Institutional Review Board
LAR	Long Acting Release
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
PFS	Progression-Free Survival
PK/PD	Pharmacokinetic/Pharmacodynamic
SAE	Serious Adverse Event
s.c.	Subcutaneous
SSA	Somatostatin Analog
SOP	Standard Operating Procedure
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit Normal

1 Introduction

1.1 Overview of Neuroendocrine Tumors

Neuroendocrine tumors are a heterogeneous group of neoplasms which include carcinoid tumors and pancreatic neuroendocrine tumors. The majority are characterized by a relatively indolent rate of growth and a propensity to produce and secrete a variety of hormones and other vasoactive substances, giving rise to diverse clinical syndromes. Histologically, carcinoid tumors arise from the endocrine (enterochromaffin) cells of the gastrointestinal tract and airways. Carcinoid tumors have distinct features depending on their site of origin. In the 1960s, Williams et al classified carcinoid tumors based on embryologic derivation, distinguishing between foregut (bronchial, stomach, duodenal), midgut (jejunal, ileal, cecal, appendiceal) and hindgut (distal colon and rectal) tumors.[1] As a rule of thumb, metastatic midgut carcinoid tumors produce serotonin and other vasoactive substances which give rise to the typical carcioid syndrome.[2] This syndrome manifests primarily as diarrhea and flushing, a vasomotor phenomenon which causes redness and warmth in the face and upper torso. Carcinoid heart disease, characterized by fibrosis of the tricuspid and pulmonic heart valves, can also occur in patients with severe and prolonged elevations of circulating serotonin. In contrast, hindgut carcinoid tumors are rarely, if ever, associated with a hormonal syndrome. Tumor growth rates also correlate with site of origin. In the metastatic setting, midgut carcinoid tumors tend to behave in the most indolent fashion, whereas neuroendocrine tumors originating in the foregut or hindgut regions tend to behave more aggressively once they have metastasized.

Pancreatic neuroendocrine tumors arise from the islets of Langerhans. These heterogeneous neoplasms can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP).[2] In contemporary studies, most pancreatic neuroendocrine tumors are unassociated with a hormonal syndrome, and are termed “nonfunctioning.”

Treatment options for metastatic neuroendocrine tumors have evolved in recent years. Somatostatin analogs such as octreotide were initially developed to palliate hormonal symptoms such as the flushing and diarrhea caused by the carcinoid syndrome.[3] More recently, accumulating data has supported their role as antiproliferative agents, capable of stabilizing tumor growth in patients with metastatic neuroendocrine malignancies.[4] Last year, results of a phase III, randomized, placebo-controlled trial were published, demonstrating that long-acting octreotide (Sandostatin LAR 30 mg) significantly prolonged time to tumor progression among patients with metastatic midgut carinoid tumors.[5]

Emerging evidence supports the use of other targeted agents, although none yet is considered standard of care. Sunitinib, a multitargeted tyrosine kinase receptor inhibitor, has recently been demonstrated to prolong progression-free survival in patients with metastatic pancreatic neuroendocrine tumors. Everolimus, an inhibitor of mammalian target of rapamycin (mTOR) has shown promise in several phase II studies.[6] Results of randomized, placebo-controlled phase III studies are pending. Bevacizumab, an inhibitor of circulating vascular-endothelial growth factor (VEGF) is also being tested in phase III studies based on encouraging phase II

evidence. Cytotoxic chemotherapy appears to produce high response rates in metastatic pancreatic neuroendocrine tumors[7]; however responses in carcinoid tumors have been discouraging.

Among the various emerging treatments, somatostatin analogs appear to be associated with the most favorable side effect profile and ease of administration. Their convenient mode of administration and tolerability are particularly important in patients with metastatic neuroendocrine tumors who often remain on treatment for many years.

1.2 Somatostatin analogs in the treatment of patients with Neuroendocrine Carcinomas

The human hormone somatostatin was initially identified as a hypothalamic inhibitor of growth hormone.[8] It was subsequently discovered to be a universal endocrine "off switch" due to its exocrine, endocrine, paracrine and autocrine inhibitory effects.[9] In the digestive tract, it reduces secretion and motility, decreases portal blood flow, and reduces the secretion of other gastrointestinal hormones. The effects of somatostatin are mediated through interaction with five somatostatin receptors (sst_{1-5}), belonging to a family of G-protein coupled receptors with seven transmembrane domains.[10]

The clinical use of native human somatostatin is limited by its short half life of approximately two minutes. In order to improve the pharmacokinetic profile, synthetic somatostatin analogs (SSAs) have been developed by shortening the polypeptide chain while retaining binding affinity to somatostatin receptors.[11] The two commercially available analogs, octreotide and lanreotide, are octapeptides that bind with high affinity to somatostatin receptor 2 (sst_2) and with moderate affinity to sst_5.

Octreotide has been used in clincial practice since the 1980s when it was shown to effectively palliate the carcinoid syndrome, as well as other syndromes caused by metastatic neuroendocrine tumors including VIPomas and glucagonomas. Octreotide was initially available in an immediate-release subcutaenous formulation. During the past decade, a long-acting repeatable (LAR) depot formulation of octreotide (Sandostatin LAR) has been available allowing for monthly intramuscular dosing.[12]

In recent years, evidence of the antineoplastic activity of SSAs has emerged. Although objective radiographic responses associated with these agents are rare, many cases of prolonged disease stability have been documented in the literature, leading to the hypothesis that SSAs exert an inhibitory effect on tumor growth. Last year, results of a phase III randomized, placebo-controlled study, the PROMID trial, were published. In this trial, 85 patients with well-differentiated carcinoid tumors originating in the distal intestine and proximal colon (midgut) were randomized to receive either octreotide LAR 30 mg or placebo. Median progression-free survival was 14.3 months in the octreotide LAR group versus 6.0 months in the placebo group ($p=0.000072$), confirming the antiproliferative effect of octreotide in this patient population.[5]

Pasireotide (SOM230) is a novel somatostatin analog with a similar binding affinity to somatostatin sst_2 and substantially stronger binding affinities to $ssts_{1, 3}$ and $_5$ (see section 1.3).[13] Preclinical data suggests that ssts $_{1, 3}$ and $_5$ play an important role in cell cycle arrest and induction of apoptosis.[14] Thus, we hypothesize that pasireotide LAR may prove to be a more potent inhibitor of neuroendocrine tumor proliferation than octreotide LAR.

1.3 Pasireotide (SOM230)

Pasireotide is an injectable somatostatin analogue. It is a novel cyclohexapeptide with the following chemical name: (2-Aminoethyl)carbamic acid (2R,5S,8S,11S,14R,17S,19aS)-11-(4-aminobutyl)-5-benzyl-8-(4-benzyloxybenzyl)-14-(1H-indol-3-ylmethyl)-4,7,10,13,16,19-hexaoxo-17-phenyloctadecahydro-3a,6,9,12,15,18-hexaazacyclopentacyclooctadecen-2-yl ester, di[(S)-2-aminosuccinic acid] salt.

