

North Central Cancer Treatment Group

**An Exploratory, Randomized, Placebo-Controlled Trial of Depot Octreotide
(Sandostatin LAR[®] Depot) for Symptomatic Ascites in Cancer Patients**

*For any communications regarding this protocol,
please call the protocol resource person on the following page.*

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Protocol Resource

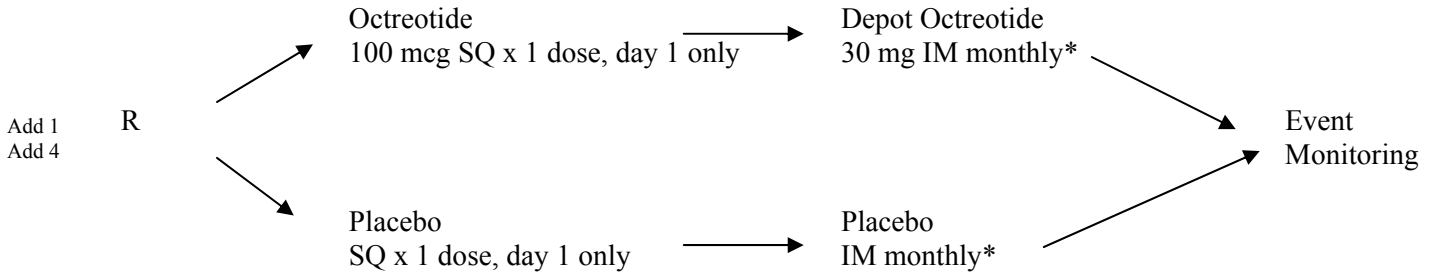
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* No waivers of eligibility per NCI

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Schema



*Octreotide/placebo may be administered monthly up to 2 years.

Add 1 Cycle = 1 month

<p>Generic name: Octreotide Brand name: Sandostatin® Sandostatin LAR® Depot Mayo abbreviation: SOM SOMLAR Availability: NCCTG Research Base Pharmacy</p>	<p>Generic name: Placebo Brand name: Placebo Mayo abbreviation: PLACEB Availability: Commercial for SOM SOMLAR placebo provided by NCCTG Research Base Pharmacy</p>
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1.0 Background

- 1.1 Symptomatic Ascites as a Cause of Suffering for Cancer Patients. Symptomatic ascites is common in cancer patients. As recently reviewed by Smith and Jayson, 10-15% of patients with gastrointestinal malignancies and 20% of patients with carcinomas of unknown primary develop ascites [1]. Although ovarian cancer represents 2% of all malignancies [1a], for some reason these patients are over-represented in consecutive series of ascites patients, representing 20% of the patients in these series [5].

Mackey and others assessed 15 cancer patients with ascites [3] and found it was associated with an “unwell” feeling, nausea, pain, dyspnea, inability to eat, abdominal distension, and a negative self-perception. Von Gruenigen and others observed that in the last 12 months of life, ascites constitutes one of the three most frequent reasons for hospitalization for ovarian cancer patients, (bowel obstruction and pleural effusion being the other two) [2]. Thus, ascites is implicated in an array of noxious symptoms and tremendous morbidity.
- 1.2 No Effective Palliative Interventions. Lee and others surveyed 80 randomly chosen physicians who see patients with malignant ascites. 98% of respondents described paracentesis as the most common intervention [6]. Yet the procedure is invasive, can be painful, requires repetition every 9-10 days [3], and carries serious complication rates as high as 24%, including bowel perforation [7]. Twenty-three physicians added comments, describing malignant ascites as “generally impossible to manage” and “a frustrating clinical situation.” One respondent noted, “a practical and effective solution is needed.” These quotes underscore a dearth of palliative options.
- 1.3 What has been tried? First, diuretics are ineffective in approximately 70% of cancer patients [8]. Diuretics tend to be effective in patients with liver metastases, a small minority of patients with symptomatic ascites. Second, in cancer patients, peritoneal-venous shunts have been associated with infection, thrombophlebitis, intraperitoneal bowel obstruction, abrupt, and widespread dissemination of metastases [9]. Third, although no studies have examined implanted external catheters in cancer patients, they are invasive and lead to cellulitis/peritonitis in as many as 43% of cirrhotic, non-cancer patients [10]. Fourthly, transjugular intrahepatic portosystemic shunts have also not been well studied in cancer patients, but 40% of cirrhotic non-cancer patients report malfunction [11]. Moreover, they too are invasive. There is a clear need to pursue promising palliative strategies.
- 1.4 Ascites Pathophysiology: At any one time, the healthy peritoneal cavity accommodates 50 milliliters of fluid [12,13]. A highly dynamic environment, the healthy peritoneal cavity transfers fluid to the plasma at a rate of 5 milliliters per hour [12,13]. With cancer, this exchange can be disrupted, giving rise to ascites, which occurs largely from lymphatic obstruction and extravasation. The latter has gained increasing attention. Garrison and others showed in a rodent model that cell-free instillation of malignant ascites into the peritoneal cavity resulted in rapid accumulation of ascites far in excess of the volume of instilled fluid [14]. These investigators invoked vascular permeability as the major mechanism behind ascites.

- 1.5 Focus on Vascular Endothelial Growth Factor (VEGF): Fifty thousand times more potent than histamine in causing vascular leak, VEGF is a major mediator of vascular permeability [15]. VEGF causes vascular leak by direct effects on the Flt-1 and KDR/Flk-1 receptors which are present on endothelium. In a 58-patient study, Verheul and others found that cancer patients with malignant ascites have higher ascitic concentrations of VEGF compared to non-cancer patients with ascites [16]. Recently, Byrne and others utilized an animal model to assess the effects of a high affinity soluble decoy receptor designed in effect to block the function of VEGF [18]. Mice inoculated with OVCAR-3 cells received either the VEGF receptor decoy or a control. Whereas mice that received the decoy had no ascites at sacrifice, the other group developed almost 3 milliliters. At least 5 other animal studies have shown similar favorable results with VEGF blockade [19-23]. Taken together, these findings underscore the critical role of VEGF in ascites formation and suggest that an anti-VEGF therapy merits clinical investigation.
- 1.6 Octreotide: Targeting VEGF. Octreotide is a somatostatin analogue and has gained widespread use as a palliative agent for carcinoid syndrome, diarrhea, and variceal bleeding. Its role as an inhibitor of certain endocrine and exocrine secretory processes and as a vasoconstrictor is well established [24]. It also carries a well-established safety profile [25]. Recently, six published studies have shown that octreotide decreases tumor VEGF expression [26-31]. For example, Cascinu and others studied 35 colorectal cancer patients. All received octreotide preoperatively over 2 weeks. Assessment of tumor and serum samples showed decreased expression of VEGF after octreotide [29].
- 1.7 Clinical Data on Octreotide as a Potentially Effective Therapy for Malignant Ascites. Case reports have described complete resolution of ascites with octreotide in non-cancer settings [32-42]. However, particularly relevant to cancer patients is a recent report by Cairns and Malone [43] that describes 3 patients with malignant, symptomatic ascites: one with colon cancer, one with an adenocarcinoma of unknown primary, and the third with breast cancer. The first patient received octreotide as part of bowel obstruction management with complete resolution of ascites. The other two patients were given octreotide and both manifested a decrease in ascites with the breast cancer patient requiring no further paracenteses. These findings are anecdotal and duration of follow-up is not clearly described. Nonetheless, this preliminary report describes the only non-invasive, potentially effective clinical therapy for symptomatic ascites.
- These data also provide some justification for choosing an appropriate dose of octreotide depot for the present trial. The short acting doses of 200-500 micrograms/day translate roughly into a octreotide depot dose of 30 mg/month.
- 1.8 Secondary Translational Component: Validation of a Lysophosphatidic Acid (LPA) Assay for Ovarian Cancer Early Detection. LPA are phospholipids with various roles in transmembrane signaling. Some diseases, such as ovarian cancer, have been associated with elevated plasma LPA concentrations (Xu Y et al. JAMA 1998; 280:719-723). Ovarian cancer is characterized by poor outcome due to late diagnosis at an advanced stage. If LPA are reliable biochemical markers for the early detection of ovarian cancer, an analytical method is needed that allows determination of LPA in a screening setting. Several methods, such as bioassays using voltage clamped *Xenopus* oocytes, and thin-layer chromatography followed by gas chromatography or by mass spectrometry or tandem mass spectrometry (MS/MS) have been described, but they are laborious and

