Protocol # 2011-031

Phase I/II trial to establish the safety and preliminary efficacy of the combination of docetaxel, prednisone, and SOM 230 (Pasireotide) in metastatic castrate resistant prostate cancer (CRPC)
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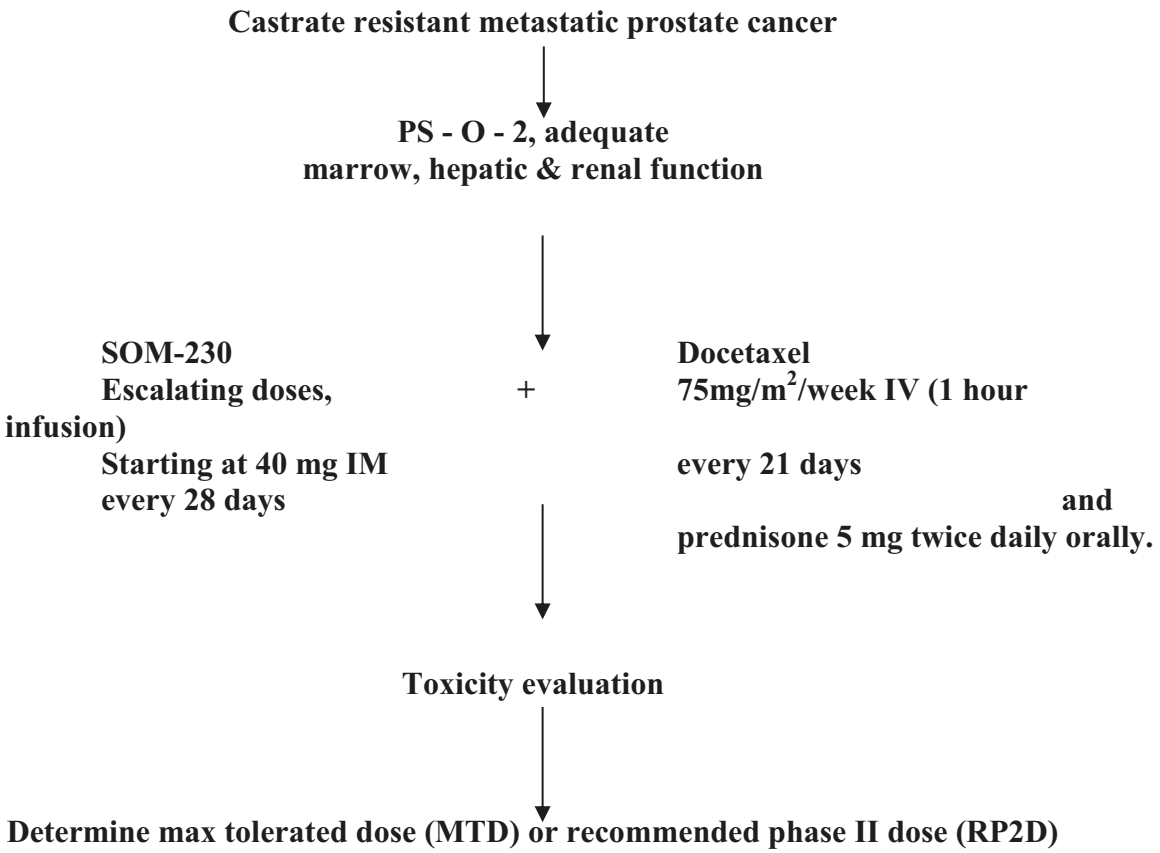
PHASE I/II TRIAL TO ESTABLISH THE SAFETY AND PRELIMINARY EFFICACY OF THE COMBINATION OF DOCETAXEL, PREDNISONE, AND PASIREOTIDE/SOM-230 IN METASTATIC CASTRATE RESISTANT PROSTATE CANCER (CRPC)

STUDY SCHEMA



Study Dose Levels

Dose levels	SOM 230 LAR	Docetaxel	Prednisone
1	40mg IM every 28 days	75mg/m^2 IV every 21 days	5 mg PO twice daily
2	60 mg IM every 28 days	75mg/m^2 IV every 21 days	5 mg PO twice daily
3	80 mg IM every 28 days	75mg/m^2 IV every 21 days	5 mg PO twice daily

Doses of SOM-230 > 80 mg IM every 28 days, are being tested in an ongoing trial. If safety data of higher doses of SOM-230 (>80 mg every 28 days) is available, and the dose level 3 of the combination is well tolerated, then consideration will be done for adding higher dose levels of SOM-230 in this protocol.

1.0 OBJECTIVES:

Primary objective

1) To establish the maximum tolerated dose (MTD) level of SOM 230 in combination with docetaxel and prednisone.

Secondary objectives:

1) To evaluate the safety and tolerability of the combination in metastatic CRPC.
2) To evaluate preliminary efficacy of the combination of SOM 230 and docetaxel and prednisone as defined by response rates (measurable and PSA), time to progression (TTP) and overall survival (OS).
3) To evaluate the pharmacokinetics (PK) of the combination.
4) To assess the pharmacodynamic (PD) effects of the combination as seen by baseline levels of and changes in IGF-1, serum chromogranin A (SCA), and neuron specific enolase (NSE), and to associate them with TTP and OS.
5) To assess the pretherapy circulating tumor cell (CTC) counts and change in CTC after therapy, and to associate them with TTP and OS.

2.0 BACKGROUND:

Docetaxel based chemotherapy is FDA approved in metastatic CRPC due to the results of 2 randomized trials [*1,2*] demonstrating improvement in progression free survival (PFS) and overall survival (OS) as compared to mitoxantrone and prednisone therapy. Despite the apparent success of docetaxel based therapy, the improvement in OS remains modest and usually does not achieve cure. The median progression free survival (PFS) with docetaxel and prednisone therapy is 6 months, hence better therapies are required to prolong the duration of remission in metastatic CRPC. After failure of docetaxel and prednisone, the management of metastatic CRPC is a significant problem. The patient morbidity is significant, since majority of the patients at this stage are symptomatic with bone pain, constitutional symptoms and anemia. Exploring novel therapeutic agents and combinations in metastatic CRPC, to improve the chance of remission and to prolong the remission with docetaxel based therapy is very important.

A number of agents such as capecitabine, calcitriol and GVAX have been evaluated in combination with docetaxel and prednisone to improve efficacy. To date none of the agents tested in combination with docetaxel have been proven to improve overall survival in a randomized trial setting. In addition, the chemotherapy based combinations have demonstrated increased risk of toxicity, and an increased rate of death as observed with the docetaxel and calcitriol and docetaxel and GVAX combinations [3,4]

Given the limited median progression free survival of 6 months noted in metastatic CRPC treated with docetaxel chemotherapy, it appears that resistance to docetaxel develops fairly quickly in majority of the prostate cancers. One of the mechanisms of resistance reported has been the multidrug resistance gene overexpression hence diminishing the exposure of the cancer cells to docetaxel. Currently a microtubule inhibitor agent called cabazitaxel [Sanofi-Aventis Inc] has demonstrated OS improvement in metastatic CRPC progressing after docetaxel therapy. This agent has efficacy possibly by overcoming the MDR pathway. One of the other mechanisms of resistance reported has been the neuroendocrine differentiation of prostate cancer cells leading to decreased efficacy of docetaxel. Overcoming these mechanisms of resistance with novel agents given in combination with docetaxel, is rational. In addition,there is a preponderance of elderly patients, with associated comorbidities in the metastatic CRPC population. Hence, the added novel agent has to be well tolerated and cannot significantly compromise docetaxel efficacy and dosing. Based on above, there

remains a need for effective and better tolerated therapies frontline in combination with docetaxel and prednisone therapy in metastatic CRPC.

Pasireotide (SOM-230) is a multitargeted somatostatin receptor (sst) analogue that binds to 4 of the 5 receptors (sst1,2, 3 and 5) [5]. The binding occurs with extremely high affinity; 30X higher for sst 1, comparable for sst 2, 5X higher for sst 3, and 40X higher for sst 5 as compared to the currently FDA approved sst analog, octreotide. The binding results in dissociation of G proteins and subsequent downstream effects of apoptosis, and inhibition of trophic factor secretion, angiogenesis and proliferation. Cytokine release is also inhibited, hence inhibiting IL-6 and TNF-alpha secretion. Sst 1, 2 and 5 are expressed on prostate cancer cells and SOM-230 demonstrated 44% inhibition in xenograft models of human PC3 tumors **[***6***]** The somatostatin analogs; octreotide and lanreotide increase the cytotoxic effect, and can overcome the resistance to docetaxel in PC3 cells, inhibit androgen-independent growth, and induce apoptosis (*7, 8*). Also the neuroendocrine component within metastatic prostate cancer is likely to be refractory to chemotherapy, but sensitive to somatostatin receptor analogues. Treatment of the human hormone and chemotherapy-refractory prostate cancer cell lines; PC3 and DU145, resulted in synergistic cytotoxic activity and apoptosis, and reduced secretion of stem cell factor and platelet-derived growth factor in PC-3 cells, and decrease in transforming growth factor-beta and basic fibroblast growth factor in DU-145 cells [*7,8].* One phase II study at UCSF investigated the effect of octreotide LAR on CRPC [*ClinicalTrials.gov identifier NCT00510224*]. Patients were treated with octreotide-LAR (30 mg every 4 weeks) together with LHRH-analogs. No steroids were permitted as concomitant medication. The primary endpoint of PSA response was not met, but IGF-1 levels were reduced and IGFBP-1 levels were increased after 3 months of therapy, hence indicating the mechanism of IGF inhibition [9]. A phase II randomized trial of somatostatin analogue and dexamethasone ,versus combination of estramustine and etoposide revealed comparable response rates, palliative effects and comparable survival in metastatic CRPC. The toxicity profile however was much more favorable in the somatostatin analogue and steroid therapy arm [*10*]. Since pasireotide has increased affinity to the somatostatin receptors as compared to the other analogues, it is rational to hypothesize a higher level of activity in metastatic CRPC and a possibility of overcoming docetaxel resistance with the combination. The preclinical activity and clinical safety of pasireotide, and the efficacy of somatostatin analogues in metastatic CRPC, creates a strong rationale for exploring the safety and activity of the combination of SOM 230 and docetaxel in metastatic CRPC.

3.0 DRUG INFORMATION:

3.1 SOM230

Study drug: Pasireotide/SOM-230 LAR (long-acting release) i.m. depot injection

Chemical name

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. CAS name (9CI): Cyclo[(2S)-2-phenylglycyl-D-tryptophyl-L-lysyl-O-(phenylmethyl)-Ltyrosyl-L-phenylalanyl-(4R)-4-[[[(2-aminoethyl)amino]carbonyl]oxy]-L-prolyl] 4,4'-

methylenebis[3-hydroxy-2-naphthalenecarboxylate]

Inactive ingredients of pasireotide LAR include: mannitol, carmellose sodium (carboxymethylcellulose sodium), poloxamer 188 and water for injection. Inactive ingredients of pasireotide s.c. include: mannitol, tartaric acid, sodium hydroxide and water for injection.

For detailed information on pasireotide, please refer to the SOM-230 Investigator Brochure Ed 9, version date Feb 2010.