Like natural somatostatin and other somatostatin analogues (SSAs), pasireotide exerts its pharmacological activity via binding to somatostatin receptors (ssts). There are five known somatostatin receptors: $ssts_{1-5}$. Somatostatin receptors are expressed in different tissues under normal physiological conditions. Somatostatin analogues activate these receptors with different potencies[15] and this activation results in a reduced cellular activity and inhibition of hormone secretion. Somatostatin receptors are strongly expressed in many solid tumors, especially in neuroendocrine tumors. The SSAs currently approved for use in the clinic (octreotide and lanreotide) have a high affinity to the sst2, with moderate or no affinity to the remaining subtypes. Pasireotide is a novel cyclohexapeptide somatostatin analogue that exhibits a unique binding profile, binding with high affinity to four of the five known human somatostatin receptors. (Table 1.1). Compared to Sandostatin® (octreotide acetate), pasireotide exhibits a binding affinity which is 30-40 times higher for human sst_1 and sst_5, 5 times higher for human sst_3, and 2.5 times lower for human sst_2. A detailed summary of available preclinical data is provided in the Investigators' Brochure.

Table 1.1 Binding profile for octreotide and pasireotide at sst_{1-5} (IC_{50}, M)

Compound	**sst 1**	**sst2**	**sst3**	**sst4**	**sst5**
octreotide	$2.8x10^{-7}$	$3.8x10^{-10}$	$7.1x10^{-9}$	$>10^{-6}$	$6.3x10^{-9}$
Pasireotide	$9.3x10^{-9}$	$1.0x10^{-9}$	$1.5x10^{-9}$	$>10^{-6}$	$1.6x10^{-10}$
Ratio of IC_{50}: octreotide to pasireotide	30	0.4	5	--	40

Additionally, preclinical studies suggest anti-tumor activity of pasireotide. Pasireotide has been found to significantly reduce cell proliferation of the neuroendocrine tumor cell line NCI-H727, whereas the conventional analogue octreotide did not.[16]

1.4 Clinical experience with pasireotide

Pasireotide is available as a short-acting subcutaneous (s.c) formulation and a long acting release (LAR) intramuscular (IM) formulation.

1.4.1 Pasireotide s.c.

Pasireotide when given subcutaneously (s.c.) was well-tolerated at doses up to 600 µg b.i.d., 900 µg b.i.d. and 1200 µg b.i.d by acromegalic, Cushing's disease and carcinoid tumor patients, respectively. In addition, healthy volunteers have received pasireotide s.c. as a continuous infusion for seven days with total daily doses of up to 2025 µg being well tolerated. For all indications the most frequently reported adverse events were gastrointestinal, predominantly diarrhea, nausea and abdominal pain. Generally these events were mild, transient and only occasionally caused patients to discontinue treatment.

Hyperglycemia was also observed for patients in all three indications. In general HbA1c was observed to increase by approximately 1%, corresponding to a blood glucose increase of approximately 30 mg/dL. Blood glucose increases tended to occur with increasing dose, and appeared to be more notable in patients who had a history of hyperglycemia or diabetes mellitus prior to receiving pasireotide. However hyperglycemia in these patients was responsive to appropriate diabetic management such as adjustments in oral antidiabetic treatment, or in some cases the addition of insulin.

Occasionally laboratory abnormalities in liver function tests and pancreatic enzymes have been observed at higher doses of pasireotide. These events however have been transient.

Further details on pasireotide s.c. can be found in the Investigator Brochure.

1.4.1.1 Phase II studies of pasireotide s.c. in neuroendocrine tumors

Preliminary safety data are available from a Phase II study [CSOM230B2202] in 45 patients with symptomatic metastatic carcinoid disease who received pasireotide s.c. doses from 300 µg s.c. b.i.d. up to 1200 µg b.i.d. for a mean of 20 weeks. Overall pasireotide s.c. has been found to be generally well-tolerated by these patients, with the most common adverse events being mild diarrhea, nausea and abdominal pain. Blood glucose increases tended to occur with increasing dose, but were moderate and generally managed easily by adjustment in oral hypoglycemic medications. Weight loss was also observed in 18 patients. Maximum weight loss occurred within 4 to 6 months on the study drug, with a stabilization of effect after approximately 6 months. There was no apparent relationship between the weight loss and pasireotide dose.

Preliminary efficacy data from this study also support that pasireotide is active in patients refractory/resistant to Sandostatin LAR, as partial or complete symptom control was observed in 12 of 44 patients (27%). Complete symptomatic response was achieved in two patients at the pasireotide 600 µg s.c. b.i.d. dose and one at the 900 µg s.c. b.i.d. dose. Nine patients achieved partial symptomatic response to treatment, three at each of the following doses: 600, 750, 900 µg s.c. b.i.d.

1.4.2 Pasireotide LAR

Most of the experience with pasireotide comes from healthy volunteer and patient studies evaluating the subcutaneous formulation of pasireotide. Pasireotide LAR is being evaluated in two studies, one healthy volunteer study and one study involving patients with acromegaly and carcinoid disease.

1.4.2.1 Pasireotide LAR in healthy volunteers

Preliminary data from the healthy volunteer study found single IM doses of pasireotide LAR, at doses of up to 40 mg and 60 mg, respectively to be well-tolerated. The most common adverse events were gastrointestinal. Diarrhea was experienced by most of the subjects and was sometimes associated with abdominal pain, flatulence, and/or nausea. The gastrointestinal events were mild or moderate in severity. About 38% of subjects reported mild injection site pain and about 15% reported headaches.

Transient elevations in liver function tests and/or pancreatic enzymes were observed in two subjects, both of which resolved and were not accompanied by any clinical symptoms. Mild increases in fasting blood glucose were observed in some subjects during the pasireotide LAR treatment period. All elevations were asymptomatic, considered not clinically significant and generally returned to normal within 3 to 4 weeks after the pasireotide LAR IM injection.

1.4.2.2 Pasireotide LAR in acromegalic patients

Preliminary safety data are available from 18 acromegalic patients treated with pasireotide LAR in an ongoing study [CSOM230C2110]. These patients had received pasireotide LAR at doses of 20 (n=5), 40 (n=6) or 60 mg (n=7) for about six weeks at the time of the summary. Pasireotide LAR was well-tolerated by acromegalic patients in this study. The most common drug-related adverse events were gastrointestinal, predominantly diarrhea. Mild erythema reported as drug-related was experienced by three patients. Two patients on the 60 mg dose were reported to experience drug-related increases in blood glucose: mild diabetes mellitus was reported for one patient and mild hyperglycemia was reported for the other patient who also had a history of diabetes mellitus at baseline. A further patient who received the 20 mg dose experienced hyperglycemia, however this event was considered to be unrelated to study drug by the investigator. All three patients were given oral hypoglycemic agents and all continued in the trial.