time consuming. The Mayo Clinic has developed a method that allows rapid quantitation of LPA in plasma using liquid-chromatography tandem mass spectrometry (LC-MS/MS).

- 1.9 The methodology behind this new assay is as follows. Plasma is extracted with butanol (1:3) after the addition of 1.0 μM 17:0 LPA as internal standard. After vortexing and centrifugation, the upper phase is collected, evaporated under heated nitrogen, and reconstituted in methanol for analysis using a triple quadrupole MS/MS (Sciex API 3000). Chromatographic separation is achieved with a Phenomenex C8 column using a mobile phase consisting of methanol: 100 mM ammonium acetate: formic acid (90:10:0.05, v: v: v). Complete analysis time is 3 minutes with LPA eluting at approximately 1.5 minutes. 16:0, 18:0, and 18:1 LPA were determined by selective reaction monitoring. Preliminary results using standard solutions of the various LPA at different concentrations (0.1 to 5.0 $\mu\text{mol/L}$) showed detectable and reproducible signals at the levels expected. The same was true for plasma samples spiked with the same standard solutions (mean recovery 100.4 \pm 6.2 %). The intra-assay precision was determined for different levels of the three LPA (\sim 0.50, 1.50, 2.50, and 5.50 $\mu\text{mol/L}$) and the CV were calculated to be 8.9, 5.7, 5.3 and 3.1% respectively (n= 6). Inter-assay precision was 11.7, 7.6, 6.2 and 5.0%, respectively on the same samples (n=6). Although these results are highly promising, this assays requires further validation. Because a large number of ovarian cancer patients are likely to participate in this trial, this trial offers a unique opportunity to complete this validation. To validate this assay it is necessary to determine LPA concentrations in patients with ovarian cancer. Thus, blood samples will be acquired from all Mayo Clinic, Rochester patients who have ovarian cancer and who participate in this study.

2.0 Goals

- 2.1 The primary goal of this study is to determine whether depot octreotide is effective in extending the time-to-paracentesis for cancer patients with symptomatic, malignant ascites.
- 2.2 A second goal will be to explore whether octreotide will reduce the number of paracenteses.
- 2.2 The third goal will be to determine whether depot octreotide can reduce VEGF concentrations in ascitic fluid.
- 2.3 The fourth goal is to determine whether depot octreotide causes any toxicity in this situation.
- 2.4 A fifth goal is to assess quality of life, as it relates to the presence of ascites and to the use of depot octreotide in this setting.
- 2.5 A sixth goal is to provide blood samples from ovarian cancer patients to help in the validation of the LPA assay.

3.0 Eligibility Criteria

3.1 Required characteristics

- 3.11 ≥ 18 years of age.
- 3.12 Current or previous histologic or cytologic proof of malignancy (except lymphoma).
- 3.13 Treating oncologist thinks that ascites is caused by cancer (positive cytology is not necessary).
- 3.14 Therapeutic paracentesis planned ≤ 3 days after randomization or completed in the preceding 2 days prior to randomization.
- 3.15 Patient views ascites as a problem (documentation not necessary).
- 3.16 Must be willing to give ascites fluid sample for research.
- 3.17 Ovarian cancer patients at Mayo Rochester must be willing to give a blood sample for research.

3.2 Contraindications

- 3.21 History of cholecystitis with no cholecystectomy.
- 3.22 Known allergy to subcutaneous octreotide (Sandostatin®) or depot octreotide (Sandostatin LAR® Depot).
- 3.23 Known latex allergy.
- 3.24 Patients with a known history of chronic renal failure (defined by serum creatinine $\geq 2 \times$ UNL). It is not necessary to obtain a serum creatinine in patients who do not have a history of renal disease.
- 3.25 Any medical condition that may interfere with ability to receive protocol treatment.
- 3.26 Life expectancy < 4 weeks.
- 3.27 Lymphomatous ascites
- 3.28 Any of the following:
 - Pregnant women
 - Nursing women
 - Men or women of childbearing potential who are unwilling to employ adequate contraception
- 3.29a Currently receiving octreotide or depot octreotide (Sandostatin LAR® Depot).

- 3.29b Patient is receiving intraperitoneal chemotherapy.
- 3.29c On coumadin or warfarin or at high risk for bleeding from a procedure. (Prophylactic warfarin 1 mg/day is permitted.)
- 3.29d Currently or about to receive first-line chemotherapy for any cancer other than pancreatic cancer. (Second-line chemotherapy or later-line chemotherapy is allowed.)
- 3.29e Currently receiving bevacizumab.
- 3.29f Known cirrhosis or portal hypertension.
- 3.29g Uncontrolled diabetes mellitus.

4.0 Test Schedule

Tests and Procedures	Active-Monitoring Phase				
	≤ 3 days after randomization	24 hours after starting short-acting octreotide/ placebo	2-weeks after starting octreotide /placebo	At any time during study treatment if repeat therapeutic paracentesis is done*	Monthly (after starting octreotide/ placebo)
History and physical examination	X ⁴				X
Platelet count	X ¹			X**	
PT and PTT				X**	
Paracentesis (include date and time of procedure)	X ⁴			X	
Recording of ascites volume withdrawn at paracentesis	X ⁴			X	
Abdominal circumference at the umbilicus prior to paracentesis	X ⁴			X	
Store 10 cc ascites in an EDTA tube for VEGF assessment ^{2, R}	X			X	
Adverse event assessment		X	X		X
Questionnaire completion (Common Liver Disease Questionnaire (CLDQ)).	X		X		X
Pregnancy test ⁵					
Blood draw ^R (required only for all Mayo Clinic Rochester patients with ovarian cancer)	X ³				

1 ≤14 days prior to randomization.