How supplied

Study drug, Pasireotide LAR i.m. depot injections will be supplied in open-label packaging by Novartis 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 1 Handling and preparation of pasireotide LAR dose

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

Doses should be prepared and administered immediately after preparation. *For additional details regarding preparation, refer* ***to "Clinical instructions for administration of pasireotide/SOM-230"****. This is attached as a Protocol Related Document.*

Novartis 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 Novartis. 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 Novartis, 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 40 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.

Mechanism of Action

Like natural somatostatin and other somatostatin analogues (SRIFa), pasireotide exerts its pharmacological activity via binding to somatostatin receptors (sst). There are five known somatostatin receptors: sst 1, 2, 3, 4 and 5. Somatostatin receptors are expressed in different tissues under normal physiological conditions. Somatostatin analogues activate these receptors with different potencies (Schmid and Schoeffter 2004) 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 where hormones are excessively secreted e.g. acromegaly (Freda 2002), GEP/NET tumors (Oberg, Kvols et al. 2004) and Cushing's disease.

The SRIFa currently approved for use in the clinic (octreotide and lanreotide) have a high affinity to the sst subtype 2 (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) Compared to Sandostatin® (octreotide acetate), pasireotide exhibits a binding affinity, which is 30-40 times higher for human sst1 and sst5, 5 times higher for human sst3, and 2.5 times lower for human sst2. A detailed summary of available preclinical data is provided in the [Investigators' Brochure].

Table 1 Binding profile for octreotide and pasireotide at hsst1-5 (IC_{50}, M)

Compound	**sst 1**	**sst2**	**sst3**	**sst4**	**sst5**
octreotide acetate (SMS 201-995)	$2.8x10^{-7}$	$3.8x10^{-10}$	$7.1x10^{-9}$	$>10^{-6}$	$6.3x10^{-9}$
Pasireotide (SDZ 227-230)	$9.3x10^{-9}$	$1.0x10^{-9}$	$1.5x10^{-9}$	$>10^{-6}$	$1.6x10^{-10}$
Ratio of IC_{50}: octreotide acetate/ pasireotide SMS/SOM230	30	0.4	5	--	40

Additionally, preclinical studies suggest anti-tumor activity of SOM230. SOM230 has been found to significantly reduce cell proliferation of the neuroendocrine tumor cell line NCI-H727, whereas the conventional analogue SMS 201-995 did not.(Ono, Suzuki et al. 2007)

Clinical experience with pasireotide

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

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.

Occassionally 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.

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 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 response to treatment, three at each of the following doses: 600, 750, 900 µg s.c. b.i.d.

Clinical Safety

Pasireotide LAR has been evaluated as 5 different formulations (1, 2, 2b, 2c, and 3) at different dose levels varying between 10 and 60 mg in healthy volunteers [CSOM230C2101]. Formulation 2b at the tested doses of 40 and 60 mg demonstrated the most favorable PK profiles and was selected for further clinical development in acromegaly, carcinoid tumors, and Cushing's disease. Therefore, only the data on formulation 2b are described here.

Clinical PK

Following a single i.m. injection of 40 mg or 60 mg in healthy volunteers [CSOM230C2101], the pasireotide LAR formulation demonstrated a controlled-release type of concentration-versus-time profile, with an initial spike phase on day 1 followed by a slow-release process for up to 42 days. The Cmax of the extended release phase was observed approximately on day 20 for both dose levels. Pharmacokinetic exposure was dose-proportional for the doses tested. The relative bioavailability of pasireotide LAR to pasireotide s.c. was approximately 100%. Based on the single-dose data for 40 and 60 mg, PK simulation demonstrated that the LAR formulation would be suitable for monthly (every 28 days, q 28 d) dosing regimen and a steady state could be achieved after 3 injections in healthy volunteers. The accumulation (based on the ratio of Ctrough,ss/Ctrough,d28) was predicted to be approximately 20%. Following monthly (q 28 d) injections of 20 mg, 40 mg or 60 mg pasireotide LAR in patients with acromegaly or carcinoid tumors [CSOM230C2110], preliminary results showed an approximately linear dose-exposure proportionality and a steady state achieved following 3 injections. The release patterns of pasireotide from the first injection of 40 and 60 mg LAR in acromegalic patients and patients with carcinoid tumors were similar to those from a single dose of 40 and 60 mg LAR in healthy volunteers. The PK exposure to pasireotide at steady state in acromegalic patients was comparable to the simulated PK exposure at steady state in healthy volunteers, whereas, the PK exposure in patients with carcinoid was roughly 2-fold that in acromegalic patients. The accumulation (based on the ratio of Ctrough,d84/Ctrough,d28) was

observed as approximately 20-40% for acromegalic patients and 20-80% for patients with carcinoid, respectively.

Clinical PK/PD of pasireotide LAR

Following 3 monthly (q 28 d) i.m. injections of pasireotide LAR in acromegalic patients

[CSOM230C2110], preliminary results from PD analysis has demonstrated dose-response relationship for both GH and IGF-1 following 3 monthly injections of 20, 40 or 60 mg pasireotide LAR. Emax, EC50, E0, and γ across dose groups for GH were estimated as 19.6 ± 32.0 ng/mL, 5.9 ± 4.1 ng/mL, 4.4 ± 7.8 ng/mL, and 1, respectively. Emax, EC50, E0, and γ across dose groups for IGF-1 were estimated as 536 ± 174 ng/mL, 6.4 ± 4.4 ng/mL, 223 ± 143 ng/mL, and 1, respectively. Pasireotide LAR demonstrated similar potency on both GH and IGF-1 suppression as the median values of EC50 were similar (4.6 and 4.8 ng/mL, respectively). The median value of EC50 for GH suppression was similar between pasireotide LAR (4.6 ng/mL) and s.c. (3.8 ng/mL for responders and 3.2 ng/mL for non-responders), suggesting a similar pharmacological activity between the s.c. and LAR formulations.

Clinical safety

Single doses of pasireotide s.c. up to 1500 μg q.d. and 750 μg b.i.d. multiple s.c. doses (7-14 days) up to 1500 μg q.d., 750 μg b.i.d, and 2100 μg b.i.d. (up to 5 days), and continuous (7-day) s.c. infusion by insulin pump, have been well-tolerated, with mostly mild, transient side effects reported. The most common adverse events (AEs) were gastrointestinal, predominantly mild diarrhea and nausea requiring no treatment or study discontinuation. These effects were seen at all doses, but occurred more frequently at higher doses in all studies. The frequency of the gastrointestinal events appeared to decrease with time in multiple-dose studies. A number of subjects also reported mild to moderate headaches; similarly these were also transient and required no treatment.

Single and multiple doses of pasireotide s.c. have generally been well tolerated by patients with acromegaly, metastatic carcinoid tumor, or Cushing's disease. Pasireotide has been tested in the Phase II studies at maximum doses of up to 600 μg b.i.d for acromegalic patients, 900 μg b.i.d for patients with Cushing's disease, and 1200 μg b.i.d for patients with carcinoid tumor, with maximum pasireotide treatment periods of 4 years, 4.8 years, and 1.6 years respectively. For all indications the most frequently reported AEs have been 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 across all indications. The effect on blood glucose was more pronounced in patients with Cushing's disease, a setting in which glucose metabolism is inherently dysregulated. 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. In acromegalic patients, median changes in glycosylated hemoglobin (HbA1c) values over time in patients generally did not exceed 0.60%, regardless of pasireotide dose level or duration of treatment.

Although no pre-clinical or clinical studies have revealed any specific pasireotide-related cardiac toxicity issues, a thorough clinical QT/QTc evaluation was performed in healthy volunteers in [CSOM230B2113]. In Part I of the study, pasireotide doses from 900 μg to 2100 μg were explored, after which the maximum tolerated dose (MTD) for pasireotide was defined as 1950 μg s.c. b.i.d. The MTD was then used as the pasireotide dose for Part II of the study (i.e. a three-way crossover design using moxifloxacin, placebo and pasireotide 1950 μg s.c. b.i.d). An effect of pasireotide (at MTD) on QTcF interval was demonstrated. This was based on the upper bound of the 95% one-sided CI for the difference from placebo in QTcF change from baseline being > 10 ms at one or more time intervals. Both pasireotide and moxifloxacin showed a peak effect at 2 hours postdose (of 17.5 ms and 8.5 ms QTcF change from baseline versus placebo, respectively). Pasireotide subjects also showed a reduction in

HR at 0 to 4 hours postdose (maximum change versus baseline of 10.7 bpm).

Pasireotide LAR in healthy volunteers

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.

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.

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.

Pasireotide LAR in carcinoid patients

An interim analysis of the results of [CSOM230B2202] showed that, at the time of response, pasireotide at total daily doses of >900 to ≤1200 µg, >1200 to ≤1500 µg, and >1500 to ≤1800 µg s.c. successfully controlled (completely or partially) the symptoms of diarrhea and flushing, for at least 15 days for 12 (27%) of the patients with metastatic carcinoid tumors that were refractory or resistant to octreotide LAR.

There was no evidence of tumor shrinkage. Patients who achieved complete or partial symptom control (treatment success) had stable disease. In responders, the median effective

concentration of pasireotide was estimated as approximately 10 ng/mL.
Clinical responses were observed at 600 µg s.c. b.i.d. and above doses. In view of the large inter-patient variability, doses above 600 µg s.c. b.i.d. will be considered for future clinical studies to maximize the clinical benefit of pasireotide in patients with metastatic carcinoid tumors. 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 in comparison with healthy volunteers, the data from studies assessing the subcutaneous formulatin of pasireotide support that pasireotide LAR at dose of 60 mg and below are expected to be well-tolerated by patients. A healthy volunteer study was conducted 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.

Possible indications and medical needs

In all animal models investigated (rodent, dog, monkey) pasireotide is a more effective inhibitor of the GH/IGF-1 axis than octreotide. Thus, pasireotide should exhibit superior efficacy in acromegaly, and may be of use in patients either not responding or becoming resistant to octreotide therapy Lamberts, van der Lely, and Hofland 2002). Since pasireotide has a higher binding affinity and functional activity for receptors other than sst2 (Schmid and Schoeffter 2004), it may also have utility in carcinoid patients whose disease has either not responded or become resistant to therapy with other somatostatin analogues. In addition to the treatment of diseases for which other somatostatin analogues are currently approved, other possible indications are being explored, such as Cushing's disease. In vitro experiments have shown that pasireotide inhibits ACTH secretion in cultured adenoma cells from patients with Cushing's disease (Hofland, et al 2003). The hypothesis that pasireotide may be able to reduce cortisol levels by inhibiting ACTH and cortisol secretion has been confirmed in recent clinical studies. In 29 efficacy-evaluable patients with Cushing's disease, there were reductions in the mean plasma ACTH and serum cortisol levels regardless of the extent of reduction in urinary free cortisol (UFC).

The final development strategy for pasireotide will be based on early proof of concept (POC) studies in healthy volunteers and in disease settings where pasireotide may be effective, such as acromegaly, Cushing's disease, or GEP-NET tumors. The pharmacodynamic and efficacy profile of pasireotide in humans elucidated in these studies will be used to refine the overall scope of possible clinical indications for pasireotide.