Following 2-3 injections of pasireotide LAR in acromegaly patients [CSOM230C2110], steady-state concentrations of pasireotide were achieved. The trough plasma concentrations of pasireotide at steady state (Cmin.ss) on day 84 were 3.8 ± 2.1, 5.6 ± 2.4, and 13.8 ± 10.2 ng/mL for 20 mg (N=9), 40 mg (N=9), and 60 mg (N=11) LAR, respectively, indicating an approximate dose proportionality.

1.4.2.3 Pasireotide LAR in carcinoid patients

Preliminary safety data are available from nine carcinoid patients treated with pasireotide LAR in an ongoing study [CSOM230C2110]. These patients had received pasireotide LAR at

doses of 20 (n=1), 40 (n=4) or 60 mg (n=4) for about six weeks at the time of the summary. Pasireotide LAR was well-tolerated by carcinoid patients. Six out of nine treated patients reported at least one AE and the most commonly reported AEs were gastrointestinal. However, most of these events were considered unrelated to study drug. Two patients reported hyperglycemia judged as related to study drug, one was mild and one moderate. The patient who experienced moderate hyperglycemia had a past history of diabetes mellitus at entry to the study and died due to carcinoid tumor progression.

Although pasireotide exposures appear to be higher in patients than in healthy volunteers, the data from studies assessing the subcutaneous formulation of pasireotide support that pasireotide LAR at doses of 60 mg and below are expected to be well-tolerated by patients. A healthy volunteer study of pasireotide s.c. by continuous infusion tested doses of up to 2,025 mcg per day [SOM230B2108]. The dose of 2,025 mcg by s.c. infusion per day was well-tolerated and is equivalent to a dose of 56.7 mg from a single 28 day IM depot injection of pasireotide LAR. Data resulting from studies [SOM230B2108] and [SOM230B2202] are described fully in the Pasireotide s.c Investigator's Brochure.

The effects of high doses of pasireotide on cardiac repolarization in healthy volunteers was tested in study CSOM230B2113. The dose of s.c pasireotide selected was 1950mcg bid. This dose was compared to moxifloxacin and placebo. The results of the study suggested the presence of an effect of pasireotide on QTcF intervals due to the fact that the upper bound of the 95% one-side CI for the difference from placebo was greater than 10ms at 1-2 hours post dose.

Given the tolerable side-effect profile of pasireotide LAR, its enhanced affinity for somatostatin receptors compared to octreotide LAR, and its putative antiproliferative effects in patients with neuroendocrine tumors, we propose a phase II study investigating pasireotide LAR in patients with metastatic neuroendocrine tumors. Unlike prior studies focusing on palliation of hormonal symptoms, the primary goal of this study is to assess radiologic progression-free survival (PFS).

2 Study objectives

The primary purpose of the study is to investigate the progression-free survival associated with pasireotide LAR in treatment-naïve patients with metastatic carcinoid and pancreatic neuroendocrine tumors.

Secondary objectives are to assess the overall survival (OS) associated with pasireotide LAR, overall radiographic response rate (ORR), adverse events (AEs), changes in tumor markers and changes in quality of life (QOL).

2.1 Selection of doses

Based on the tolerable side-effect profile of pasireotide LAR at doses of 60mg every 4 weeks (see section 1.4.2.3) and pharmacokinetic data demonstrating therapeutic drug levels at that level, the dose of pasireotide in this study will be 60mg IM every 4 weeks. No doses of pasireotide LAR exceeding 60mg will be tested in this trial. If tolerability issues occur, the treatment dose may be reduced to 40mg.

3 Endpoints

3.1 Primary endpoints

- Progression-free survival (PFS)
- Rate of PFS at one year

3.2 Secondary endpoints

- Overall survival (OS)
- Overall radiographic response rate (ORR)
- Adverse events (AEs)
- Changes in neuroendocrine tumor markers (such as chromogranin A or pancreatic polypeptide), or hormonal assays (such as urine 5-HIAA, gastrin, insulin, glucagon, vasoactive intestinal peptide, etc) if elevated at baseline.
- Changes in quality of life (as measured by EORTC questionnaires EORTC QLQ-C30 and QLQ GI.NET21

3.3 Exploratory endpoint

- To assess the correlation between somatostatin receptor profiling (via immunohistochemistry) and PFS

4 Study design

This is a multi-institutional, prospective phase II open-label trial.

4.1 Treatment

The investigational drug used in this study is pasireotide LAR 60mg. Pasireotide will be administered as an intramuscular injection at the beginning of every cycle which is defined as 28 days (+/- 3 days). Study treatment should begin within 14 days following enrollment into the study and continue until disease progression, unacceptable toxicity, or withdrawal of consent. Safety and efficacy will be assessed throughout the treatment period.

4.1.1 Rescue treatment for diarrhea and other breakthrough hormonal symptoms

Patients with hormonal symptoms caused by neuroendocrine tumors (such as the carcinoid syndrome) may experience symptom flares requiring short-acting rescue medications. For these patients, short-acting pasireotide sc may be prescribed at the discretion of the investigator at a dose of 600 mcg bid prn. Patients who continue to experience breakthrough diarrhea due to carcinoid syndrome or other hormonal syndromes may use antidiarrheal medications such as loperamide or diphenoxylate and atropine. SOM230 may

cause malabsorption and steatorrehea which can be controlled with pancreatic enzyme supplementation.

4.2 Follow-up

All patients will be followed for adverse events and serious adverse events for 28 days following the last dose of pasireotide, or until resolution or stabilization of the event, whichever comes first.

5 Population

The study population will consist of patients with advanced (metastatic or unresectable) well and moderately differentiated neuroendocrine tumors of the gastrointestinal tract and lungs (carcinoid tumors) and pancreatic neuroendocrine tumors.

5.1 Inclusion/exclusion criteria

The investigator or his/her designee must ensure that all patients who are offered enrollment in the study meet all of the following inclusion and exclusion criteria:

5.1.1 Inclusion criteria

1. Locally unresectable or metastatic carcinoid or pancreatic neuroendocrine tumors.
2. Tumors must be considered well or moderately differentiated (or low to intermediate grade). Patients with poorly differentiated neuroendocrine carcinomas or small cell carcinomas are excluded from the study.
3. No prior systemic antineoplastic neuroendocrine tumor treatment (including prior somatostatin analogs). However patients who have received a short course of SQ octreotide (<10 days) in the past are eligible if > 1 week has elapsed from their last octreotide injection.
4. Age ≥ 18 years.
5. Minimum of four weeks since any major surgery.
6. Measureable disease by RECIST.
7. ECOG performance status ≤1
8. Life expectancy 12 weeks or more.
9. Adequate bone marrow function as shown by: ANC ≥ 1.0 x 10^9/L, Platelets ≥ 75 x 10^9/L, Hgb > 8 g/dL.
10. Adequate liver function as shown by: serum bilirubin ≤ 2.0 x upper limit of normal (ULN), and serum transaminases activity ≤ 2 x ULN, with the exception of serum transaminases (< 3 x ULN) if the patient has liver metastases.
11. Adequate renal function as shown by serum creatinine ≤ 2.0 x ULN.