2 (See Section 14.1)

3 Blood samples will be obtained for validation of the LPA assay and will be required for all Mayo Clinic Rochester patients with ovarian cancer. 10 cc of blood will be collected in purple-top tubes that contain EDTA (plasma). They will be left in a refrigerator for no more than 3 hours. The blood tubes will be centrifuged at 1,750 g for 15 minutes at room temperature. Supernatants will then be transferred to Eppendorf tubes and stored at -70 degrees centigrade in the laboratory of Dr. Dieter Matern. (See Section 14.21)

4 Can be done ≤ 2 days prior to randomization.

5 For women of childbearing potential only. Must be done ≤7 days prior to registration.

R Research funded

* Clinicians are advised to discuss with patient that abdominal distension, abdominal pain, and shortness of breath may all be reasons to initiate another paracentesis.

** Decision to re-check these parameters and proceed with paracentesis based on results is up to the discretion of the treating oncologist.

5.0 Stratification Factors

- 5.1 Ongoing chemotherapy anticipated: Yes vs. no.
- 5.2 Frequency of paracentesis prior to enrollment: Never vs. other.
- 5.3 At registration, patient has received chemotherapy: Never vs. only first-line chemotherapy vs. second-line chemotherapy vs. other
- 5.4 The number of stratification factors produces a total of 16 different level combinations. This is below the recommended maximum level of stratification factor levels of one-half of the treatment group size (34 patients per group, 17 levels allowed.⁵⁰ Stratification of the variables listed previously will be achieved through established NCCTG procedures, which balance the marginal distributions.⁵¹
- 5.5 Treatment assignment will be calculated using a dynamic allocation procedure that balances the marginal distributions of the stratification factors between the two treatment arms.⁵⁰ The factors defined in Section 5.0 will be used as stratification factors. Patients will be allocated equally between the two treatment arms.

6.0 Registration/Randomization Procedures

- 6.1 Registration Procedures
 - 6.11 To register a patient, call (507/284-4130) or fax (507/284-0885) a completed eligibility checklist to the Randomization Center between 8 a.m. and 4:30 p.m. central time Monday through Friday.
 - 6.12 Randomization Center will register patients separately to the translational research component of this study (see Section 14.0).
 - Patient has given permission to give ascites sample for research testing. (mandatory)
 - Patient has given permission to give blood sample for research testing. (required for Mayo Rochester patients with ovarian cancer.)
 - 6.13 IRB approval(s) is required for each treating site. A signed Cancer Trials Support Unit (CTSU) IRB Certification Form is to be on file at the CTSU Regulatory Office (fax 215-569-0206). This form can be found at the following Web site: www.ctsu.org/rss2_page.asp. Guidelines can be found under Quick Fact Sheets.

- 6.14 At the time of registration/randomization, Randomization Center personnel will verify the following:
- IRB approval at the registering institution
 - Patient eligibility
 - Existence of a signed consent form
 - Existence of a signed authorization for use and disclosure of protected health information. (USA institutions only)
- 6.15 Treatment on this protocol must commence at the accruing membership under the supervision of a NCCTG member physician.
- Add 1 6.16 Treatment cannot begin prior to registration and must begin ≤ 48 hours after paracentesis.
- 6.17 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.
- 6.18 All required baseline symptoms must be documented and graded.
- 6.19 Study drug availability checked.
- 6.2 Randomization Procedures:
- 6.21 After the patient has been registered into the study, the values of the stratification factors (Section 5.0) will be recorded, and the patient will be randomly assigned to one of the following treatment groups:
- Depot octreotide (Sandostatin LAR® Depot)
 - an identical-appearing placebo
- 6.22 To ensure that both the patient and the medical professionals who care for the patient are blinded to the identity of the treatment assignment, the randomization specialist will follow the double-blinding procedures outlined below.
- 6.3 Procedures for Double-Blinding the Treatment Assignment
- 6.31 After the treatment assignment has been ascertained by randomization, the randomization specialist will notify the designated data manager/nurse/pharmacist at the patient's institution. The name of this contact person is to be given to the randomization office prior to registering the patient. This contact person may not be involved in assessing toxicity or any other outcome measure in that patient. (See Section 7.1)
- 6.32 The treatment assignment will be either active drug or placebo.
- 6.33 The pharmacies in the participating institutions will maintain records that indicate the identity of the patients participating in the study and the patient's corresponding treatment assignment.

7.0 Protocol Treatment

7.1 Treatment Schedule

Agent	Dose Level	Route	Day	ReRx
Octreotide acetate	100 mcg/1 mL	SQ	1	
Octreotide acetate for injectable suspension	30 mg	IM	2	Monthly
Placebo	0.9% Sodium Chloride injection, 1 mL	SQ	1	
Placebo for injectable suspension	2 mL 0.9% Sodium Chloride Injection	IM	2	Monthly

Add 1,2

Add 1 7.11 Treatment with octreotide or placebo will commence no later than 48 hours after paracentesis. Patients will initially receive one subcutaneous injection of 100 mcg/1 mL octreotide acetate injection, or one subcutaneous injection of 1 mL 0.9% Sodium Chloride Injection.

Add 1,2 7.12 The patient will then be assessed the following working day for toxicity, according to the criteria in section 8.0 of the protocol. If the study drug or placebo is satisfactorily tolerated, patients will then receive octreotide acetate for injectable suspension (Sandostatin LAR Depot), 30 mg IM or an IM injection of 2 mL of normal saline (as the placebo).

- Add 1
- Placebo is to be handled in a manner identical to active drug. Syringes used for administration of the active drug are to be identical to those used for administration of placebo. The active drug is supplied in a kit which includes a syringe containing diluent. This syringe is to be used to dilute the Sandostatin LAR Depot powder and should then be discarded. A new syringe and 19 gauge, 1 1/2 " needle should be used to withdraw the subject's dose from the vial.
 - The drug or placebo will be drawn into the syringe out of sight of the patient and in such a way that the patient never sees the vial from which the drug is dispensed.
 - The healthcare professional who administers the drug or placebo must not inform the patient of the identity of the product that is being administered.
 - A person who administers study drug or placebo to a patient may not be involved in assessing toxicity or any other outcome measure in that patient.

- A person who administers study drug or placebo to a patient will not identify which was given to other individuals involved in the conduct of the study
- 7.2 The research base is to be notified immediately if it is determined that a patient, or a health care provider involved in the assessment of the patient, inadvertently becomes unblinded. A patient will be considered to be unblinded only if the identity of the agent (drug or placebo) has been clearly revealed to the patient. For example, a patient who thinks that octreotide has been administered because of an experience of certain symptoms (e.g. a decrease in diarrhea) would not be considered to be unblinded. Please call the Randomization Center at 507-284-4130 if unblinding occurs. All cases of unintentional unblinding will be documented in patients' charts.
- 7.3 Patients should be advised that that abdominal distension, abdominal pain, and shortness of breath may all be reasons to initiate another paracentesis, and patients should be encouraged to call should such symptoms arise.
- 7.4 Patients will be seen monthly by a physician, nurse, nurse practitioner, physician's assistant or clinical nurse specialist to assess toxicity and tolerance to treatment and the study drug. Please refer to section 4.0 for a detailed account of the information to be collected at these visits.
- 7.5 Patients will be given booklets with the CLDQ questionnaire to complete at baseline, two weeks post study medication initiation, and monthly when they are seen by their healthcare provider.
- 7.6 In the event of an emergency, call the Randomization Center at (507) 284-4130 to break the code on Monday through Friday, 8:00 a.m. to 4:30 p.m. central time.