3.2 DOCETAXEL (TAXOTERE®)

3.21 **Description:** Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}$• $3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. TAXOTERE (docetaxel) for Injection Concentrate is a clear yellow to brownish-yellow viscous solution. Docetaxel is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2.0 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

Clinical Pharmacology: Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

A. Preparation of the Initial Diluted Solution

1. Gather the appropriate number of vials of docetaxel for injection concentrate and diluent (13% Ethanol in Water for Injection). If the vials were refrigerated, allow them to stand at room temperature for approximately 5 minutes.

2. Aseptically withdraw the contents of the appropriate diluent vial into a syringe and transfer it to the appropriate vial of docetaxel for injection concentrate. **If the procedure is followed as described, an initial diluted solution of 10mg docetaxel/ml will result.**

3. Gently rotate the initial diluted solution for approximately 15 seconds to assure full mixture of the concentrate and diluent.

4. The initial diluted docetaxel solution (10 mg docetaxel/ml) should be clear; however, there may be some foam on top of the solution due to the polysorbate 80. Allow the solution to stand for a few minutes to allow any foam to dissipate. It is not required that all foam dissipate prior to continuing the preparation process.

The initial diluted solution may be used immediately or stored either in the refrigerator or at room temperature for a maximum of eight hours.

B. Preparation of the Final Dilution for Infusion

1. Aseptically withdraw the required amount of initial diluted docetaxel solution (10 mg docetaxel/ml) with a calibrated syringe and inject into a **NON- PVC** infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of **0.3 to 0.74 mg/ml**.

2. Thoroughly mix the infusion by manual rotation.

3. As with all parenteral products, docetaxel should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel initial dilution (in vial) or final dilution for infusion is not clear or appears to have precipitation, it should be discarded.

Contact of the docetaxel concentrate with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel dilution for infusion should be stored in bottles (glass, polypropylene) or **NON-PVC** plastic bags (polypropylene, polyolefin) and administered through **NON-PVC** polyethylene-lined administration sets.

Stability: The initial diluted solution in the manufacturers vial may be used immediately or stored either in the refrigerator or at room temperature for a maximum of 8 hours.

Fully prepared docetaxel infusion solution (in either NON -PVC 0.9% sodium chloride solution or NON-PVC 5% dextrose solution) stored between 2º and 25º C (36º and 77º F) is stable for 4 hours (which must include the IV administration time).

3.22 HOW SUPPLIED

Docetaxel for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, **diluent** (13% ethanol in water for injection) vial. The following strengths are available:

TAXOTERE® 80 MG (NDC 0075-8001-80)
TAXOTERE® (docetaxel) 80 mg Concentrate for Infusion: 80 mg docetaxel in 2 ml polysorbate 80 and diluent for docetaxel 80 mg. 13% (w/w) ethanol in water for injection. Both items are in a blister pack in one carton.

TAXOTERE® 20 MG (NDC 0075-8001-20)
TAXOTERE® (docetaxel) 20 mg Concentrate for Infusion: 20 mg docetaxel in 0.5 ml polysorbate 80 and diluent for docetaxel 20 mg. 13% (w/w) ethanol in water for injection. Both items are in a blister pack in one carton.

3.23 **Storage:** Refrigerate between 2º and 25° C (36º and 77º F). Retain in the original package to protect from bright light. Freezing does not adversely affect the product.

3.24 **Weekly Dosing:** Infuse docetaxel at starting dose of 75 mg/m^{2}over a minimum of 60 minutes.

3.25 **Human Toxicology**

Acute toxicities are uncommon, as is peripheral neuropathy. Prolonged treatment with weekly docetaxel results in chronic toxicities, which include asthenia (fatigue), anemia, edema, excessive lacrimation (epiphora), and onycholysis. Chronic toxicities are most prominent when docetaxel is administered on a continuous weekly basis, without a break, and are delayed in onset by providing breaks in treatment (for example, treating 6 of 8 weeks or 3 of 4 weeks); these chronic toxicities occur at a lower cumulative dose when a continuous weekly schedule of docetaxel is utilized.

The following covers current toxicity information for docetaxel at 100 mg/m^2 infused on an every 3 to 4 week schedule, the highest dose, single-agent regimen:

The dose limiting toxicity for docetaxel is neutropenia with 76% of patients with normal liver function (transaminases ≤ 1.5 times ULN or alkaline phosphatase ≤ 2.5 times ULN or isolated elevations of transaminases or alkaline phosphatase up to 5 times ULN) having grade IV neutropenia when docetaxel is used as a single agent at a dose of 100 mg/m^2. Other toxicities include hypersensitivity reactions (with recommended premedication) in 15.7% of patients (severe, 0.9%), skin toxicity in 58.5% (severe, 5.6%), and fluid retention (with recommended premedication) in 48.5% (severe, 5.2%). The latter symptoms can be ameliorated by pre-medication dexamethasone 8 mg PO bid starting the day prior to docetaxel, and then continuing the dexamethasone for 2-4 additional days. Fluid retention has been described in patients receiving docetaxel, and is manifested by peripheral edema and less frequently by pleural effusion, pericardial effusion, ascites, or weight gain. When fluid retention occurs, peripheral edema usually begins in the lower extremities and may become generalized. In clinical studies, the median weight gain in patients with fluid retention was 2 kg (Taxotere ®Prescribing Information, Jan. 2000). Severe fluid retention has been characterized by poorly tolerated edema, generalized edema, effusion requiring urgent drainage, dyspnea at rest, tamponade, or pronounced abdominal distention (due to ascites) (Taxotere® Prescribing Information). It is important to note that fluid retention has not been accompanied by acute episodes of dehydration, oliguria, or hypotension (Taxotere® Prescribing Information, Jan. 2000). There are no common clinical features with acute capillary leak syndrome induced by exogenous cytokines such as IL-2 (Data on file, Aventis Pharmaceuticals). A corticosteroid regimen (eg, oral dexamethasone 8 mg BID for 3-5 days) was instituted during Phase II studies. This regimen should be administered for 3-5 days beginning 1 day prior to each docetaxel cycle to reduce the incidence and severity of fluid retention (Taxotere® Prescribing Information).

Fluid retention, when seen has been cumulative in incidence and severity, and usually did not occur until several courses of docetaxel treatment had been administered. In Phase II clinical trials, this event was completely reversible following discontinuation of docetaxel (median: 29 weeks, range: 0 to 42+ weeks). Among 229 patients who received the recommended corticosteroid regimen, moderate fluid retention was observed in 17.4%,

severe fluid retention occurred in 6% and only 1.7% of patients required treatment discontinuation due to fluid retention (Taxotere® Prescribing Information, Jan. 2000).

The median cumulative dose to onset of moderate or severe fluid retention was 705 mg/m^2 in patients receiving the recommended corticosteroid regimen, compared with 490 mg/m^2 in patients who did not receive corticosteroids (Taxotere® Prescribing Information, Jan. 2000). In a recently reported study by Ravdin and colleagues, the incidence of fluid retention was assessed prior to and following the addition of the recommended corticosteroid regimen in 263 patients receiving docetaxel for treatment of advanced breast cancer. The analysis confirmed that treatment with corticosteroids significantly ($P<0.001$) decreased the incidence, time to onset, severity and treatment discontinuation due to fluid retention.

It is important to note that dexamethasone does not alter docetaxel clearance (Taxotere® Prescribing Information, Jan. 2000). Patients with preexisting effusions should be closely monitored from the first dose for possible exacerbation of the effusions. Patients developing peripheral edema may be treated with standard measures (eg, salt restriction, oral diuretic[s]) (Taxotere® Prescribing Information, Jan. 2000). Commercially available docetaxel and capecitabine is used in this study.

4.0 ELIGIBILITY CRITERIA

4.1 Inclusion Criteria

1. Histologically confirmed prostate adenocarcinoma with metastasis, and objective progression or rising PSA despite androgen deprivation therapy and antiandrogen withdrawal when applicable. Patients with rising PSA must demonstrate a rising trend with 2 successive elevations at a minimum interval of 1 week. A minimum PSA of 5 ng/ml or new areas of bony metastases on bone scan are required for patients with no measurable disease. No minimum PSA requirement for patients with measurable disease.
2. Patient must not have received any prior chemotherapy for metastatic disease. All patients must be documented to be castrate with a testosterone level $\leq$ 0.5 ng/ml. LHRH agonist therapy must be continued, if required to maintain castrate levels of testosterone. Patients must be off antiandrogens for a minimum of 4 weeks for flutamide and 6 weeks for bicalutamide or nilutamide.
3. Age $\geq$ 18 years.
4. Minimum of four weeks since any major surgery, completion of radiation, or completion of all prior systemic anticancer therapy (adequately recovered from the acute toxicities of any prior therapy).
5. ECOG performance status $\leq$ 2.
6. Life expectancy 12 weeks or more.
7. Adequate bone marrow function as shown by: ANC $\geq 1.5 \times 10^9$/L, Platelets $\geq 100 \times 10^9$/L, Hgb > 9 g/dL.
8. Adequate liver function as shown by: serum bilirubin $\leq$ 1.5 x upper limit of normal (ULN), and serum transaminases (AST/ALT) activity $\leq$ 3 x ULN
9. Adequate renal function as shown by serum creatinine $\leq$ 1.5 x ULN.

10. 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 and repeat fasting lipids should be within the inclusion range.
11. Patients must be advised of the importance of using effective birth control measures during the course of the study.
12. 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.

4.2 Exclusion criteria

1. Prior treatment with any cytotoxic chemotherapy, radiation, immunotherapy, or any investigational drug within the preceding 4 weeks
2. Patients who have undergone major surgery within 4 weeks prior to study enrollment
3. Chronic treatment with immunosuppressive agents except steroids.
4. Patients should not receive immunization with attenuated live vaccines during study period or within 1 week of study entry.
5. Uncontrolled brain or leptomeningeal metastases, including patients who continue to require glucocorticoids for brain or leptomeningeal metastases.
6. 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.
7. Patients with uncontrolled diabetes mellitus, which is defined as a hemoglobin A1C >8% on therapy or >7% without therapy, or a fasting plasma glucose > 1.5 ULN. Note: At the principle investigator's discretion, non-eligible patients can be re-screened after adequate medical therapy has been instituted.
8. Patients with symptomatic cholelithiasis
9. Patients who have congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, ventricular fibrillation, clinically significant bradycardia, advanced heart block or a history of acute myocardial infarction within the six months preceding enrollment
10. QT-related exclusion criteria:
    - Patients with baseline QTc $\geq$470 msec.
    - History of syncope or family history of idiopathic sudden death.
    - Sustained or clinically significant cardiac arrhythmias.
    - Patients with risk factors for Torsades de Pointes such as hypokalemia, hypomagnesemia, cardiac failure, clinically significant/symptomatic bradycardia, or high-grade AV block.
    - Concomitant disease(s) that could prolong QT such as autonomic neuropathy (caused by diabetes or Parkinson's disease), HIV, cirrhosis, uncontrolled hypothyroidism or cardiac failure
11. Concomitant medication(s) known to prolonge the QT interval
12. Patients with the presence of active or suspected acute or chronic uncontrolled infection or with a history of immunocompromised disease.
13. 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

14. Known hypersensitivity to somatostatin analogues or any component of the pasireotide or octreotide LAR formulations
15. History of noncompliance to medical regimens
16. Patients unwilling to or unable to comply with the protocol.
17. Men and any female partners of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control) prior to study entry and for the duration of study participation and for additional 2 months after finishing therapy. Should a patient's sexual partner become pregnant or suspect she is pregnant while patient is participating in this study, he should inform the treating physician immediately.
18. History of liver disease, such as cirrhosis or chronic active hepatitis B and C.
19. Presence of Hepatitis B surface antigen (HbsAg)
20. Presence of Hepatitis C antibody test (anti-HCV)
21. History of, or current alcohol misuse/abuse within the past 12 months
22. Known gallbladder or bile duct disease, acute or chronic pancreatitis

5.0 TREATMENT PLAN:

5.1 Patient Registration and Data Collection:

All patients shall be registered with the Cancer Center Clinical Trials Office at (313) 576-9372 (Brenda Dickow) or 313-576-9368 Cindy Silski or Stacy Freeman 313-576-8495 or Kimberlee Dobson 313-576-9837.