12. Fasting serum cholesterol ≤300 mg/dL OR ≤7.75 mmol/L AND fasting triglycerides ≤ 2.5 x ULN. NOTE: In case one or both of these thresholds are exceeded, the patient can only be included after initiation of appropriate lipid lowering medication.
13. Women of childbearing potential must have a negative serum pregnancy test within 14 days of the administration of the first study treatment. Women must not be lactating. Both men and women of childbearing potential must be advised of the importance of using effective birth control measures during the course of the study.
14. Signed informed consent to participate in the study must be obtained from patients after they have been fully informed of the nature and potential risks by the investigator (or his/her designee) with the aid of written information.

5.1.2 Exclusion criteria

1. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.
2. Patients with prior or concurrent malignancy except for the following: adequately treated basal cell or squamous cell skin cancer, or other adequately treated in situ cancer, or any other cancer from which the patient has been disease free for five years.
3. Patients with uncontrolled diabetes mellitus or a fasting plasma glucose > 1.5 ULN or HbA1c >8%. Note: At the principle investigator's discretion, non-eligible patients can be re-screened after adequate medical therapy has been instituted.
4. Patients with symptomatic cholelithiasis
5. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, or a history of acute myocardial infarction within the six months preceding enrollment.
6. Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
   - Severely impaired lung function
   - Any active (acute or chronic) or uncontrolled infection/ disorders.
   - Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the treatment with the study therapy
7. Known hypersensitivity to somatostatin analogues or any component of the pasireotide LAR formulation
8. Corrected QT interval (QTcF) of >470msec on screening ECG
9. Risk factors for Tosades de Pointes such as cardiac failure, clinically significant/symptomatic bradycardia.
10. Clinically significant hypokalemia or hypomagnesemia that are not correctable.
11. History of sustained ventricular tachycardia, ventricular fibrillation, advanced heart block, idiopathic syncope thought to be related to ventricular arrhythmia, or congenital long QT syndrome.

12. Concomitant medication(s) known to increase the QT interval (see appendix A)
13. History of noncompliance to medical regimens or unwillingness to comply with the protocol.

6 Study Medication

6.1 Study drug: Pasireotide (SOM 230)

Study drug: pasireotide LAR (long-acting release) i.m. depot injection

Inactive ingredients of pasireotide LAR include: mannitol, carmellose sodium (carboxymethylcellulose sodium), poloxamer 188 and water for injection. For detailed information on pasireotide, please refer to Sections 1.3 and 1.4 or the pasireotide Investigator Brochures.

How supplied

Study drug, Pasireotide LAR i.m. depot injections will be supplied in open-label packaging by Recordati Inc. as a powder in vials containing 20 mg and 40 mg labeled as SOM230 LAR, with ampules containing 2 mL of vehicle (for reconstitution). No syringes or needles will be provided with the pasireotide study drug supplies.

Preparation and storage

Prior to reconstitution, vials should be brought to room temperature. Pasireotide LAR should then be prepared as follows:

Table 6-1 Handling and preparation of pasireotide LAR dose

Dose	Volume to be injected
40 mg	1 x 40 mg vial + 2 mL vehicle: whole volume to be injected
60 mg	1 x 20 mg vial + 1 x 40 mg vial + 2 mL vehicle; whole volume to be injected

Doses should be prepared and administered immediately after preparation.

Recordati Inc. will supply pasireotide LAR as long as the patient remains on study, shows continuous benefit from treatment, and there are no safety concerns. Medication labels will comply with the legal requirements of the U.S. and will be printed in English. The storage conditions for pasireotide LAR will be described on the medication label. Bottles must be stored in a safe, secure location.

All study medication will be supplied to each site directly by Recordati Inc. Under the responsibility of each site's lead investigator, drug supplies must be kept in an appropriate, secure area (e.g. locked cabinet) and stored in accordance with the conditions specified on the drug labels. The investigator must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. Unless specifically instructed by Recordati Inc., the investigator must not destroy any drug labels, or any unused drug supply.

The storage condition for the study drug will be described on the medication label.

Administration

Pasireotide LAR will be administered i.m., intragluteally, every 4 weeks. The starting dose will be 60 mg. The reconstitution has to be performed just prior to administration of the suspension. A minimal standing time can be tolerated for the reconstituted suspension in the vial. Prior to administration, the reconstituted suspension in the vial should be shaken again before withdrawal in the syringe. The i.m. injection must be given immediately after withdrawal of the reconstituted suspension from the vial to the syringe. All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded. Recordati Inc. will supply pasireotide free of charge for study participants.

6.2 Permitted study drug adjustments

Toxicity will be assessed using the NCI-CTC for Adverse Events, version 4.0 (CTCAEv4.0, (http://evs.nci.nih.gov/ftp1/CTCAE/About.html)). For patients who are unable to tolerate pasireotide 60mg every 4 weeks, the dose may be changed to 40mg every 4 weeks (see table 6-2).

Table 6-2 Criteria for dose-modification of pasireotide

Adverse event	Action
*Grade ≤ 2	No study drug adjustments
*Grade ≥ 3 and judged as at least possibly drug related	• Reduce dose to 40mg • If AE improves to grade ≤2 before the next administration, increase dose to 60mg. If the dose is increased and that AE recurs at CTC grade ≥ 3 the dose will be reduced back to the lower dose and shall not be increased again during the study period. • If AE does not improve to grade ≤2 on the lower dose befoe the next administration, the patient will discontinue the study drug and be followed for safety.
**This guidance should be use for all probably related AEs except for changes in blood glucose which should be addressed as described in Section 6.3.1 and changes in QTc interval which should be addressed as described in Section 6.3.2..*	

6.3 Follow-up for toxicities

Patients who interrupt or permanently discontinue pasireotide due to an adverse event or abnormal laboratory value must be followed at least weekly for 28 days after the last dose of pasireotide, and subsequently at monthly intervals until resolution or stabilization of the event,

whichever comes first. If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient should be discontinued from the study.
All patients will be followed for adverse events and serious adverse events for 28 days following the last dose of pasireotide.

6.3.1 Management Guidelines for Hyperglycemia

During the study, all patients with HbA1c ≥ 7 % and or fasting plasma glucose (FPG) > 130 mg/dL (7.2 mmol/L), should be considered for the following:

- Provided information and receive teaching on diabetes disease management
- Initiation of drug therapy with anti-hyperglycemic medications
- Referral to a diabetes specialist for evaluation and appropriate management
- Monitoring of blood glucose by fingerstick twice daily (fasting morning blood glucose and 2-hour post-meal) if not already done. Patients, who monitor blood glucose should keep a diary of their glucose values and present the collected data to their physician/ diabetes specialist for evaluation and appropriate management.