8.0 Dosage Modification Based on Toxicity

Toxicity	Agent	Modification
Grade 3 or worse diarrhea, biliary toxicity,** abdominal pain, <u>or</u> any increase in any of these toxicities from grade 0 or 1 at baseline to grade 2 following treatment with octreotide on the first day of protocol therapy	SOM/PLACEB	Discontinue study medication.* Do not proceed to therapy with depot octreotide or placebo. Do not break code.
≥ grade 3 diarrhea, abdominal pain, biliary toxicity,** constipation, or hyperglycemia.	SOMLAR/PLACEB	Discontinue study medication.* Do not break code.

*In an individual patient, it should not be assumed that toxicity is due to medication.

**All cases of biliary toxicity are to be reported as an ADR.

9.0 Ancillary Treatment

9.1 Patients should continue to take their usual medications.

9.11 Octreotide has been associated with alterations in nutrient absorption, so it may have an effect on absorption of orally administered drugs. Concomitant administration of octreotide injection with cyclosporine may decrease blood levels of cyclosporine and result in transplant rejection.

Patients receiving insulin, oral hypoglycemic agents, beta-blockers, calcium channel blockers, or agents to control fluid and electrolyte balance, may require dose adjustments of these therapeutic agents.

Concomitant administration of octreotide and bromocriptine increases the availability of bromocriptine. Limited published data indicate that somatostatin analogs might decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormones. Since it cannot be excluded that octreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g., quinidine, terfenadine) should therefore be used with caution.

9.2 Other supportive measures: In patients who have other symptoms, all other supportive care measures should be utilized.

- 9.3 Under no circumstances should patients be treated for ascites with any other interventions besides paracentesis, study treatment, or ongoing diuretics. (Chemotherapy is allowed.) Should a patient receive other treatment, efficacy data will be censored but the patient will continue to be followed.

10.0 Adverse Event (AE) Reporting and Monitoring

- 10.1 This study will utilize the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 for adverse event monitoring and reporting. The CTCAE v3.0 can be downloaded from the CTEP home page (<http://ctep.info.nih.gov/reporting/ctc.html>). All appropriate treatment areas should have access to a copy of the CTCAE v3.0.

- 10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE. Next, determine whether the event is expected or unexpected (refer to Section 15.0 and/or product literature) and if the adverse event is related to the medical treatment or procedure (see Section 10.12). With this information, determine whether an adverse event should be reported as an expedited report (see Section 10.2) or as part of the routinely reported clinical data.

Expedited adverse event reporting requires submission of a written report, but may also involve telephone notifications. Telephone and written reports are to be completed within the timeframes specified in Section 10.2. All expedited adverse event reports should also be submitted to the local Institutional Review Board (IRB).

- 10.12 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the investigational agent(s).

Probable - The adverse event *is likely related* to the investigational agent(s).

Possible - The adverse event *may be related* to the investigational agent(s).

Unlikely - The adverse event *is doubtfully related* to the investigational agent(s).

Unrelated - The adverse event *is clearly NOT related* to the investigational agent(s)

10.2 Expedited Adverse Event Reporting Requirements

The FDA has determined that on this trial octreotide is exempt from investigational adverse event reporting requirements (investigator-held IND). Commercial reporting requirements apply.

	Grade 4 or 5 Unexpected with Attribution of Possible, Probable, or Definite	Increased Incidence of an Expected AE ¹	Other Grade 4 or 5 <i>or</i> Any Hospitalization During Treatment ²	Secondary AML/MDS ³
FDA Form 3500 (MedWatch) to NCCTG within 5 days ⁴	X ⁵	X		
Notification form: Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form to NCCTG within 5 working days ^{2,4}			X	
NCI/CTEP Secondary AML/MDS Report Form to NCCTG within 15 working days ⁴				X

1. Any increased incidence of a known AE that has been reported in the package insert or the literature, including adverse event resulting from a drug overdose.
2. If the FDA Form 3500 (MedWatch) has been completed, this form does not need to be completed. Any death more than 30 days after the patient's last study treatment or procedure which has an attribution of at least possibly treatment related must be reported as a Grade 5 AE, with CTCAE type and attribution assigned.
3. Reporting for this AE required during or after treatment.
4. Fax or mail to the NCCTG Operations Office, 200 First Street SW, Rochester, MN 55905, Fax 507-284-1902. NCCTG will forward the report to the FDA and NCI as applicable.
5. NCCTG will forward the report to Novartis Pharmaceuticals CS & E Department (fax #888-299-4565)

All forms noted above are available for downloading from the NCCTG website. Upon receipt of the above reports, the NCCTG Operations Office will forward reports to all regulatory agencies (including NCI, FDA, and others) as applicable. Specifically, and in accordance with the relevant section of the *NCI Guidelines: Expedited Reporting Requirements for NCI Investigational Agents*, the Operations Office will forward FDA Form 3500 (MedWatch) reports to the FDA and to NCI within the allotted (total) 10 working days and using one of the cited submission mechanisms.

- 10.3 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grading unless otherwise stated:

Category	Adverse Event/Symptoms	Baseline	Each evaluation
Gastrointestinal	# stools per day	X	
	Constipation	X	X
	Diarrhea		X
	Proctitis	X	X
Hepatobiliary/ Pancreas	Cholecystitis	X	X
Pain	Gastrointestinal -Abdominal NOS	X	X
Dermatology/ Skin	Injection site reaction		X

- 10.31 Submit to the NCCTG Research Base via the Nadir/AE Log the following AEs experienced by a patient and not specified in Section 10.3:
- 10.311 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- 10.312 Grade 3, 4, and 5 AEs and deaths within 30 days of the patient's last treatment, regardless of attribution to the study treatment or procedure, with the exception of signs or symptoms of definitely related to the patient's disease or disease progression.
- 10.313 Any death more than 30 days after the patient's last study treatment or procedure which is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.
- 10.32 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation

- 11.1 Schedule for treatment evaluation
- 11.11 All patients should be evaluated monthly or more frequently if they require an interim therapeutic paracentesis.

- 11.2 Endpoint to be evaluated
 - 11.21 Time-to next-paracentesis after enrollment.
 - 11.22 Quality of life with Common Liver Disease Questionnaire (CLDQ).
 - 11.23 Adverse Events, as recorded with CTCAE3.0 criteria
 - 11.24 Other goals as outlined in section 2 will be addressed in a descriptive manner based on the information gathered in this protocol.