At the time of registration, a pre-study form and all information required to verify eligibility shall be necessary on each patient prior to treatment. Data will be collected and maintained on study specific case report forms.

5.2 Agent Administration

Docetaxel and SOM-230 cycles should be designated by the number of cycles of each administered. For protocol purposes the day of administration should be specified, until the DLT period is completed. Then only cycle number of docetaxel and of SOM-230 can be designated.

Starting doses of the agents are as follows:

AGENT	DOSE	ROUTE	DAYS	FREQUENCY
Docetaxel	75mg/m^2	IV over at least 1 hour	1	Every 21 days
SOM-230	40mg	IM	1	Every 28 days

Prednisone	5 mg	Orally twice daily	daily	continuous

Doses should be prepared and administered immediately after preparation. *For additional details regarding preparation, refer* ***to "Clinical instructions for administration of pasireotide/SOM-230"****. This is attached as a Protocol Related Document.*

Cohorts of 3 patients each will be treated for 56 days with escalating doses of SOM-230 according to the dose levels defined until dose limiting toxicity **DLT is observed. Dose escalation and expansion of cohorts to 3-6 patients will proceed according to the criteria listed in Section 6.0. DLT will be defined from the safety profile of cycles 1 and 2 for each dose level (Section 6.0). The MTD is the dose level at which 0/6 or 1/6 patients experiences DLT with at least 2 patients experiencing DLT at the next higher dose level.**
The escalating dose levels are given below and first cohort will be started with dose level 1. If 3 patients in each dose level do not demonstrate (DLT) then therapy will proceed to the next dose level. If 1 of 3 patients demonstrates DLT as defined below then 3 additional patients will be treated at the same dose cohort. If 2 or more patients have DLT at a dose level then this will be considered MAD and patients will then be treated at one dose level lower which will be considered the MTD (maximum tolerated dose). The patients are monitored for DLT in the first 56 days of therapy. If no DLT observed at dose level 1 during the first 56 days of therapy, then escalation to dose level 2 will be performed in the next cohort. **Toxicities requiring dose modification of prednisone will not be included in the dose limiting toxicity (DLT).**

Dose levels	**SOM 230 LAR**	**Docetaxel**	**Prednisone**
1	40mg IM every 28 days	75mg/m^2 IV every 21 days	5 mg PO twice daily
2	60 mg IM every 28 days	75mg/m^2 IV every 21 days	5 mg PO twice daily
3	80 mg IM every 28 days	75mg/m^2 IV every 21 days	5 mg PO twice daily

Doses of SOM-230 > 80 mg IM every 28 days, are being tested in an ongoing trial. If safety data of higher doses of SOM-230 (>80 mg every 28 days) is available, and the dose level 3 of the combination is well tolerated, then consideration will be done for adding higher dose levels of SOM-230 in this protocol.

5.2.1 Docetaxel administration

On day 1 of each cycle docetaxel will be administered if ANC $\geq$ 1500 and platelets $\geq$ 100K. If not, repeat CBC in 7 days and administer if above criteria met. If still no recovery, repeat CBC weekly, until recovery and then reduce docetaxel by one dose level (60 mg/m^2). If dose reduction is required for toxicity related to docetaxel after the first 56 days of therapy then protocol therapy can be continued with dose reduced to 60 mg/ m^2 . If toxicity requiring dose modification of docetaxel recurs then patients should be taken off protocol therapy. Patients can continue on SOM-230 if ANC$\geq$ 500/mm^3 and platelets $\geq$ 50,000/ mm^3 and no other grade 3 or 4 non hematologic

toxicities related to SOM-230 are noted, except hyperglycemia. If grade 3 or 4, or any grade clinically relevant hyperglycemia occurs it should be treated appropriately. Premedications will be administered as appropriate per treating physician discretion. Docetaxel can be discontinued if toxicity recurs despite dose modification and SOM-230 can be continued if patient continuing to demonstrate tolerance and clinical benefit.

5.2.2 Prednisone Administration

Starting day 1, prednisone at a dose of 5 mg orally twice daily will be administered after meals. If patients have grade 2 or greater toxicity, attributable to prednisone, decrease the dose to 5 mg once daily. If toxicity recurs, or any grade 3 or higher toxicity attributable to prednisone occurs, discontinue therapy or taper off prednisone. For grade 3 or 4 hyperglycemia, decrease or stop prednisone first and initiate medical management, then if recurs despite this then consider SOM230 dose reduction and call it a DLT.

5.2.3 SOM-230 administration

Patients will receive SOM-230 at specified dose IM on day 1, after docetaxel therapy, and subsequently every 28 days. On the days of SOM-230 administration only, it can be administered if ANC≥500/ mm^3 and platelets ≥ 50,000/ mm^3 and no other grade 3 or 4 non hematologic toxicities related to SOM-230 are noted , except hyperglycemia. If grade 3 or 4 hyperglycemia is noted then proceed with SOM-230 therapy and initiate appropriate therapy. If grade 3 or greater hyperglycemia recurs despite discontinuing prednisone and initiating optimal therapy then decrease SOM-230 by 1 dose level. If this occurs at dose level 1 then discontinue SOM-230. If hyperglycemia persists or recurs despite above steps, then discontinue SOM-230 therapy.

5.3 Retreatment

Retreatment on day 1 of each docetaxel cycle

CBC will be obtained on Day 1 of each cycle of docetaxel. During the first cycle CBC will be obtained weekly. On day 1 of each cycle of docetaxel therapy, patients will be retreated with docetaxel if the following criteria are met:

- ANC ≥ **1,500/mm^3**
- Platelets ≥ **100,000/mm^3**
- Non-hematologic toxicity attributed to docetaxel should have resolved to baseline or ≤ grade 1, with the exception of. alopecia and hyperglycemia.

If patient cannot be treated on scheduled day 1 of docetaxel due to toxicity, then evaluate weekly until therapy can be resumed. If day 1 therapy has to be delayed >3 weeks from the scheduled treatment date of docetaxel, due to toxicity then discontinue docetaxel therapy. SOM-230 can be continued if patient continuing to have clinical benefit, but this patient cannot be included for determination of MTD and will need to be replaced in that cohort.

Laboratory tests may be performed up to 3 days prior to the scheduled study visit, and if the retreatment criteria are met, the patient may be retreated. If the retreatment

criteria are not met, the patient may not be retreated until they are met and the tests should be repeated weekly.

5.4 Antiemetic Prophylaxis and Premedication for Docetaxel

Anti-emetic prophylaxis and other premedication for docetaxel will be at the discretion of treating physician. However a prophylactic minimum steroid dose equivalent of dexamethasone 8 mg is highly recommended prior to docetaxel therapy. 5-HT3 antagonists should be used with caution.

5.5 Growth Factors

Growth factors may be administered as per the judgment of the clinical investigator after the occurrence of cytopenias and in subsequent cycles. Prophylactic growth factor use is not permitted.

5.6. Toxicity to be evaluated weekly for the first 8 weeks, and subsequently on the days of therapy, and radiologic response to be assessed every 12 weeks for the first 36 weeks and then every 16 weeks. PSA to be assessed on the days of therapy.

5.7 Retreatment with SOM-230 therapy

On the days of SOM-230 administration, it can be administered if ANC$\geq$500 and platelets $\geq$50K and no other grade 3 or 4 non hematologic toxicities related to SOM-230 are noted. If SOM-230 therapy has to be delayed > 4 weeks from the scheduled treatment date due to toxicity, then discontinue SOM-230 therapy. If any of the discontinuation criteria below are met, SOM-230 should be discontinued immediately.

- ALT or AST > 3 x ULN and Total Bilirubin $\geq$ 2 x ULN and ALP < 2 x ULN
- ALT or AST > 5 x ULN and $\leq$ 8 x ULN persistent for more than 2 weeks
- ALT or AST > 8 x ULN

In addition, proper safety follow-up management should be performed as outlined in section 6.7. Re-challenge of study medication is prohibited once discontinuation criteria are met.

5.8 Reasons for Discontinuing Protocol therapy

Patients will continue on treatment until they fulfill one of the following criteria for removal from treatment:

i. Completion of two cycles of therapy, after documentation of a complete response.
ii. Disease progression as defined in section
iii. Unacceptable, severe grade 3 or 4 toxicity
iv. >4 weeks delay in treatment due to toxicity.
v. The patients may withdraw from the study at any time for any reason
vi. Early study closure based on an unexpected high rate of toxicity or disease progression, major shift in disease management or loss of funding support

5.9 All patients will be followed every 3 months for progression and survival after study therapy is discontinued, unless consent is withdrawn by the patient. All reasons for termination of treatment should be clearly documented.

6.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATION:

6.1 All toxicities will be graded as per NCI Common Toxicity version 4.0.

Toxicity evaluation weekly for first 8 weeks and subsequently on days of administration of docetaxel or SOM-230 therapy. Radiologic evaluation every 12 weeks with scans, and PSA levels every 21 days.

Three patients will be enrolled at each dose level (3 planned dose levels currently). The patients in a cohort will be monitored for toxicity for 56 days (time when Cmax of SOM-230 is achieved), before accrual begins for the next dose level cohort .
Toxicities requiring dose modification of prednisone will not be included in the dose limiting toxicity (DLT).

The **DLT** will be defined as any one of the following occurrences if they are at least possibly related per treating physician, to either docetaxel or SOM-230 in the **first 56 days** of therapy:

1) Absolute neutrophil count nadir $<500/mm^3$ for >7 days duration or occurrence of febrile neutropenia.
2) Platelet count <50K for >7 days duration or Platelet count <50K of any duration with clinically significant bleeding.
3) Persistent fasting hyperglycemia $\geq$ grade 3, despite optimal therapy.
4) Other grade 3 or higher non hematologic toxicities attributable to therapy, except alopecia, fatigue, nausea and emesis, except for grade 3 or higher fatigue (unrelieved by rest, and limiting self-care ADLs) lasting greater than 7 days or grade 3 or higher emesis that lasts >5 days despite optimal medical therapy.