6.3.2 Management Guidelines for QTc prolongation on ECG

Table 6-3-2 provides guidelines for management of prolonged QTc interval.

Table 6-3-2 Guidelines for Management of QTc Prolongation

QTc CTC grade 1 (≤ 480 msec)	No study drug adjustments
QTc CTC grade 2 (> 480 or ≤ 500 msec) either drug related or drug unrelated	Patient is to be referred to a cardiologist for evaluation and appropriate management, and the patient can remain in the study Patient's study drug dose will be reduced to 40 mg.
QTc CTC grade ≥ 3 (> 500 msec), or increase in QTcF ≥60ms over baseline	Discontinue study drug Follow patient for safety

6.3.3 Management Guidelines for Abnormal Liver Function

Table 6-3-3: SOM230 Abnormal liver function management

Perform within **72 hours** of awareness of abnormal LFTs:
 Perform liver-directed medical history and physical examination (i.e. assess occupational hazards, concomitant medications including OTC meds, intercurrent illness, etc)
 Liver chemistry tests: ALT, AST, total bilirubin, (fractionate to direct/indirect bilirubin if total bilirubin is > 2.0x ULN), Alb, PT (INR), ALP, and GGT
 Perform hepatitis screen: anti-HAV, IgM (to confirm acute hepatitis A), HbsAg, Anti-HBc, anti-HCV (if positive PCR viral load should be assessed), Anti-HEV, ANA antibodies, anti-smooth muscle anti-bodies, CMV, EBV
 Perform abdominal ultrasound (liver and biliary tree)
 Collect PK sample and record the dose level and the dosing time for the last dose the patient has taken prior to PK sampling.

Liver chemistry tests should be monitored **every 3-4 days** for s.c. and LAR studies until resolution or return to baseline status.
 For ALT or AST > 5x ULN and ≤ 8x ULN:
o Study medication should be temporarily interrupted and liver chemistry tests monitored **every 3-4 days** for s.c. and LAR studies until resolution or return to baseline
o If resolution or return to baseline does not occur after 2 weeks, the patient should be discontinued.
o If ALT or AST returns to less than 5x ULN, study drug can be resumed and patient can continue study per protocol
o If ALT or AST rises above 5x ULN anytime after study drug is resumed, then study drug should be discontinued immediately.

Table 6-3-3-1: SOM230 Abnormal liver function discontinuation criteria
Hepatic-related discontinuation criteria for all ongoing studies
Study medication should be discontinued immediately if any of the discontinuation criteria below are met:
 ALT or AST > 3x ULN and Total Bilirubin > 2x ULN and ALP < 2x ULN
 ALT or AST > 5x ULN and ≤ 8x ULN persistent for more than 2 weeks
 ALT or AST > 8x ULN

Re-challenge of study medication is prohibited once discontinuation criteria are met.

6.3.4 Concomitant therapy

Patients will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the patient about any new medications he/she is or has taken after the start of the study drug.

All Concomitant medications/Significant non-drug therapies taken ≤ 30 days prior to start and after start of study drug, including physical therapy and blood transfusions, should be recorded.

The use of concomitant medications that might lead to QT prolongation (appendix A) is prohibited and requires the discontinuation of the patient prior to starting the respective QT prolonging medication.

Pasireotide is a moderate inhibitor of CYP2C9 and 2D6. Substrates of CYP2C9 and 2D6 (appendix D) with a narrow therapeutic index should be used with caution. Patients on Warfarin should have their INR monitored more closely while receiving SOM230.

6.3.5 Study drug discontinuation

Patients experiencing unacceptable toxicity (AE grade 3 or higher) that the investigator considers directly attributable to the study drug should have their dose adjusted as per dose modification guidelines in Table 6-2. If a patient has already decreased 1 dose level, no further dose reduction is permitted, and the patient will be permanently discontinued from treatment. For QTc related protocol discontinuation, please see section 6.3.2. For LFT related protocol discontinuation, see section 6.3.3.

6.4 End of treatment

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

- Disease progression
- Death
- Withdrawal of consent
- Delay of treatment >21 days.
- Uncontrolled diabetes mellitus (DM)
- Pregnancy
- Adverse event(s) ≥grade 3 despite dose reduction
- QTc prolongation (see section 6.3.2)

7 Visit schedule and assessments

7.1 Pretreatment Evaluation

Baseline tumor and patient characteristics including:

- Patient demographics: age, gender and race (Caucasian, Black, Hispanic, Asian, other).
- Medical history
- Medications
- ECOG performance status.
- Type of neuroendocrine tumor: primary site (if known) vs. unknown.
- Differentiation or grade (if available).
- Known sites of metastases.
- Estimation of tumor burden in the liver (none vs. <10% vs. >10%).
- Presence or absence of radiotracer uptake on OctreoScan (if available).
- Presence or absence of hormonal syndrome (carcinoid syndrome, gastrinoma syndrome, insulinoma syndrome, etc.)
- Presence or absence of a pathologically elevated hormone or biomarker.
- EORTC QLQ C-30 and EORTC QLQ GI-NET21 questionnaires

Tests to be performed within 28 days prior to initiation of therapy (if day 28 falls on a weekend or holiday the deadline may be extended to the next working day):

- Radiologic assessment of tumor burden by CT scan or MRI
- Assessment of secretory proteins. All patients will undergo an initial assessment of chromogranin A. Patients with suspected serotonin-producing tumors (and all patients with midgut carcinoid tumors) will have a 24 hour urine 5-HIAA measured at

baseline. Other possible neuroendocrine tumor markers/hormones (e.g. pancreatic polypeptide, gastrin, glucagon, etc.) may be collected at the discretion of the investigator based on clinical symptoms and tumor location.

Tests to be performed within 14 days prior to initiation of therapy (if day 14 falls on a weekend or holiday the deadline may be extended to the next working day):

- History and physical evaluation including height, weight, vital signs and performance status.
- Baseline hematological and biochemical profiles including CBC with differential and comprehensive metabolic panel (fasting glucose, sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, SGOT (AST) SGPT (ALT) total bilirubin, alkaline phosphatase, calcium and magnesium).
- Hemoglobin A1c
- Serum pregnancy test for women of childbearing potential
- Electrocardiogram

7.2 Evaluations During Treatment

Beginning of every cycle (defined as 28 days +/- 3 days) (every 6 months after 5 years on therapy)

- Physical examination
- Toxicity assessment
- Vital signs
- ECOG performance status
- CBC with differential
- Fasting comprehensive metabolic panel
- Assessment of adverse events

Data to be obtained every 3 cycles of treatment (every 12 months after 5 years on therapy):

- Radiologic assessment of tumor burden by CT scan or MRI. Patients who have been on study for **>** 2 years will undergo scans every 6 cycles. Patients who have been on study for > 5 years will undergo scans every 12 cycles, at treating physician discretion.
- Electrocardiogram (baseline, 6 hours after 1st injection, 21days after 1st injection, 21 days after 3rd injection, Cycle 6, and every 3 cycles thereafter.)
- Liver function testing 21 days after 1st injection and 21 days after 3rd injection
- Assessment of chromogranin A and/or other tumor markers or hormones if elevated at baseline (see section 7.1).
- EORTC QLQ C-30 and EORTC QLQ GI-NET21 questionnaires

7.3 End of Treatment Evaluation

Data to be obtained at completion of study:

- Physical examination
- Toxicity assessment
- Vital signs
- Weight
- ECOG PS
- CBC with differential
- Comprehensive metabolic panel
- Glycosylated hemoglobin
- ECG
- Assessment of adverse events
- Radiologic assessment of tumor burden (if patient is discontinued for any reason other than radiographic disease progression).