12.0 Descriptive Factors

- 12.1 Cancer type: Ovarian cancer vs. primary peritoneal cancer vs. gastrointestinal cancer vs. other.
- 12.2 Ongoing diuretic therapy anticipated: Yes vs. no.
- 12.3 Liver metastases in > 25% of the liver: Yes vs. no.

13.0 Treatment/Follow-up Decision at Evaluation of Patient

- 13.1 Therapy with octreotide or placebo will be continued as outlined in sections 7.0 and 8.0.
- 13.2 If on the second day of protocol treatment (prior to administration of depot octreotide or placebo), a patient develops grade 2 or worse diarrhea, biliary toxicity or abdominal cramping, protocol therapy will be discontinued and the patient will not receive any depot octreotide or placebo.
- 13.3 The treatment code may *not* be broken except for emergencies.
- Add 1 13.4 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material must be submitted. No further data submission is necessary
- Add 1 13.5 Patients who remain on octreotide/placebo for two years do not go on to event monitoring.
- Add 1 13.6 When the patient completes treatment with octreotide/placebo, the Randomization Center may be called to find out which study therapy the patient was receiving. The patient will be told whether he/she received octreotide or placebo.

14.0 Translational/Pharmacologic Studies

- 14.1 Vascular Endothelial Growth Factor(VEGF)
 - 14.11 Collection of specimens
 - Add 3 14.111 **Kits are required for this study.**
 - Update 2 14.1111 Kits will be supplied through MML. Participating institutions may obtain kits by faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form.
 - Add 3 14.1112 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

Add 3 14.1113 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

Add 3 14.1114 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **NCCTG will not cover the cost for rush delivery of kits.**

14.112 **ALL** sections of the form/specimen collection labels **must** be completed.

14.113 **NOTE:** Because we are now being charged for all outgoing kits, a **small**, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry.

Update 1 14.114 MML at Mayo Clinic Rochester will receive the samples and send to the
Update 2 Biospecimen, Accessioning, and Processing (BAP) laboratory, Stable 13-10A, attention BAP Supervisor.

14.12 BAP will receive 10 cc of ascites fluid in an EDTA tube. All ascites fluid will be sent to the Immunochemical Core Laboratory. VEGF in ascites will be measured with a quantitative two-site enzyme immunoassay from R&D Systems (Minneapolis, Minnesota). The inter-assay coefficient of variation (CV) is 16.6% at 42 pg/mL.

14.2 Lysophosphatidic Acid (LPA) assay

14.21 Blood samples will be obtained for validation of the LPA assay and will be required for all Mayo Clinic Rochester patients with ovarian cancer. Ten cc of blood will be collected in purple-top tubes that contain EDTA (plasma) and forwarded to the Biospecimen Accessioning and Processing Laboratory (BAP), Stable 13-10A. They will be left in a refrigerator for no more than 3 hours. The blood tubes will be centrifuged at 1,750 g for 15 minutes at room temperature.

Update 1

Supernatants will then be transferred to Eppendorf tubes and stored at – 70 degrees centigrade in the laboratory of Dr. Dieter Matern.

15.0 Drug Information

15.1 Sandostatin for Subcutaneous Injection Investigational Supply (SOM)

15.11 Formulation and storage: Sandostatin For Subcutaneous Injection (Octreotide Acetate Injection) is supplied as a sterile solution. Ampuls containing 100 mcg/mL octreotide (as acetate) will be provided. The ampuls should be stored at refrigerated temperatures 2°C - 8°C (36°F - 46°F) and protected from light.

Add 3

15.111 Placebo: A subcutaneous injection of 1 mL of Sodium Chloride Injection USP will be administered for the placebo dose. The saline will be obtained from the commercial drug supply at the NCCTG institution (see Section 15.3)

15.12 Preparation and Mixing: Withdraw 100 mcg (1 mL) from the ampule and inject subcutaneously.

15.13 Administration: Administer as a deep subcutaneous injection.

15.14 Known potential toxicities:

Adverse effects, which are more frequent: Abdominal pain, diarrhea/loose stools, flatulence, and steatorrheic stools. Nausea and vomiting. Transient pain, redness, bleeding, or swelling at the injection site. Hyperglycemia, hypothyroidism

Adverse effects, which are less frequent: Treatment emergent gallbladder and biliary tract abnormalities including asymptomatic or symptomatic gallstones, sludge, biliary duct dilatation, gallbladder dilatation. Hypoglycemia, bradycardia, reversible thrombocytopenia, dizziness, vasomotor flushing (hot flashes). Elevation in liver function tests. Hair loss, rash, headache.

Adverse effects, which are rare: Hypertension, pancreatitis, hepatitis, galactorrhea, fatigue, anxiety, depression, shortness of breath, heartbeat irregularities, heart failure, chest pain, dry mouth, numbness, visual disturbances, fever, and throat discomfort.

15.15 Drug procurement: The NCCTG research base pharmacist will obtain the octreotide acetate injection from Novartis. Each institution will order the drug from the NCCTG research base pharmacist. Submit the NCCTG Clinical Drug Order/Return Form request to:

Investigational Pharmacist
Mayo Clinic
Gonda 10-178
Rochester, MN 55905
FAX (507) 284-3464

15.151 Each NCCTG site must have IRB approval and must have a patient enrolling in the trial before study medication will be provided. The sodium chloride placebo will not be provided by Novartis or the NCCTG research base.

Return any outdated or remaining drug to the research base pharmacy

15.16 Nursing guidelines:

15.161 Pain/burning/erythema at the injection site have been a common occurrence, but usually persist for only approximately 15-20 minutes, and may diminish in frequency and severity with continued use. Warm, moist packs may be used immediately after injection to reduce effects.

15.162 Abdominal pain, cramping, diarrhea, nausea and vomiting can occur. Bloating and flatulence are also common. The GI effects develop during the first few days to weeks of treatment and diminish over time suggesting GI adaptation.

- 15.163 Octreotide may alter GI absorption of dietary fats that could develop into steatorrhea. Advise patients to report any troubles to their doctors and/or nurses.
- 15.164 Octreotide has been associated with development of gallstones or slush in some studies. Instruct patients to report any epigastric pain or right upper quadrant pain and/or jaundice, with or without nausea that persists for more than 30 minutes. Pain may occur after heavy meals.
- 15.165 Headache, dizziness, weakness, fatigue has been reported to occur in about 1-2% of patients. Advise patients to report side effects to health care team. Treat accordingly.
- 15.166 Advise insulin-dependent diabetic patients to carefully monitor blood sugar levels. Octreotide may improve glycemic control and insulin requirements. However, in type II diabetes, drug may cause less glycemic control due to decreased residual insulin secretion.