If 1 or more patients experience a DLT, then three additional patients will be enrolled at that dose level. The MAD will be determined if more than 2 of the 6 patients treated experience a DLT. Once MAD is determined, the recommended dose for phase II testing/MTD will be one dose level below the MAD dose level and a total of 12 patients will be treated at this dose level.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Proceed to the next dose level
1 out of 3	Enter three additional patients to a total of 6 at this dose level: If 0 of these patients experience DLT, proceed to the next dose level. If 1 additional patient or 2 of the 6 patients suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose .
2 or more of 6 treated	**This dose level will be declared the maximum administered dose**

patients	**(MAD).** Dose escalation will be stopped. No further patients will be entered at this dose level

6.2 Docetaxel dose modifications:

On day 1 of each cycle docetaxel will be administered if ANC $\geq$ 1500 and platelets $\geq$ 100K. If not, repeat CBC in 7 days and administer if above criteria met. If still no recovery, repeat CBC weekly, until recovery and then reduce docetaxel to one dose level lower (60 mg/m^2). If dose reduction is required for toxicity related to docetaxel within the first 56 days of therapy then consider taking patient off protocol after discussion with the Principal Investigator. If dose reduction is required for toxicity related to docetaxel after the first 56 days of therapy then protocol therapy can be continued with docetaxel dose reduced to 60 mg/ m^2 .

If patient experiences a DLT and still wishes to resume therapy then one dose level decrease of the agent causing toxicity (docetaxel, or SOM-230, or both, depending on attribution of toxicity, as determined by the treating physician) is required, after resolution of the treatment related toxicities to grade 1 or less (except alopecia). If toxicity occurs on starting dose level of SOM-230 then discontinue the therapy. If toxicities recur at grade 2 or higher, or > 3 weeks delay from the scheduled date of therapy for docetaxel and >4 weeks from the scheduled date of therapy for SOM-230 is required, then discontinue protocol therapy. Docetaxel or SOM-230 only can be continued, at the discretion of the investigator, and if patient is continuing to benefit from therapy.

6.3 Prednisone Dose Modifications:
Toxicities requiring dose modification of prednisone will not be included in the dose limiting toxicity (DLT). If any toxicity grade 3 or higher attributable to prednisone, then decrease dose to 5 mg once daily. If grade 3 or 4 toxicity recurs then consider tapering further, or discontinuing therapy, at the treating physician's discretion.

6.4 Criteria for dose-modification of SOM230

Dose Level	SOM-230 dose
1	40 mg IM every 28 days
2	60 mg IM every 28 days
3	80 mg IM every 28 days

SOM-230 dose levels: Level 1 is the starting dose, if modification needed in the starting dose cohort for SOM-230 related toxicity then discontinue SOM-230. For liver toxicity attributable to

SOM-230 LAR, please see guidelines for dose modifications/interruptions and monitoring as shown below and detailed in appendix VIII.

If any of the criteria below are met, SOM-230 should be discontinued immediately.

- ALT or AST > 3 x ULN and Total Bilirubin ≥ 2 x ULN and alkaline phosphatase (ALP) < 2 x ULN
- ALT or AST > 5 x ULN and ≤ 8 x ULN persistent for more than 2 weeks
- ALT or AST > 8 x ULN

In addition, proper safety follow-up management should be performed as outlined in section 6.7. Re-challenge of study medication is prohibited once discontinuation criteria are met.

Adverse event	Action
*Grade ≤ 2	No study drug adjustments
*Grade ≥ 3 and judged as at least possibly drug related (except liver toxicity for which separate guidelines are included above and in appendix)	• Further injections should be held for at least 7 days and until toxicity improves to ≤ Grade 1. • If toxicity improves to grade ≤ 1 within 7 days, no dose reduction is required. • If toxicity improves to grade ≤ 1 in 8-14 days, resume treatment with a single dose level reduction. • If toxicity improves to grade ≤ 1 in 15-28 days, resume treatment with two dose level reductions. • If toxicity fails to improve to grade ≤ 1 within 28 days, study treatment must be discontinued unless there is clear evidence of therapeutic benefit from the study regimen, in which case continued treatment is left to the discretion of the Overall Principal Investigator. • If any toxicity recurs at CTCAE grade ≥ 3, treatment must be discontinued.
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 1 dose level down
QTc CTC grade ≥ 3 (> 500 msec)	Discontinue study drug Follow patient for safety[A]
*This guidance should be use for all possibly related AEs except for: • Changes in blood glucose which should be addressed as described in Section 6.6 • Dose adjustment criteria for QTc interval are based on the QTc interval noted on the day of SOM-230 therapy.	

6.5 Follow-up for toxicities

Patients who interrupt or permanently discontinue SOM230 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. If a patient requires a SOM230 dose delay of > 28 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 SOM230.

6.6 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), or 2-hour post-prandial capillary glucose (PPG) > 180 mg/dL (10 mmol/L) on two consecutive measurements that are within 14 days, should be considered for the following:

- Referral to a diabetes specialist for evaluation and appropriate management
- Provided information and receive teaching on diabetes disease 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.

6.7 Safety

Safety assessments will consist of monitoring and recording all adverse events, including serious adverse events, the regular monitoring of hematology (including glycosylated hemoglobin and coagulation parameters), blood chemistry (including fasting glucose, thyroid function tests, GH, IGF-1, prolactin), urinalysis, regular monitoring of vital signs, gallbladder ultrasound, echocardiography, ECGs and body weight. Liver function tests: total bilirubin, AST, ALT and alkaline phosphatase should be evaluated and assessed prior to each dose of SOM-230 administration. Concomitant medications and significant non-drug therapies will be recorded from study enrollment until study completion.

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.

Vital signs

Body weight, body temperature, supine blood pressure, and supine pulse rate will be assessed. Height will be noted during the screening/baseline period.

Performance status

To be determined per ECOG score (Appendix I), and to be documented at baseline and the days of administration of therapy.

Laboratory evaluations

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. Laboratory samples will be analyzed locally at the clinical sites, unless indicated otherwise.

Albumin, alkaline phosphatase, total bilirubin, calcium, chloride, creatinine, CPK, γ-GT, fasting blood glucose, LDH, inorganic phosphorus, lipase, α-amylase, potassium, total protein, SGOT, SGPT, sodium, total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, urea/BUN and uric acid.

Thyroid function tests

Free T4 and TSH will be assessed at baseline and every 12 weeks for the first 36 weeks and then every 16 weeks thereafter.

Urinalysis

Specific gravity, pH, glucose, protein, bilirubin, ketones, leukocytes and blood will be assessed.

Hormones

IGF-1 will be assessed at baseline, day 22 and day 43.

Chromogranin and neuron specific enolase will also be assessed at baseline, day 22 and day 43.

Gallbladder ultrasound

A gallbladder ultrasound will be performed at baseline and repeated if clinically indicated. Patients with a history of symptomatic cholelithiasis are excluded from participating in the study.

Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will be performed at baseline and pretherapy. Due to concern with prolonged QT interval, all patients treated with pasireotide/SOM-230 will have repeat EKGs performed on day 1 post SOM-230 therapy, 21 days after first and third dose of SOM-230 (Day 22 and day 78), every 14 days for 8 weeks, then every 28 days prior to SOM230 administration for the remainder of the study period. If a clinically significant abnormality is detected, the electrocardiogram will be repeated at the discretion of the Investigator until the abnormality has been resolved.

Echocardiogram

To be done only if clinically indicated.

Other concomitant medications

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.

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 the Table. If a patient has already decreased 2 dose levels of SOM-230 and 1 dose level of docetaxel, no further dose reductions are permitted, and the patient will be permanently discontinued from treatment.

7.0 STUDY CALENDAR:

Prestudy labs should be done within 28 days of day 1. Day 1 labs can be done within 3 days of day 1. **A time period of +/- 3 days is permitted for each of the days listed in the calendar.**

Testing	Pre	D 1	D 8, 15, 36 and 50	D 22	D 29	D 43	D 57	Day 85	Doce post day 57	SOM-230 post day 57	Q 12 wks for first 36 wks on study	Q 16 wks after first 36wk on study
H and P	X	X		X	X	X	X	X	X	X		
VS, Wt	X	X		X	X	X	X	X	X	X		
PS	X	X		X	X	X	X	X	X	X		
Tox	X	X		X	X	X	X	X	X	X		
CBCdiff,plt	X	X	X	X	X	X	X	X	X	X		
Multiphasic[1]	X	X	X	X	X	X	X	X	X	X		
Other Labs[2]	X	X			X		X	X		X		
PT, INR[3]	X											
PSA	X	X		X	X	X	X	X	X	X		
Testosterone	X											
TSH, free T4	X										X	X
UA	X			X	X		X					
EKG[5]	X	X	X	X	X	X	X	X		X		X
Gall bladder US	X					X						
CXR[4]	X										X	X
CT[5]	X										X	X
Bone scan[5]	X										X	X
PK[6]		X			X	X	X	X				
Docetaxel		X		X		X		X	X			
SOM-230		X			X		X	X		X		
CTC[7]		X		X		X						
PD[8]		X		X		X						
Follow up9		X										

1. Multiphasic includes lytes, BUN and creatinine albumin, alkaline phosphatase, total bilirubin, calcium, total protein, AST, and ALT assessment. Fasting glucose should be measured. 2. Other labs include: Prestudy Hemoglobin A1C, Hepatitis B surface antigen (HbsAg) and anti-Hepatitis C virus antibody testing should be conducted. Magnesium, Total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, and uric acid.γ-GT, LDH, inorganic phosphorus, lipase, amylase and CPK to be done on days of SOM-230 adminstration only. Magnesium and potassium levels

will be monitored and corrected prior to drug administration both at screening and prior to each dose of SOM-230.

3. PT, INR to be done prestudy only; repeated weekly if patient is on warfarin > 2 mg daily.

4. CXR is required pretherapy unless pulmonary metastases are noted. If pulmonary metasatses, then chest CT is needed at baseline and for subsequent tumor assessment If CT chest is done pretherapy then CXR is not needed.
5. All tumor measurement scans, and prestudy labs and EKG must be within 28 days prior to treatment. CT abdomen /pelvis, and bone scan are required for pretreatment and subsequent tumor assessments. A 12-lead electrocardiogram (ECG) will be performed at baseline and pretherapy. Due to concern with prolonged QT interval, all patients treated with pasireotide/SOM-230 will have repeat EKGs performed pre and post SOM-230 therapy on day 1 only, and will be done once on days 15, 22, 29, 43, 57 and 78. On days 29 and 57, EKG should be done prior to SOM-230 therapy. After day 78, EKG will be done on the days of SOM230 therapy (prior to administration) for the remainder of the study period.
6. Cycle 1 day 1: Samples will be collected at predosing, end of infusion, 2, 3, 4 ,7, 24 and 48 h timepoints after the start of docetaxel infusion. Day 43: Blood samples will be collected at: pre-dosing (for docetaxel and pasireotide/SOM-230), at the end of infusion, 2, 3, 4, 7, 24 h (day 44), and 48 h (day 45) after the start of infusion. Trough (pre-treatment) samples for pasireotide will be obtained on days 29, 57, and 85 prior to the administration of pasireotide. A time window of +/- 2 hours is permitted for the 24 and 48 hour PK draws. A maximum of 12 patients will have PK studies done.
7. CTC samples will be drawn day 1, day 22 (pretherapy) and day 43 (pretherapy). Cell save tube minimum 7.5 ml collection and sent promptly for processing.
8. PD samples for IGF-1, chromogranin and NSE will be drawn at prestudy, day 22 (pretherapy) and day 43 (pretherapy). IGF-1 – SST tube (min 1.0 mL) Chromogranin A – red top (min 1.0 mL) –lab sendout test. NSE – red top (min 0.2 mL)- lab sendout test.
9. Patients will be followed for progression/survival every 3 months, for a maximum of 24 months after discontinuing protocol therapy.