Table 7-3 lists all of the assessments and indicates the visits at which they are to be performed with an "X". All data obtained from these assessments must be supported in the patient's source documentation.

Table 7-3 Visit evaluation schedule

Evaluation	Screening/ Baseline[a]	6 hours after 1st injection, 21 days after 1st and 3rd injections	Each Cycle (day 1)[k]	Cycle 6	Every 3 Cycles	End[b]
Informed consent	X					
Demographics	X					
Relevant medical history/ current medical conditions	X		X			X
Diagnosis and extent of cancer	X					
Physical exam	X		X			X
Vital signs	X		X			X
ECG[c]	X	X		X	X	X
LFT testing		X				
ECOG Performace Status	X		X			X
CBC with differential[d]	X		X			X
Glycosylated hemoglobin	X					X
Fasting	X		X			X

Comprehensive metabolic panel[e]						
Pregnancy test and review of contraception[f]	X					X
Secretory hormones[g] and serum chromogranin A	X				X	
Radiologic assessment of tumor burden[h]	X				X	X
Adverse events[i]	X		X			X
Concomitant medications[j]	X		X			X
EORTC QLQ C-30 and EORTC QLQ GI-NET21 questionnaires	X				X	

[a] Screening includes review of: demography/informed consent, inclusion/exclusion criteria, relevant medical history/concomitant medications, diagnosis and extent of cancer.

[b] Patients who interrupt or permanently discontinue pasireotide due to an adverse event or abnormal laboratory value must be followed at least weekly for 28 days after the last dose of SOM230, and subsequently at monthly intervals until resolution or stabilization of the event, whichever comes first.

[c] All ECGs should be done before SOM230 injection on the same day. ECG should be done at any time when clinically indicated.

[d] Complete blood count must include: hemoglobin, hematocrit, platelets, total while blood cell count and differential.

[e] Comprehensive metabolic panel should include fasting glucose, sodium, potassium, chloride, bicarbonate, creatinine, blood urea nitrogen, albumin, total protein, SGOT (AST), SGPT (ALT), total bilirubin, alkaline phosphatase, calcium and magnesium. Patients are to fast overnight for 8 hours prior to all biochemistry samples being taken. Blood samples are to be taken in the morning. Water is allowed during this time. Clinically significant electrolyte abnormalities are to be addressed prior to each SOM230 administration.

[f] For women of child-bearing potential: Women of childbearing potential must have a negative serum preganancy test within 14 days of enrollment. Acceptable contraception must be used while on study and for at least 60 days after last dose of pasireotide.

[g] If patients present with hormonally active tumor, secretory hormone levels corresponding to the syndrome (e.g. urine 5-HIAA, gastrin, glucagon, insulin, etc.) should be measured at baseline and each restaging cycle.

[h] Baseline radiologic tests (CT or MRI with iv contrast) should include all known sites of metastatic disease. For most midgut carcinoid tumors, a CT or MRI scan of the abdomen and pelvis is indicated. For pancreatic neuroendocrine tumors, a CT or MRI scan of the abdomen may be sufficient. Patients who have been on study for > 2 years will undergo scans every 6 cycles. Patients who have been on study for > 5 years will undergo scans every 12 cycles.

[i] See section 9.1 for definitions of adverse events

[j] All concomitant medications, including over the counter drugs, should be documented each visit. Particular attention should be paid to dose of diabetic medications. Patients with diabetes are to be instructed to check blood glucose levels via a fingerstick several times daily, particularly for the first few days of treatment.

[k] For patients who have been on study for >5 years, all procedures, with the exception of vitals and treatment administration, will occur only once every 6 months (EP, labs, EKGs, questionnaires); scans will occur once every 12 months.

8 Outcome Measures

The primary efficacy endpoint is progression-free survival, defined as the time from the date of first study treatment to the date of the first documented disease progression (by RECIST criteria) or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off or the anti-cancer therapy date.

8.1 RECIST Criteria for response

The Response Evaluation Criteria in Solid Tumors (RECIST 1.0) guidelines will be employed in this study. For the purposes of this study, target lesions are defined as metastatic lesions that are bidirectionally measurable with one diameter measuring at least 2 cm (or 1 cm with spiral CT scan). All lesions up to a maximum of 10 lesions representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repetitive measurements (either by imaging techniques or clinically). A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

Measurable disease: lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as $\geq$ 2 cm with conventional techniques or as $\geq$ 1 cm with spiral CT scan.

Non-measurable disease: all other lesions, including small lesions (longest diameter < 2 cm with conventional techniques or < 1 cm with spiral CT scan).

Complete response (CR): complete disappearance of all target lesions, confirmed by repeat assessments at no less than 4 weeks after the criteria for response are first met.

Partial response (PR): at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum longest diameter. This must be confirmed by repeat assessment at no less than 4 weeks after the criteria for response are first met.

Progressive disease (PD): at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum longest diameter recorded since the treatment started or the appearance of one or more new lesions.

Stable Disease (SD): neither sufficient decrease to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum longest diameter since the treatment started.

Non-target Lesions: all other lesions (or sites of disease) not included in the "target disease" definition should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent".

Complete Response: Disappearance of all non-target lesions.

Non-complete response/Non-progression: Persistence of one or more non-target lesions.

Progression: Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

Cytology and Histology: if the measurable disease is restricted to a solitary lesion, its neoplastic nature should ideally be confirmed by cytology or histology. These techniques can be used to differentiate between PR and CR in rare cases.

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response, stable disease, and progressive disease

Evaluation of Best Overall Response: the best overall response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 8.1 Evaluation of best overall response

Target Lesions	Non-target Lesions	New Lesions	Overall Response

CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

8.2 Guidelines for Evaluation of Measurable Disease

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules, palpable lymph nodes). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

CT scan: Conventional CT scan should be performed with cuts of 10mm or less in slice thickness contiguously. Spiral CT scan should be performed using a 5mm contiguous reconstruction algorithm.