15.2 Sandostatin LAR Depot Investigational Supply (SOMLAR)

- Add 1 15.21 Formulation and storage: Sandostatin LAR Depot (octreotide acetate for injectable suspension) is supplied as 5 mL vial of 30 mg octreotide acetate with a syringe containing 2.5 mL of diluent. Store the product at refrigerated temperatures between 2°C - 8°C (36°F - 46°F) and protect from light during storage.
- Add 3 15.211 Placebo: An intramuscular injection of 2 mL of Sodium Chloride Injection USP will be administered for the placebo dose. The saline will be obtained from the commercial drug supply at the NCCTG institution (see 15.3)
- Add 1 15.22 Preparation and Mixing: Prepare the Sandostatin LAR Depot as instructed on a Novartis Instruction sheet, video, or CD. These will be available on a limited basis from the NCCTG pharmacy. You can also find on-line mixing instructions at www.us.sandostatin.com or call 1-877-LAR-HELP for information on preparation. Syringes used for administration of the active drug are to be identical to those used for administration of placebo.
- Use only 1 and 1/2 inch 19 gauge needles. Administer immediately after suspension. If needle clogs, replace with a new 1 and 1/2 inch 19 gauge needle. Incorrect preparation and/or administration could result in failure of drug delivery.
- 15.23 Administration: Administer via intramuscular injection, deep into the upper, outer quadrant of the right or left gluteus
- 15.24 Known potential toxicities:
- Adverse effects, which are more frequent: Abdominal pain, diarrhea/loose stools, flatulence, and steatorrheic stools. Nausea and vomiting. Transient pain, redness, bleeding, or swelling at the injection site. Hyperglycemia, hypothyroidism

Adverse effects, which are less frequent: Treatment emergent gallbladder and biliary tract abnormalities including asymptomatic or symptomatic gallstones, sludge, biliary duct dilatation, gallbladder dilatation. Hypoglycemia, bradycardia, reversible thrombocytopenia, dizziness, vasomotor flushing (hot flashes). Elevation in liver function tests. Hair loss, rash, headache.

Adverse effects, which are rare: Hypertension, pancreatitis, hepatitis, galactorrhea, fatigue, anxiety, depression, shortness of breath, heartbeat irregularities, heart failure, chest pain, dry mouth, numbness, visual disturbances, fever, and throat discomfort.

- 15.25 Drug Procurement: Novartis will supply octreotide acetate for injectable suspension to the NCCTG Coordinating Center Pharmacy:

Add 2

Investigational Pharmacist
Mayo Clinic
Gonda 10-178
Rochester, MN 55905
FAX (507) 284-3464

Each NCCTG site must have IRB approval and must have a patient enrolling in the trial before study medication will be provided.

Return any outdated or remaining drug to the research base pharmacy

15.26 Nursing Guidelines

- 15.261 Pain/burning/erythema at the injection site have been a common occurrence, but usually persist for only approximately 15-20 minutes, and may diminish in frequency and severity with continued use. Warm, moist packs may be used immediately after injection to reduce effects.
- 15.262 Abdominal pain, cramping, diarrhea, nausea and vomiting occur. Bloating and flatulence are also common. The GI effects develop during the first few days to weeks of treatment and diminish over time suggesting GI adaptation.
- 15.263 Octreotide may alter GI absorption of dietary fats that could develop into steatorrhea. Advise patients to report any troubles to their doctors and/or nurses.
- 15.264 Octreotide has been associated with development of gallstones or slush in patients in some studies. Instruct patients to report any epigastric pain or right upper quadrant pain and/or jaundice, with or without nausea that persists for more than 30 minutes. Pain may occur after heavy meals.
- 15.265 Headache, dizziness, weakness, fatigue has been reported to occur in about 1-2% of patients. Advise patients to report side effects to health care team. Treat accordingly.

15.266 Advise insulin-dependent diabetic patients to carefully monitor blood sugar levels. Octreotide may improve glycemic control and insulin requirements. However, in type II diabetes, drug may cause less glycemic control due to decreased residual insulin secretion.

Add 2

15.3 Saline Placebo

- 15.31 Formulation and supply: Several companies supply 0.9% Sodium Chloride Injection (Normal Saline). Each treatment site will be responsible for obtaining their own commercial supply of Normal Saline to be used as a placebo for this trial.
- 15.32 Preparation and Mixing: Draw up the appropriate volume of Normal Saline and administer via the appropriate route based on the treatment section of the protocol.
- 15.33 Blinding: The drug company cannot supply NCCTG with matching placebo. Normal Saline will be used as the placebo. The person administering the drug or placebo will not be blinded to the study medication/placebo. We should be able to maintain double blinding, as described below:
1. The person administering the drug must not be involved in assessing the study endpoints (i.e. the patient's symptomatic response).
 2. Nothing should appear in the patient's clinical or research chart identifying whether the patient received drug or placebo.
 3. Sandostatin LAR Depot is opaque, while Normal Saline is not. Immediately after preparation of the syringe is complete, an opaque piece of tape will be used to cover the syringe to facilitate blinding of the patient.
 4. If the identity of the drug/placebo is inadvertently unblinded to the patient or health care providers involved in assessing study endpoints, a mechanism is in place for notifying the NCCTG office. (See Section 7.2)

16.0 Statistical Considerations and Methodology

16.1 Endpoints:

- 16.11 The primary endpoint is the median time-to-paracentesis for each treatment group.
- 16.12 Secondary endpoints include per treatment group summaries of :
- The number of paracenteses
 - VEGF concentrations in ascitic fluid
 - Toxicity incidence
 - Average QOL

16.2 Analysis plans:

- 16.21 Primary endpoint: Kaplan Meier curves will be constructed for each group; patients lost to follow up will be censored. A log rank test will be used to compare groups. We will adjust for the volume of fluid withdrawn at paracentesis and for change in abdominal circumference between baseline and the next procedure because a patient may require an extra paracentesis if only a small volume is withdrawn at baseline.
- 16.22 Secondary endpoints: As a secondary exploratory endpoint, we will compare the number of paracenteses between groups. Parametric or nonparametric testing will be used as appropriate. Because this trial focuses on patients who are at the end of life, we anticipate a high patient drop out rate. We will therefore include time-on-study as a covariate in these analyses.

For VEGF analyses in ascitic fluid, we define a 50% drop from baseline at one month as a clinically relevant. This definition is based on data from Zebrowski and others, where this drop represents half a standard deviation of VEGF in ascites, or a moderate effect size [44]. The above sample size of 34 per group enables detection of a 50% VEGF drop in 38% of octreotide patients and 10% of placebo patients with 80% power and a 5% type I error rate. Although we will report and analyze serum changes of VEGF over one-month, this endpoint is considered minor because serum VEGF has not been found consistently to be a sensitive indicator of disease activity.

We acknowledge that if Sandostatin LAR is highly effective in controlling ascites, we will not be able to acquire ascitic fluid for VEGF analyses. We are willing to accept this limitation if the clinical benefits of octreotide are so apparent.

Toxicity will be presented descriptively in a tabular form.

Quality of life will be recorded and analyzed in a descriptive, exploratory fashion. We acknowledge that this study will represent the first to attempt a prospective assessment of quality of life in patients with symptomatic ascites. The underlying hypothesis of this quality of life assessment is that patients who are receiving octreotide will enjoy a better quality of life compared to patients who receive placebo. Quality of life scores from the CLDQ will be summed for all patients on a monthly basis. Again we anticipate high patient drop out rates over time within these two cohorts. With due diligence, we will attempt to ascertain the reason for each patient drop out, and appropriate imputation techniques will be employed for each. We will be conservative with the imputation of missing values, and if it remains unclear why a patient has dropped out of the study, we will assume a poor outcome, and a quality of life score of zero will be imputed and included in the summed score for that treatment group. Comparisons between groups will be undertaken with parametric or non-parametric techniques as indicated. We will utilize number of paracenteses within each group as a covariate in these analyses.