8.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION:

8.1 The RECIST 1.1 criteria with unidimensional measurement are to be used for measurable disease response evaluation [11].

8.2 Methods of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g., for body scans but not for lung).Lesions on a chest X-ray may be considered measurable lesions if they are clearly defined and surrounded by aerated lung. However, CT is preferable.
Clinical lesions will only be considered measurable when they are superficial and ≥10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Ultrasound (US) should not be used to measure tumor lesions.

8.3 Baseline Disease Assessment

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
Measurable lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
• 10 mm by CT scan (CT scan slice thickness no greater than 5 mm; when CT scans have slice thickness >5 mm, the minimum size should be twice the slice thickness).
• 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as nonmeasurable).
• 20 mm by chest X-ray.
• Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
• Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable if the soft tissue component meets the definition of measurability described above.
• 'Cystic lesions' thought to represent cystic metastases can be considered measurable if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Non-measurable lesions
Non-measurable lesions are all other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis), as well as truly non-measurable lesions.
• Blastic bone lesions are non-measurable.
• Lesions with prior local treatment, such as those situated in a previously irradiated area or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.
Target Lesions
• All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline.
• Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, as well as their suitability for reproducible repeated measurements.
• All measurements should be recorded in metric notation using calipers if clinically assessed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions
Non-target Lesions
All lesions (or sites of disease) not identified as target lesions, including pathological lymph nodes and all non-measurable lesions, should be identified as non-target lesions and be recorded at baseline. Measurements of these lesions are not required and they should be followed as 'present', 'absent' or in rare cases, 'unequivocal progression'.

8.4 Evaluation of target lesions

Complete Response (CR):

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR):
At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters.
Progressive Disease (PD):
At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this may include the baseline sum). The sum must also demonstrate an absolute increase of at least 5 mm.
Stable Disease (SD):
Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

8.5 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials.
However, in all other circumstances, (i.e., in randomized phase II or III trials or studies where stable disease or progression are the primary endpoints), confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.
In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

8.6 Prostate Cancer Specific Response criteria: [12]

For measurable disease response, RECIST criteria 1.1 will be used [11]. The Prostate Cancer Clinical Trials Working Group (PCWG2) criteria will also be used to determine a response in non measurable disease [12]. PCWG2 recommends a two-objective paradigm in metastatic CRPC: (1) controlling, relieving, or eliminating disease manifestations that are present when treatment is initiated and (2) preventing or delaying disease manifestations expected to occur. PSA decline and changes in imaging will also be reported. The progression for measurable disease will be per RECIST criteria, and for bone metastases will be defined as above.

8.7 Response Evaluable Patients

All patients registered on the protocol and completing a minimum of one cycle of therapy followed by clinical, and radiologic or PSA assessment of disease status.

8.8 Toxicity- Evaluable patients

All patients registered on the protocol and starting therapy with protocol medication, will be considered toxicity evaluable.

8.9 Follow up /Overall survival

Overall survival will be measured from date of registration to death or last follow up.
After treatment is discontinued for any reason patients will be followed every 3 months for progression and survival for a maximum of 24 months after discontinuing protocol therapy.

9.0 CRITERIA FOR REMOVAL FROM PROTOCOL TREATMENT:

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

a) Lack of efficacy
b) Uncontrolled diabetes mellitus (DM)
c) Unacceptable Adverse event(s)
d) Abnormal laboratory value(s)
e) Abnormal test procedure result(s)
f) Protocol violation
g) Subject withdrew consent
h) Lost to follow-up
i) Administrative problems
j) Death
j) New therapy for disease being investigated
k) Disease progression

10.0 CORRELATIVE STUDIES

Pharmacokinetic Studies:
Treatment Schedule:

On day 1, docetaxel will be given as 1-h intravenous infusion over 1 hour, followed by intramuscular administration of pasireotide. The subsequent doses of docetaxel will be given every 21 days (i.e., on days 22, 43, 64…), and subsequent doses of pasireotide will be given every 28 days (i.e., days 29, 57, and 85…). The PK evaluation is optional and will be done on a maximum of 12 patients.

Pharmacokinetic (PK) Evaluation:

In vitro liver microsome and *in vivo* animal studies have indicated that pasireotide is highly metabolically stable. Therefore, docetaxel is not expected to influence the PK of pasireotide. However, pasireotide was found to be a weak inhibitor of CYP1A2, 2C8, 2C19, 2E1 and CYP3A4/5 with IC50 values ranging from ~10 to >100 μM, and a moderate inhibitor of CYP2C9 and CYP2D6 with IC50 values of ~5 μM. Though no drug-drug interaction between pasireotide and CYP450 substrates such as docetaxel is expected at the intended therapeutic levels (<0.1 μM) of pasireotide, we will examine the PK of docetaxel in the presence of steady-state concentration of pasireotide in all treated patients.

Sampling time:

Cycle 1 day 1 (to characterize baseline docetaxel PK): Samples will be collected at predosing, end of infusion, 2, 3, 4 , 7, 24 and 48 h timepoints after the start of docetaxel infusion. A time window of +/- 2 hours is permitted for the 24 and 48 hour PK draws.
Cycle 1 day 43: (to characterize the PK of docetaxel in the presence of steady-state concentration of pasireotide). A time window of +/- 2 hours is permitted for the 24 and 48 hour PK draws.

Previous studies have shown that pasireotide reaches the steady-state after at least 42 days of therapy, therefore the docetaxel PK will be obtained on day 43.
Blood samples will be collected at: pre-dosing (for docetaxel and pasireotide), at the end of infusion, 2, 3, 4, 7, 24 h (day 44), and 48 h (day 45) after the start of infusion. A time window of +/- 2 hours is permitted for the 24 and 48 hour PK draws.

Trough (pre-treatment) samples for pasireotide will be obtained on days 29, 57, and 85 prior to the administration of pasireotide.

Sample processing:

At each time point specified above, 4 ml blood sample will be collected into a heparinized tube, and immediately placed on ice or in refrigerator (4^0C) until processed. The actual day and time of sample collection will be recorded on the PK worksheet. Within 1 h of the collection, the blood sample will be centrifuged at 4^0C, at 3000 rpm for 10 min, and plasma will be collected immediately after centrifugation and transferred to 2 screw-cap polypropylene cryogenic tubes (2 aliquots, each with ~1 ml plasma). The tube will be labeled with the patient's initial, study number, sample collection day and time, and frozen at -70^0C or below until analysis.

The PK samples for docetaxel will be shipped to the Karmanos Cancer Institute Pharmacology Core for analyses. The shipping address is:

Jing Li, PhD
Assistant Professor of Pharmacology
Director, Pharmacology Core
Karmanos Cancer Institute
Wayne State University
4100 John R
HWCRC, Room523
Detroit, MI 48201
Phone: 313-576-8258
Email: lij@karmanos.org

Bioanalysis assays:

The plasma concentrations of docetaxel will be determined using a validated high-performance liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods in the Karmanos Cancer Institute Pharmacology Core Laboratory, Detroit, MI. The plasma concentrations of pasireotide will be determined in a Norvatis laboratory.

SOM-230 PK

All blood samples will be taken by either direct venipuncture or indwelling cannula inserted in a forearm vein. 2.5 mL of blood will be collected into an EDTA tube to yield 1mL of plasma for analysis of pasireotide plasma concentration. Immediately after blood is drawn into EDTA tubes, they should be inverted gently several times to ensure the mixing of tube contents. Prolonged exposure to the rubber stopper should be avoided. The tube should be placed upright in tube rack surrounded by ice until centrifugation. Within 20 minutes, the sample should be centrifuged between 3 and 5ºC for 10 minutes at approximately 1000 x g. Immediately after centrifugation, 1.0 mL plasma should be transferred to a polypropylene screw cap tube immersed in dry ice. The storage temperature for PK samples should be at or below -18°C.

Bioanalytical method SOM-230 plasma concentrations will be measured using a validated radio-immunoassay (RIA) with a lower limit of quantification (LLOQ) of at least 0.15 ng/mL (150 pg/mL).

PK samples will be batched and shipped to the following address:

Jean Paul Freche
Atlanbio SA
Route de Saint-Andre des Eaux
Z I de Brais
BP 40309
44605 Saint-Nazaire Cedex
FRANCE
Telephone: +33 2 51 10 10 88
Fax: +33 2 51 10 01 09
Email: jeanpaul.freche@atlanbio.com

PK data analysis:

PK parameters for individual patients will be estimated using non-compartmental and compartmental analysis with the software WinNonlin 5.2 (Pharsight Corp., Mountain View, CA).

Pharmacodynamic Studies

Chromogranin A and NSE levels in serum will be tested at baseline and on days 22 and 43. These are markers of neuroendocrine differentiation and have demonstrated correlation with prognostic outcome in prostate cancer [*13*]. Also since neuroendocrine differentiation is a possible mechanism of resistance to chemotherapy, assessment of these markers will enable us to study the effect of combination of docetaxel and pasireotide on the neuroendocrine component of metastatic prostate cancer. **The local CLIA certified laboratory would be performing these tests.**

The somatostatin analogues affect the dimerization of the IGF-1 pathway hence resulting in downregulation of secretion of IGF-1 protein in prostate cancer cell lines such as LNCaP. [*14*] **Plasma IGF-1 levels will be evaluated by ELISA assay at baseline, and on days 22 and 43 [*15*]. The local CLIA certified laboratory would be performing these tests.** SOM-230 has demonstrated potent IGF-1 inhibition that is superior to octreotide and hence evaluating the change in IGF-1 levels from baseline to post therapy could be useful as an early predictor of outcome. Plasma IGF-1 levels will hence be evaluated by ELISA assay at baseline, and on days 22 and 43 of the study.

Circulating Tumor Cells (CTC)

In metastatic CRPC, CTC are gaining importance as a method to assess response. In a disease where the sites of metastases are mainly in bone which is not measurable disease the CTC counts

are a critically important less invasive method of predicting response and outcome. **CTC counts will be measured at baseline (day 1), day 22 and day 43.** The pre and post-therapy CTC counts ;<5/7.5 ml which is considered favorable, vs ≥5/7.5 ml which is considered unfavorable, have been shown to be prognostic in metastatic CRPC patients treated with cytotoxic chemotherapy [*16*]. In multivariable analysis, CTC count using Veridex technology was an independent risk factor, influencing overall survival (OS) in a multivariable analysis. The differences in survival associated with CTC count status were clinically and statistically significant (e.g., ~1 year, depending on the comparison). Investigators are now exploring the role of CTC counts as surrogate markers of survival in CRPC, especially when used in conjunction with cytotoxic chemotherapy. **The CTC counts would be performed by the KCI pharmacokinetics core.**

Recently, phenotypic characterization of CTCs is gaining interest in several cancer types, especially with regard to prognosis [*17*]. In metastatic CRPC, ERG gene rearrangement and PTEN expression have been demonstrated in CTCs, establishing the feasibility of biomarker evaluation in CTCs in our population of interest *[18]*. Furthermore, we pioneered evaluation of CTC phenotype in prostate cancer, when we correlated disease recurrence to the proportion of micrometastatic cells actively proliferating [*19*].