8.3 Confirmation Measurement/Duration of Response

Confirmation: To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat studies that should be performed no less than 4 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression Free Survival (PFS): PFS is defined as the time from the date of first study treatment to the date of the first documented disease progression or death due to any cause. If a patient has not progressed or died at the date of the analysis cut-off or when he/she receives any further anti-cancer therapy, PFS is censored at the time of the last tumor assessment before the cut-off or the anti-cancer therapy date.

8.4 PFS and Censoring

Since disease progression is assessed periodically, the true date of disease progression is known only to occur at a time point after the last radiological assessment of stable disease (or better) and prior to the date of the scan detecting progression. Table 8.4 provides instructions on classification of the primary endpoint (PFS) depending on various clinical scenarios.

Table 8.4: Classification of Primary Outcome

Situation	Outcome	Date of Progression or Censoring
Progression documented between scheduled visits	Progressed	Earliest of: Date of radiologic assessment showing new lesion (if progression is based on new lesion); or Date of last radiologic assessment of measured lesions (if progression is based on increase in sum of measured lesions)
No progression	Censored	Date of last radiologic assessment of measured lesions
Treatment discontinuation for undocumented progression	Censored	Date of last radiologic assessment of measured lesions
Treatment discontinuation for	Censored	Date of last radiologic assessment of

toxicity or other reason		measured lesions
New anticancer treatment started	Censored	Date of last radiologic assessment of measured lesions
Death before first progressive disease assessment	Progressed	Date of death
Death between adequate assessment visits	Progressed	Date of death
Death after one to two missed visits	Progressed	Date of death
Progression after one to two missed visits	Progressed	Earliest of: Date of radiologic assessment showing new lesion (if progression is based on new lesion); or Date of last radiologic assessment of measured lesions (if progression is based on increase in sum of measured lesions)
Death or progression after more than two missed visits	Censored	Date of last radiologic assessment of measured lesions

9 Safety monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology and blood chemistry parameters and regular physical examinations. Adverse events will be evaluated continuously throughout the study. Safety and tolerability will be assess according to the NIH/NCI Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) that is available at: http://evs.nci.nih.gov/ftp1/CTCAE/About.html

9.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory

values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigators' Brochure or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

9.1.1 Serious adverse events

Information about all serious adverse events will be collected and recorded. To ensure patient safety each serious adverse event must also be reported to Recordati Inc. within 24 hours of learning of its occurrence. A serious adverse event is an undesirable sign, symptom or medical condition which:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- social reasons and respite care in the absence of any deterioration in the patient's general condition

- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

9.1.2 Recordati Inc. instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Recordati Inc. Pharmaceuticals Integrated Medical Safety (IMS).

All events reported to the FDA by the investigator are to be filed utilizing the Form FDA 3500A (MedWatch Form).

All events must be reported, by FAX (888-299-4565), to Recordati Inc. Pharmaceuticals IMS Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences, all deaths during treatment or within 30 days following completion of active protocol therapy.

Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Recordati Inc. study drug (or therapy) is suspected.

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

9.1.3 Pregnancies

Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Recordati Inc. within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

9.2 Data Monitoring Board

The participating investigator will report all adverse events and serious adverse events to the Principal Investigator (or Protocol Chair) and to the IRB according to the local IRB's policies and procedures in reporting adverse events.

10 Data collection

Once eligibility has been established and the participant successfully registered, the participant is assigned a protocol case number. This number is unique to the participant on this trial and must be used for case report form (CRF) completion.

Investigators must enter the information required by the protocol onto CRFs.

11 Statistical methods and data analysis

11.1 Sample size

35 patients will be enrolled, with up to 3 additional patients to account for potential dropouts.

11.2 Sample size justification

We plan to conduct a single-arm phase II trial, with the 12-month progression-free survival rate as the primary endpoint, and using a one-sided alpha level of 10%.

The null hypothesis is that PFS rate at 12 months will be 19%. With n=30 (plus up to 3 additional patients (10%) to account for early dropouts), we will have 90% power to reject the null, if the true 1-year PFS rate from this treatment regimen is 40% (these PFS rates correspond to null and alternative hypothesis median PFS of 5 and 9 months, respectively). The sample size calculations were conducted using nQuery Advisor 6.01.

The sample size was derived for the estimation of PFS at 1-year using binomial theory. If the survival distribution is exponential, a much tighter confidence interval for the 1-year survival is possible. We will first test for the exponentiality of the survival distribution using the Hollander=Proschan[17] test. If the p-value for this preliminary test is greater than 0.20, we will provide the 90% lower confidence bound assuming an exponential distribution.

11.3 Subset analyses

Neuroendocrine tumors are characterized by a heterogeneous rate of growth. Tumors originating in the distal small intestine and proximal colon (midgut carcinoid tumors) are characterized by a slower rate of metastatic growth than neuroendocrine tumors of other sites, including the lungs, stomach, pancreas and rectum. Therefore, a post-study subset analysis will evaluate PFS data based on site of primary tumor, distinguishing between two subsets:

Subset 1: Patients with neuroendocrine tumors of the distal small intestine and cecum (midgut carcinoids). Patients with mesenteric masses whose primary tumors are unidentified will be considered to have midgut carcinoid tumors.

Subset 2: Patients with advanced (metastatic or unresectable) neuroendocrine tumors of other primary sites (lung, stomach, duodenum, distal colon, rectum, pancreas) or unknown primary site.

Other subset analyses will distinguish patients with low-grade (grade 1) tumors versus intermediate grade (grade 2) tumors, and patients with low hepatic tumor burden (<10%) versus high hepatic tumor burden (>10%).

12 Exploratory Analysis

If available, archival tissue containing a tumor block (preferred) or 10 unstained slides (3-5 micron thick) representing biopsies from patient's primary or metastatic neuroendocrine tumor should be sent to Moffitt Cancer Center for correlative immunohistochemical studies. Specimens should be placed in a secure, airtight container, labeled with the patient name and study number.
Site should contact Moffitt Cancer Center at (813) 745-3275 with expected delivery date.

Shipping address:
Attention Dr. Domenico Coppola
Anatomic Pathology Dept.
H. Lee Moffitt Cancer Center
12902 Magnolia Ave
Tampa, FL 33612

Immunohistochemistry (IHC) will be used to evaluate the expression of somatostatin receptors (SSTs $_{1-5}$). Sections of 3-4 microns in thickness will be cut from the selected formalin-fixed paraffin embedded tissue and subjected to IHC staining protocol using the Dakocytomation Autostainer (DakoCytomation, Carpitenria, Calif). Microwave antigen retrieval with IHC Select EDTA buffer, pH 7.5, will be utilized. Rabbitt polyclonal primary antibodies against SST $_{1-5}$ with cross-reactivity against human SST subtypes will be diluted and incubated for 60 minutes at room temperature. Using a semiquantitative scoring system, the intensity of IHC staining for various SST subtypes will be scored as either 0 (negative), 1+ (mild positive staining), 2+ (moderate positive) and 3+ (strong positive staining). The correlation between SST staining patterns and clinical outcomes (PFS) will be analyzed in a descriptive fashion.