The data on LPA from ovarian cancer will be pooled by Dr. Matern and validation will be performed after other samples from healthy controls are acquired.

16.23 Sample size: This trial will include 34 patients per group (68 total). Sample size is based on a median time to paracentesis of 9 days in the placebo group [3] with a prolongation to 20 days in the octreotide group. This large effect size is sought because logistics of scheduling a paracentesis may artificially prolong time-to-paracentesis by a day or 2. This sample size enables detection of this 11-day effect size with 90% power and a 5% type I error rate.

16.3 Interim analyses and stopping rules:

Add 3

16.31 This study will be monitored by the Mayo Clinic Data Safety Monitoring Board (DSMB). Reports containing patient characteristics, toxicity and administrative information will be provided to the DSMB every six months, with the first report due at the first reporting period after study initiation. Reports will be due January 31 and July 31 or April 30 and October 31, unless otherwise specified by the DSMB.

Add 2

Stopping rules: We again acknowledge that drop out rates will be high and that attribution of adverse events is difficult in patients at the end of life. We also acknowledge that octreotide had been used in patients with a variety of malignancies and that its safety profile in this setting is well established. However, if at any time, the investigative team observes 4 or more grade 4 events that are directly attributable to the study drug or 1 or more grade 5 events that are directly attributable to the study medication, trial accrual will be suspended and the safety data will be assessed in an unblinded fashion.

16.4 Missing Data: We have compiled a series of macros for carrying out sensitivity analyses with respect to missing data through our work and through collaborations with Diane Fairclough.^(45,46) These routines handle missing data in a number of ways including complete case analysis and imputation via nearest neighbor, mean value, last value, and zero value carried forward approaches.^(47,48) Multiple approaches will be used so that the sensitivity of results to alteration in imputational assumptions may be assessed. These methods will be applied to the primary endpoint of median time to paracenteses as well as all of the continuous level secondary endpoints (e.g. QOL).

16.41 Categorical event variables will be handled in an intent-to-treat fashion⁽⁴⁹⁾. Any patient with missing data for this endpoint will be considered to have experienced a treatment failure

16.5 Inclusion of Women and Minorities

16.51 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.52 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.53 The geographical region served by NCCTG has a population which includes approximately 5% minorities. Although this study is open to both males and females, it is expected that 95% of the subjects will be female. Expected sizes of racial by gender subsets are shown in the following table:

Ethnic Category	Sex/Gender			Total
	Females	Males	Unknown	
Hispanic or Latino	1	0	0	
Not Hispanic or Latino	63	4	0	
Unknown	0	0	0	
Ethnic Category: Total of all subjects*	64	4	0	68*
Racial Category				
American Indian or Alaskan Native	0	0	0	
Asian	1	0	0	
Black or African American	4	0	0	
Native Hawaiian or other Pacific Islander	0	0	0	
White	59	4	0	
More than one race	0	0	0	
Unknown	0	0	0	
Racial Category: Total of all subjects*	64	4	0	68*

**These totals must agree. Enter actual estimates (not percentages)*

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations: None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable (all materials are forwarded to the NCCTG Operations Office unless otherwise indicated)

Forms	Active-Monitoring Phase (Compliance with Test Schedule)			Event-Monitoring Phase ¹ (Completion of Active-Monitoring Phase)	At each occurrence		
	Initial Material	Follow-up Material			Grade 4 or 5 Non-AER Reportable Events/ Hospitalization	ADR/ AER	Late Adverse Event
	≤2 weeks after registration	At each evaluation ²	At end of treatment	q 6 months ¹			
On-Study Form	X						
Baseline Adverse Events/Symptoms	X						
Blood Specimen Submission Form	X						
VEGF Specimen Submission Form	X	X					
Paracentesis Data Collection Form	X	X					
Evaluation/Treatment Form		X					
Concurrent Treatment Log	X	X	X				
End of Treatment Form			X				
Adverse Event Log ³		X	X				
Event-Monitoring Form				X			X
Patient Questionnaire	X	X ⁴	X				
Patient Questionnaire Booklet Compliance Form	X ⁵	X ⁵					
ADR/AER (see Section 10.0)						X	
Grade 4 or 5 Non-AER Reportable Events/ Hospitalization Form					X		

Add 1

Add 2

Add 2

Add 2

Footnotes are on the following page.

1. For 2 years from on-study. Patients who remain on octreotide/placebo for two years do not go on to event monitoring.
- Add 1 2. Monthly. (If a paracentesis is done during the month, it will be reported at the 1 month evaluation)
3. The 24 hour and 2 week adverse event assessment will not be submitted individually but should be recorded within the Cycle 1 (1st month) Adverse Event Log. The **highest** grade observed this cycle and the relationship to study medication is to be recorded when completing the Adverse Event Log.
4. The patient questionnaire booklet is submitted after the 2 week evaluation and then monthly.
- Add 2 5. This form must be completed **only** if the patient questionnaire booklet contains absolutely **NO** patient provided assessment information.

19.0 Budget

- 19.1 Costs charged to patient: routine clinical care
- 19.2 Tests to be research funded: Vascular endothelial growth factor and LPA assays. (existing grant funding)
- 19.3 Other budget concerns:
 - 19.31 Octreotide to be provided free of charge by Novartis.
 - 19.32 Specimen kits (existing grant funding).

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Appendix I

NCI Informed Consent Template for Cancer Treatment Trials

(English Language)

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer...What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035> or call 1-800-4- CANCEr (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

N04C2, An Exploratory, Randomized, Placebo-Controlled Trial of Depot Octreotide (Sandostatin LAR[®] Depot) for Symptomatic Ascites in Cancer Patients

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have fluid in your abdomen from cancer.

Why is this research study being done?

The purpose of this research study is to....

- learn if long-acting octreotide is helpful in preventing the need for paracentesis (taking fluid out of the abdomen) in patients with ascites (fluid in the abdomen) from cancer
- see if there are any side effects with long acting octreotide
- learn if long acting octreotide improves quality of life
- see if octreotide causes a decrease in vascular endothelial factor, a substance thought to cause ascites, in patients with ascites.
- evaluate in Mayo Clinic patients with ovarian cancer whether a certain substance called Lysophosphatidic Acid can be accurately measured with a new procedure being tested at Mayo.

How many people will take part in the research study?

About 68 people will take part in this study.

What will happen if I take part in this research study?

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance as in the flip of a coin. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in any group.

You will have fluid taken out of your abdomen before you have treatment with the study drug. Research testing may be done on a sample of this fluid. Each time you have fluid taken from your abdomen during the study, research testing will be done on a sample of this fluid.

FOR MAYO ROCHESTER PATIENTS ONLY:

If you have ovarian cancer, blood will be drawn from a vein in your arm for research testing.