As new therapies enter the marketplace, development of prognostic biomarkers needs to occur simultaneously, but has tended to lag behind, and is currently an unmet need in appropriate selection of therapies in metastatic CRPC. Identification of biomarkers that correlate with clinical outcome will result in enrollment of an enriched patient population for targeted therapy trials, and aid in the identification of mechanisms of resistance. Most importantly, it will assist clinicians in choosing between the therapies currently available in metastatic CRPC as well as assist in novel drug development.

In metastatic CRPC, CTCs likely emanate from metastatic deposits in the skeleton and other metastatic sites (as opposed to the primary tumor), because the metastatic sites carry the heaviest tumor burden. Therefore, the biology of CTCs is likely to reflect the biology of the metastatic deposits. Based on our pre-clinical work, we hypothesize that pre-treatment CTC phenotype with regard to the PTEN-PDGF and PTEN-MT1-MMP axes will reflect the biology of the metastatic deposits and thus be prognostic with regard to TTP and survival. In addition, assessment of post-treatment phenotype may allow insights into mechanisms of treatment resistance and disease progression. **The CTC phenotype will be performed only if funding is available.**

11.0 STATISTICAL CONSIDERATIONS:

11.1 **Study Design, Objectives, and Endpoints**

The Treatment Plan (see Section 5 above) predefines 3 dose levels of the SOM 230 and docetaxel (and prednisone) combination. This trial will utilize a traditional Phase I study design with dose cohorts of 3-6 patients to determine the MTD (which will also be the RP2D). The MTD will be one dose level below the MAD. At whatever dose level is eventually determined to be the MTD, we plan to expand that dose cohort to 12 patients to further assess the PK/PD profiles of the drug regimen. The prednisone dose is constant throughout the trial.

The objectives and outcome measurements for the study are listed below:

Primary objective: To establish the MTD level of SOM 230 in combination with

docetaxel and prednisone.

The outcome measures associated with this objective are the following:

- Occurrence of DLTs and the associated NCI CTCAE grade
- Occurrence of adverse events and the associated grade per NCI CTCAE version 4.0
- Identification of the MTD of SOM 230 in combination with docetaxel and prednisone.

Secondary objectives:

1) To evaluate the safety and tolerability of the combination in metastatic CRPC.

   The outcome measures associated with this objective are the following:

   - All specific types of toxicity will be assessed via NCI CTCAE Version 4.0, and be tabulated separately by grade and by dose level.

2) To evaluate preliminary efficacy of the combination of SOM 230 and docetaxel and prednisone as defined by response rates (measurable and PSA per PSA working group II criteria, see section 8.9), time to progression (TTP) and overall survival (OS).

   The outcome measures associated with this objective are the following:

   - Measurements of tumor using RECIST criteria before and after treatment with the combination of SOM 230 in combination with docetaxel.
   - Percentage PSA decline noted.
   - TTP (defined in Section 8.6)
   - OS (defined in Section 8.12)

3) To evaluate the pharmacokinetics (PK) of the combination.

   The outcome measures associated with this objective are the following:

   - PK parameters, including, but not limited to, maximum observed plasma concentration (C_{max}), time to maximum plasma concentration (tmax), plasma terminal half-life ($t_{1/2}$), area under the plasma concentration–time curve (AUC), maximum observed plasma concentration at steady state (Css, max), and minimum observed plasma concentration at steady state (Css, min).

4) To assess the pharmacodynamic (PD) effects of the combination as seen by baseline levels of and changes in IGF-1, serum chromogranin A (SCA), and neuron specific enolase (NSE), and to associate them with TTP and OS.

   The outcome measures associated with this objective are the following:

   - Measurement of levels of IGF-1, SCA, and NSE, pre-therapy, post-therapy, and the change between timepoints.
   - Duration of TTP and OS

5) To assess the pretherapy circulating tumor cell (CTC) counts and the change in CTC after therapy, and to associate them with TTP and OS.

The outcome measures associated with this objective are the following:

- Measurements of CTC counts pre-therapy, post-therapy, and the change between timepoints.
- Duration of TTP and OS

11.2 Sample Size

This is an open label Phase I trial of two agents used in combination, with 3 predefined dose levels. We plan to use dose level cohorts consisting of 3 patients each. Three patients will be enrolled at each dose level and monitored for toxicity for 56 days before opening the next dose level cohort. If 1 or more patients have grade 3 or 4 toxicity attributable to therapy, then three additional patients will be enrolled at that dose level. If 2 or more patients have DLT at a dose level then this will be considered MAD and patients will then be treated at one dose level lower which will be considered the MTD (maximum tolerated dose). Once MTD is determined, a total of 12 patients will be treated at this dose level.

The absolute *minimum* number of patients required for this Phase I trial would result from the unlikely (but possible) scenario in which there were ≥ 2 DLT's among the first 3 patients treated at dose level 1, such that it became the MAD. We would then treat 3-6 patients at a new dose level -1 (to be determined after conferring with the sponsor), and that dose level would likely then become the MTD. We would then treat an additional 6-9 patients at dose level -1 to complete the goal of an MTD expansion cohort of 12 patients. In this scenario, the absolute minimum number of patients required for this Phase I trial would then be 3 + 12 = 15.

The *maximum* number of patients required for this Phase I trial would result from the following scenario: first, needing a full cohort of 6 patients at each of dose levels 1-3; and then finding dose level 3 to be the MTD. As per Section 6.1, that would make dose level 2 the MTD, and we would treat an additional 6 patients at that dose to complete the goal of an MTD expansion cohort of 12 patients. Thus, the maximum number of patients required for this Phase I trial would then be (6*3) + 6 = 24.

11.3 Expected Accrual Rate and Accrual Duration

Our anticipated accrual rate is 12-15 metastatic CRPC patients/year. Hence it would take 20-24 months to accrue the maximum of 24 patients for this Phase I study. Should fewer patients be required to determine the MTD, then the trial would be completed even faster.

11.4 Statistical Analysis of Endpoints

The Primary Objective of determining the MTD, as well as the specific DLT's is just an identification process, hence no statistical analysis or estimation is required.

For the Primary Objective of determining all adverse events, and for Secondary Objectives 1 and 2, the occurrence rate of binary endpoints (eg, specific types of toxicity at a certain dose level and severity grade, response, etc.) will be described by point estimates and exact 90% confidence intervals (CIs) for proportions using Wilson's method.

For Secondary Objectives 3-4, the continuous endpoints (e.g., PK and PD parameters, and the pre/post therapy change in PD parameters) will be summarized with standard descriptive statistics (N, median, IQR, mean, standard deviation, minimum, maximum, and the 90% CI for the mean). Statistical graphics (e.g., dot plots, box plots) will also be used to better visualize the PK and PD distributions and summary statistics. For Secondary Objective 5, similar descriptive statistics will be computed for CTC counts: pre-therapy, post-therapy, and the pre/post therapy change.

For Secondary Objective 5, purely exploratory analysis of the association of each of the 3 PD endpoints (IGF-1, SCA, NSE) and CTC count with clinical outcome (e.g., TTP and OS) will be performed, using all the patients. For the pre-therapy levels of each of the 3 PD endpoints and CTC count, a univariable Cox regression model will be fit to the TTP data. These models will be exploratory only.

The statistical goals would be to determine the direction, magnitude, and precision of the association, as indicated by the hazard ratio (HR) being > 1 or < 1, how far away from 1, and its 90% CI width, respectively. These HR estimates would provide a hint as to whether there might be any potential relationship between a given pre-therapy PD endpoint (or CTC count) and the duration of TTP.

A similar exploratory investigation of the association of each of the 3 PD endpoints and CTC count with OS will also be undertaken.

The association of *post-therapy* levels of the 3 PD endpoints and CTC count with TTP will also be explored. These 4 associations (and those involving the pre/post therapy *change* in the same 4 predictors) will utilize the landmark method [20]. A suitable landmark timepoint (e.g., 12 weeks, a point at which therapy should be completed in all patients in consideration of Section 5.8) will be chosen. Post-therapy levels of the 4 candidate predictors will be determined at the landmark. A univariable Cox regression model of each of these 4*2 = 8 predictors will be fit to the TTP as measured *from* the landmark (thus changing the definition of TTP time zero). Patients who are censored before the landmark or die without prior evidence of progression must be excluded from landmark analyses.

A similar exploratory investigation of the association (using the landmark method) of the *post-therapy* levels and the *change* in each of the 3 PD endpoints and CTC count with OS will also be undertaken.

12.0 ADVERSE EVENTS REPORTING

12.1 Regulatory and reporting requirements-

These will be followed per IND requirements (if applicable) as well as Novartis Inc. requirements and WSU IRB requirements.

12.2 REPORTING OF SERIOUS TREATMENT EMERGENT ADVERSE EVENTS

An adverse event for the purposes of this protocol is the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) occurring after signing the informed consent even if the event is not considered to be related to the study drug(s). Please refer to the adverse event section of the protocol for the protocol-specific definitions of study drug and study treatment.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events [CTCAE] version 4.0. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, **or** grades 1 - 4, will be used. CTCAE grade 5 (death) will not be used in this study; rather, this information will be collected in the End of Treatment or Survival Information CRF page. Adverse event monitoring should be continued for at least 4 weeks following the last dose of study treatment.

Adverse events (but not serious adverse events) occurring before starting study treatment but after signing the informed consent form are recorded on the Medical History/Current Medical Conditions Electronic Case Report Form. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant or require therapy (e.g., any hematologic abnormality that requires transfusion or cytokine treatment); and should be recorded on the Adverse Events CRF under the signs, symptoms or diagnosis associated with them. In addition, isolated abnormal laboratory values that are considered clinically significant (e.g., cause study discontinuation or constitutes in and of itself a Serious Adverse Event) should be recorded on the Adverse Events CRF. SAEs occurring after signing the Informed Consent are recorded on the Adverse Event CRF.

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 (CTCAE grade 1-4)
2. Its relationship to each study drug (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 is serious, where a serious adverse event (SAE) is defined as one 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 signing the informed consent
- 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

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see protocol section on Serious Adverse Event reporting.

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, an assessment should be made at each visit (or more frequently, if necessary) of any changes in its severity, its suspected relationship to the study drug(s), any of the interventions required to treat it, and its outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigator's 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.

Information about all serious adverse events will be collected and recorded. To ensure patient safety each serious adverse event must also be reported to Novartis 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

Novartis instructions for rapid notification of serious adverse events [Appendix VII A and B]

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Drug Safety & Epidemiology (DS&E). 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 (877-778-9739), to Novartis Pharmaceuticals D S & E department within 24 hours of learning of it's 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 must be reported within 1 working day.

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 Novartis 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.

Pregnancies /Lactating mothers:

Not applicable since this is a study in men only.