We will also explore the correlation between early biochemical response and PFS. Early biochemical responders will be defined as patients with elevated chromogranin A (CgA) who experience a major reduction (>50%) or normalization of their CgA between their baseline (pretreatment) measurement and their follow-up assessment 3 months later.

13 Quality of Life Assessment

Patient quality of life will be measured using the EORTC QLQ-C30 (version 3) and the EORTC QLQ GI.NET21 questionnaires (appendices B and C). The EORTC QLQ-C30 questionnaire is designed to assess the health-related quality of life of cancer patients participating in clinical trials. It is composed of 5 functional scales, three symptom scales, a global health status scale, and six single items. The EORTC QLQ GI.NET21 questionnaire is

designed to assess physical and psychological symptoms related to neuroendocrine tumors of the gastrointestinal tract.
Both questionnaires will be scored and handled as recommended in the user manual. Missing items will be imputed with the mean of the non-missing items scored at that assessment time point. Ambiguous items will be considered as missing items. At each assessment time point, summary statistics of the raw score and linear transformation score (on a 0-100 scale) will be provided.

14 Protocol amendments, or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Recordati Inc. and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Recordati Inc. Examples of amendments requiring such approval are:

1. increases in drug dose or duration of exposure of subjects,
2. significant changes in the study design (e.g. addition or deletion of a control group),
3. increases in the number of invasive procedures,
4. addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Recordati Inc. in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Recordati Inc. must be notified and the IRB at the center must be informed immediately.

15 Procedures and Instructions

15.1.1 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Recordati Inc. and prior to any outside submission. Recordati Inc. must receive copies of any intended communication in advance of publication (at least fifteen working days for presentational materials and abstracts and thirty working days for manuscripts). These requirements acknowledge Recordati Inc.'s responsibility to provide peer input regarding the scientific content and conclusions of such publications or presentations. Principal Investigation/Institution shall have the final authority to determine the scope and content of its publications, provided such authority shall be exercised with reasonable regard for the interests of Recordati Inc. and, in accord with the trial contract and shall not permit disclosure of Recordati Inc. confidential or proprietary information.

15.1.2 Disclosure and confidentiality

The investigator agrees to keep all information provided by Recordati Inc. in strict confidence and to request similar confidentiality from his/her staff and the IRB/IEC/REB. Study documents provided by Recordati Inc. (investigators' brochures and other material) will be stored appropriately to ensure their confidentiality. The information provided by Recordati Inc. to the investigator may not be disclosed to others without direct written authorization from Recordati Inc., except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

15.1.3 Discontinuation of study

Recordati Inc. reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

15.2 Ethics and Good Clinical Practice

This study must be carried out in compliance with the protocol and the principles of Good Clinical Practice, as described in Recordati Inc. standard operating procedures and:

ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.

US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

Declaration of Helsinki and amendments, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

15.2.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB). A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC/REB must be given to Recordati Inc. before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Recordati Inc. approved by this committee.

15.2.2 Informed consent

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with it for IRB/IEC/REB approval.

15.2.3 Declaration of Helsinki

The investigator must conduct the trial in accordance with the principles of the Declaration of Helsinki. Copies of the Declaration of Helsinki and amendments will be provided upon request or can be accessed via the website of the World Medical Association at http://www.wma.net/e/policy/17-c_e.html.

16 References

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Appendix A: List of Drugs Known to Promote QT Prolongation

This is <u>not</u> a comprehensive list of medications which may prolong the QT interval.

Albuterol*
Amiodarone
Arsenic trioxide
Bepridil
Chlorpromazine
Chloroquine
Cisapride
Clarithromycin
Disopyramide
Dofetilide
Domperidone
Droperidol
Erythromycin
Halofantrine
Haloperidol
Ibutilide
Levomethadyl
Mesoridazine
Methadone
Pentamidine
Pimozide
Procainamide
Quinidine
Salbutamol*
Sotalol
Sparfloxacin
Thioridazine
*Parenteral preparations only; inhaled treatments at usual doses are acceptable

Appendix B EORTC QLQ-C30 (version 3)

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

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

During the past week:

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

Please go on to the next page

ENGLISH

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

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

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

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

Appendix C EORTC QLQ-GLNET21

ENGLISH

EORTC QLQ – GI.NET21

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:		Not at all	A little	Quite a bit	Very much
31. Did you have hot flushes?		1	2	3	4
32. Have you noticed or been told by others that you looked flushed/red?		1	2	3	4
33. Did you have night sweats?		1	2	3	4
34. Did you have abdominal discomfort?		1	2	3	4
35. Did you have a bloated feeling in your abdomen?		1	2	3	4
36. Have you had a problem with passing wind/gas/flatulence?		1	2	3	4
37. Have you had acid indigestion or heartburn?		1	2	3	4
38. Have you had difficulties with eating?		1	2	3	4
39. Have you had side-effects from your treatment? *(If you are not on treatment please circle N/A)*	N/A	1	2	3	4
40. Have you had a problem from repeated injections? *(If not having injections please circle N/A)*	N/A	1	2	3	4
41 Were you worried about the tumour recurring in other areas of the body?		1	2	3	4
42. Were you concerned about disruption of home life?		1	2	3	4
43. Have you worried about your health in the future?		1	2	3	4
44. How distressing has your illness or treatment been to those close to you?		1	2	3	4
45. Has weight loss been a problem for you?		1	2	3	4
46. Has weight gain been a problem for you?		1	2	3	4
47. Did you worry about the results of your tests? *(If you have not had tests please circle N/A)*	N/A	1	2	3	4
48. Have you had aches or pains in your muscles or bones?		1	2	3	4
49. Did you have any limitations in your ability to travel?		1	2	3	4
During the past four weeks:					
50. Have you had problems receiving adequate information about your disease and treatment?		1	2	3	4
51. Has the disease or treatment affected your sex life (for the worse)? *(If not applicable please circle N/A)*	N/A	1	2	3	4

Appendix D: Substrates of CYP2C9 and 2D6:

2C9

NSAIDs:
diclofenac
ibuprofen
piroxicam

Oral Hypoglycemics:
tolbutamide
glipizide

Angiotensin II Blockers:
losartan
irbesartan

Others:
celecoxib
fluvastatin
naproxen
phenytoin
rosiglitazone
sulfamethoxazole
tamoxifen
tolbutamide
torsemide
warfarin l

2D6

Beta Blockers:
S-metoprolol
propafenone
timolol

Antidepressants:
amitriptyline
clomiprmine
desipramine
imipramine
paroxetine

Antipsychotics:
haloperidol
risperidone
thioridazine

Others:
aripiprazole
codeine
dextromethorphan l
duloxetine
flecainide
mexilletine
ondansetron
tamoxifen
tramadol
venlaxine

Appendix E: Pasireotide LFT managment algorithm