You will get a shot into your skin from a nurse or other healthcare provider with either short-acting octreotide or a placebo (inactive substance). On the next day, you will be seen by a doctor, physician's assistant or nurse to make sure that you are doing well with the drug. If you are doing well with the short-acting drug, you will get a shot with either long-acting octreotide or a placebo into a muscle. A second shot will be given a month later. You will keep getting the shots once a month as long as you and your doctor think they are helpful.

You will be seen once a month in your health care provider's office. If you need a paracentesis before the one-month visit, then you should call your healthcare provider earlier to get it set up.

You may be asked to fill out a brief questionnaire before you start the study medication, two weeks after you start the study medication, and once a month.

At the end of treatment with the study medication, you will find out whether you were taking octreotide or the placebo.

Add 1

You will be followed in this study for as long as you are able to be followed but not beyond 2 years.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the octreotide can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what followup care and testing could be most helpful for you. The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the octreotide. In some cases, side effects can be serious, long lasting, or may never go away. There also is a risk of death.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the octreotide include those which are:

Likely

- pain due to the shots

Less Likely

- stomach pain or discomfort
- loose stools/diarrhea
- gas
- upset stomach
- vomiting
- liver problems
- slight elevation in liver function tests
- flushing
- swelling and redness of skin where you have the shot
- hair loss
- rash
- headache
- dizziness
- hot flashes
- lowering or elevating your blood sugar level
- decrease in your thyroid function.

Rare

- dry mouth
- numbness
- slow heart rate
- visual disturbance
- gallstones or other gallbladder or bile duct problems
- chills
- fever
- high blood pressure
- pancreas problems
- liver inflammation
- unwanted discharge of milk from the breasts
- throat discomfort
- bleeding because of changes in your blood counts
- fatigue
- anxiety
- depression
- shortness of breath
- palpitations

- heart failure
- chest pain

Octreotide can cause gallstones in some patients. When gallstones occur, they usually do not result in problems for patients, such as pain or discomfort. In some cases, however, patients may experience symptoms from gallstones, such as stomach pain, and require treatment with drugs or surgery to correct this problem.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breast feed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your health care provider about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study. Women who can still become pregnant must have a pregnancy test before taking part in this study. You will be told if you are pregnant or not. If you are pregnant, you will not be able to take part in the study.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. Your ascites may be lessened or prevented. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

The alternative to participation in this trial is to receive the regular treatment for your ascites, such as paracentesis, which involved taking fluid out of your abdomen with a needle. The use of long acting octreotide to treat or prevent ascites cannot be recommended outside of a clinical trial. You should talk to your doctor about each of these choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- NCCTG investigators
- Novartis, the company supplying study drug

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Novartis, a commercial drug company, is supplying the short and long acting octreotide at no cost to you. If you receive placebo, you will not have to pay for this agent. However, you or your health plan may need to pay for costs of the supplies and personnel who give you the (drug).”

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at <http://cancer.gov/clinicaltrials/understanding/insurance-coverage>. You can print a copy of the “Clinical Trials and Insurance Coverage” information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ [*investigator’s name(s)*], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [*telephone number*].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ [name(s)] at _____ [telephone number].

For questions about your rights while taking part in this study, call the _____ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at _____ (telephone number). *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

This study also has laboratory tests that will be performed to study small samples of ascites. A small sample of the ascites fluid that is removed from your abdomen when you have a paracentesis will be used for research tests.

The ascites fluid will be sent to laboratories associated with NCCTG where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

Add1

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at <http://cancer.gov/>

- For NCI's clinical trials information, go to: <http://cancer.gov/clinicaltrials/>
- For NCI's general information about cancer, go to <http://cancer.gov/cancerinfo/>

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

Signature of person obtaining informed consent:

Date _____

This model informed consent form has been reviewed by the DCP/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This should be specific for each institution.

Directions: Please circle the number next to the best answer to the following questions.

1. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

2. How much of the time have you been tired or fatigued during the last 2 weeks?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

3. How much of the time during the last 2 weeks have you experienced bodily pain?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

4. How often during the last 2 weeks have you felt sleepy during the day?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

5. How much of the time during the last 2 weeks have you experienced abdominal pain?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

6. How much of the time during the last 2 weeks has shortness of breath been a problem for you in your daily activities?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

7. How much of the time during the last 2 weeks have you not been able to eat as much as you would like?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

8. How much of the time during the last 2 weeks have you been bothered by decreasing strength?
 1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

9. How often during the last 2 weeks have you had trouble lifting or carrying heavy objects?

1. All of the time.
2. Most of the time.
3. A good bit of the time.
4. Some of the time.
5. A little bit of the time.
6. Hardly any of the time.
7. None of the time.

10. How often during the last 2 weeks have you felt anxious?

1. All of the time.
2. Most of the time.
3. A good bit of the time.
4. Some of the time.
5. A little bit of the time.
6. Hardly any of the time.
7. None of the time.

11. How often during the last 2 weeks have you felt a decrease level of energy?

1. All of the time.
2. Most of the time.
3. A good bit of the time.
4. Some of the time.
5. A little bit of the time.
6. Hardly any of the time.
7. None of the time.

12. How much of the time during the last 2 weeks have you felt unhappy?

1. All of the time.
2. Most of the time.
3. A good bit of the time.
4. Some of the time.
5. A little bit of the time.
6. Hardly any of the time.
7. None of the time.

13. How often during the last 2 weeks have you felt drowsy?

1. All of the time.
2. Most of the time.
3. A good bit of the time.
4. Some of the time.
5. A little bit of the time.
6. Hardly any of the time.
7. None of the time.

PATIENT QUESTIONNAIRE (CLDQ)pg 4 of 7

14. How much of the time during the last 2 weeks have you been bothered by a limitation of your diet?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
15. How often during the last 2 weeks have you been irritable?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
16. How much of the time during the last 2 weeks have you had difficulty sleeping at night?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
17. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal discomfort?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

18. How much of the time during the last 2 weeks have you been worried about the impact your disease has on your family?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
19. How much of the time during the last 2 weeks have you had mood swings?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
20. How much of the time during the last 2 weeks have you been unable to fall asleep?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
21. How often during the last 2 weeks have you had muscle cramps?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

PATIENT QUESTIONNAIRE (CLDQ)

22. How much of the time during the last 2 weeks have you been worried that your symptoms will develop into major problems?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
23. How much of the time during the last 2 weeks have you had a dry mouth?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
24. How much of the time during the last 2 weeks have you been worried about your condition getting worse?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
25. How much of the time during the last 2 weeks have you had trouble concentrating?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.

26. How much of the time have you been troubled by itching during the last 2 weeks?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
27. How much of the time during the last 2 weeks have you been worried about never feeling any better?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.
28. How much of the time during the last 2 weeks have you been concerned about needing a medical or surgical procedure to make you comfortable?
1. All of the time.
 2. Most of the time.
 3. A good bit of the time.
 4. Some of the time.
 5. A little bit of the time.
 6. Hardly any of the time.
 7. None of the time.