12.3 Safety Reporting Requirements for IND Holders (if applicable)

In accordance with 21 CFR 312.32, sponsor-investigators of studies conducted under an IND must comply with following safety reporting requirements:

a. Expedited IND Safety Reports:

7 Calendar-Day Telephone or Fax Report:
The Sponsor-Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the investigator to be possibly related to the use of SOM-230. An unexpected adverse event is one that is not already described in the Investigator Brochure. Such reports are to be telephoned or faxed to the FDA within 7 calendar days of first learning of the event. Each telephone call or fax transmission (see fax number below) should be directed to the FDA new drug review division in the Center for Drug Evaluation and Research or in the product review division for the Center for Biologics Evaluation and Research, whichever is responsible for the review of the IND.

15 Calendar-Day Written Report:
The Sponsor-Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered possibly related to

the use of SOM-230. An unexpected adverse event is one that is not already described in the Investigator Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed with the IND concerning similar events should be analyzed. The new report should contain comments on the significance of the new event in light of the previous, similar reports.

Written IND safety reports with Analysis of Similar Events are to be submitted to the FDA, Genentech Drug Safety, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500a Form but alternative formats are acceptable (e.g. summary letter).

FDA fax number for IND Safety Reports:

1 (800) FDA-0178.

AND:

Study Coordination Center/Principal Investigator:
Ulka Vaishampayan M.D.
Contact Information 4HWCRC, 4100 John R
Detroit MI 48201.
Tel# 313-576-8715 and fax # 313-576-8487

b. IND Annual Reports

In accordance with the regulation 21 CFR § 312.32, the Sponsor-Investigator shall within 60 days of the anniversary date that the IND went into effect submit a brief report of the progress of the investigation. Please refer to Code of Federal Regulations, 21 CFR § 312.32 for a list of the elements required for the annual report. All IND annual reports submitted to the FDA by the Sponsor-Investigator should be copied to Novartis Inc. Copies of such reports should be mailed to:

12.4 WSU HIC Adverse Event reporting

All adverse event reporting will be done in compliance with the Wayne State Human Investigation Committee as follows:

A. Death or Life Threatening Adverse Reaction or Unexpected Event:
If a death or immediately life-threatening Adverse Reaction/Unexpected Event occurs, it must be reported to the HIC office within three (3) business days of the PI becoming aware, even if the information in the report is incomplete. As more information is forthcoming, one or more additional reports should be filed with the HIC. The initial report of the Adverse Reaction or Unexpected Event and follow-up reports should be filed using the HIC Adverse Reaction and Unexpected Event Form.

B. Serious Adverse Reaction or Unexpected Event:

If a Serious Adverse Reaction/Unexpected Event occurs (one that necessitates or prolongs hospitalization, results in a permanent or significant disability or congenital anomaly, or is judged to be serious by the principal investigator), and is **unexpected**, (not listed in the consent form) it must be reported to the HIC within five (5) business days of the PI becoming aware. If the Serious Adverse Event **is** listed in the consent form but a relationship to the study intervention/activity **cannot be ruled out by the PI**, it must be reported to the HIC within five (5) business days. If the information is incomplete on the initial filing, follow-up reporting is required. The HIC Adverse Reaction and Unexpected Event Form should be used in all reports pertaining to these reactions/events.

C. Non-Serious (Moderate or Minor) Adverse Reaction or Unexpected Event:
If a non-serious Adverse Reaction occurs that is **unexpected** (not listed in the informed consent), it must be reported to the HIC within ten (10) business days of awareness, **unless the Principal Investigator can rule out the relationship to the study agent or intervention.** If a non-serious Adverse Reaction occurs that is **expected** (listed in the informed consent), but is more frequent, more intense or longer lasting that expected, or requires medical treatment, it must be reported to the HIC within ten (10) business days. If the reaction that is listed in the consent form occurs as described in the informed consent, **it does not need to be reported to the HIC.**
If an Unexpected Event occurs, it must be reported to the HIC within ten (10) business days of the awareness by the Principal Investigator. The Adverse Reaction/ Unexpected Event Form should be used for these submissions.

D. Possibly-Related Adverse Reactions/ Unexpected Events
In the rare case where a sponsor requires that a non-reportable (i.e., possibly related) Adverse Reaction/ Unexpected Event be reported to the HIC, an amendment should be submitted by the PI requesting that the non-reportable safety report be appended to the HIC file. It remains the primary responsibility of the WSU PI, the study sponsor, and any associated DSMB to identify trends that might require the event to be elevated to definitely or probably related status.
If a trend is identified that elevates the Adverse Reaction to definitely or probably related status, an Adverse Reaction/ Unexpected Event Form should be completed, along with an amendment for consent form changes, if needed, and submitted to the HIC.

13.0 References

1) D.P. Petrylak, C.M. Tangen and M.H. Hussain et al., Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer, N Engl J Med 351 (2004), pp. 1513–1520.

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3) Scher H, Chi KN, De Wit R, et al. Docetaxel (D) plus high-dose calcitriol versus D plus prednisone (P) for patients (Pts) with progressive castration-resistant prostate cancer (CRPC): Results from the phase III ASCENT2 trial. 2010 Proc ASCO abstract# 4509.

4) Small E, Demkow T, Gerritsen WR, et al. A phase III trial of GVAX immunotherapy for prostate cancer in combination with docetaxel versus docetaxel plus prednisone in symptomatic, castration-resistant prostate cancer (CRPC). GU Cancer Symposium 2009, abstract # 7.

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11) Eisenhauer A, Therasse P, Bogaert J, et al. New response evaluation criteria in solid tumors. Eur J Cancer 2009, 45: 228-47.

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14) Schmid HA. Pasireotide (SOM230): development, mechanism of action and potential applications. Mol Cell Endocrinol. 2008 May 14;286(1-2):69-74.

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18) Attard, G., et al., Characterization of ERG, AR and PTEN gene status in circulating tumor cells from patients with castration-resistant prostate cancer. Cancer Res, 2009. 69(7): p. 2912-8.
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14.0 Data and Safety Monitoring

14.1 Scheduled meetings will be held monthly or more frequently depending on the activity of the protocol. These meetings will include the protocol investigators and data managers involved with the conduct of the protocol.

14.2 During these meetings the investigators will discuss matters related to:

- Safety of protocol participants (Adverse Event reporting)
- Validity and integrity of the data
- Enrollment rate relative to expectation of target accrual, characteristics of participants
- Retention of participants, adherence to the protocol (potential or real protocol violations)
- Data completeness on case report forms and complete source documentation

14.3 Completed Data and Safety Monitoring Reports of these regular investigator meetings will be kept on file in the office of the Clinical Trials Core (see form in appendix IV). The data manager assigned to the clinical trial will be responsible for completing the report form. The completed reports will be reviewed and signed off by the Principle Investigator (PI) or by one of the Co-PI's in the absence of the PI. The signed off forms will then be forwarded to the Director, Clinical Trials Core for review of completeness and processing with the Data and Safety Monitoring Committee.

14.4 The Barbara Ann KARMANOS Cancer Institute, Data and Safety Monitoring Committee will meet on a monthly basis to review the prior month Serious Adverse Event forms and Data and Safety Monitoring study specific reports that have been filed.

15.0 Protocol Conduct and Guidelines

15.1 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 and approved. 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 Novartis. 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 Novartis 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 Novartis must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes. Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

1. changes in the staff used to monitor trials
2. minor changes in the packaging or labeling of study drug.

15.2 Publication of results

Any formal presentation or publication of data from this trial may be published after review and comment by Novartis and prior to any outside submission. Novartis 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 Novartis' 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 Novartis and, in accord with the trial contract and shall not permit disclosure of Novartis confidential or proprietary information.

15.3 Disclosure and confidentiality

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

15.4 Discontinuation of study

The sponsor (Novartis Inc) reserves the right to discontinue the study under the conditions specified in the clinical trial agreement.

12.9 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 Novartis 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.

15.5 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 Novartis before study initiation. Any amendments to the protocol, other than administrative ones, must be reviewed by Novartis approved by this committee.

15.6 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.

15.7 Declaration of Helsinki

The investigator will 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.

16.0 APPENDICES

Appendix I

Performance Status Criteria

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

Appendix II
MANAGEMENT OF ACUTE HYPERSENSITIVITY WITH DOCETAXEL

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	· consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient · then, complete docetaxel (Taxotere®) infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	· interrupt docetaxel (Taxotere®) infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV; monitor patient until resolution of symptoms · resume docetaxel (Taxotere®) infusion after recovery of symptoms; depending on the physician's assessment of the patient, docetaxel (Taxotere®) infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, *(e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the 1-h infusion rate)* · depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, *(e.g. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate)*
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	· immediately discontinue docetaxel (Taxotere®) infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms · the same treatment guidelines outlined under moderate symptoms (i.e. the third and fourth bullets) should be followed.
Anaphylaxis (NCI grade 4 reaction)	· NO FURTHER STUDY DRUG THERAPY

APPENDIX III

MANAGEMENT OF EDEMA / FLUID RETENTION WITH DOCETAXEL

No dose reduction is required. Patients developing new onset edema, progression of existing edema, or another sign of fluid retention (e.g. 2 pound weight gain) are to be treated with oral diuretics. Regimens found to be effective in the management of fluid retention due to Taxotere are listed below.

- HCTZ/triamterene (Dyazide®, or generic equivalent) one capsule po daily, increase up to tid.
- Furosemide 40 mg (Lasix® or generic equivalent) po daily if edema progresses despite Dyazide® (or equivalent) therapy. Potassium supplementation should be given as needed.
- If after a two week trial, furosemide 40 mg po daily is ineffective, the patient may be treated with furosemide 20 mg po daily plus metolazone 2.5 mg po daily with potassium supplementation as needed.

Further therapy should be customized depending upon the clinical situation. The clinical tolerance of the patient, the overall tumor response and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment.

Appendix IV

Docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4. Inhibitors of CYP3A4 and/or PgP

Co-administration with strong inhibitors of CYP3A4 (e.g., ketoconazole, itraconazole, ritonavir) or P-glycoprotein (PgP) should be avoided.

Co-administration with moderate CYP3A4 inhibitors (e.g., erythromycin, fluconazole) or PgP inhibitors should be used with caution. If patient requires co-administration of moderate CYP3A4 inhibitors or PgP inhibitors, consider holding protocol therapy.

Seville orange, star fruit, grapefruit and their juices affect P450 and PgP activity. Concomitant use should be avoided.

Inducers of CYP3A4 and/or PgP

Avoid the use of strong CYP3A4 inducers. If patient requires co-administration of strong CYP3A4 inducers (i.e., phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital, St. John's wort) considering discontinuing therapy temporarily or permanently.

Clinically relevant drug interactions: substrates, inducers, and inhibitors of isoenzyme CYP3A

INDUCERS
Barbiturates, carbamazepine, glucocorticoids, modafinil, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, troglitazone, efavirenz, nevirapine, topiramate
INHIBITORS
Strong inhibitors: clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandamycin, voriconazole, Posaconazole (Krishna et al, 2009) **Moderate inhibitors:** aprepitant, atazanavir, cimetidine, ciprofloxacin, darunavir, diltiazem, erythromycin, fluconazole, grapefruit juice, imatinib, tofisopam, verapamil,

Table Clinically relevant drug interactions mediated by PgP

PgP Substrates	PgP Inhibitors in vivo	PgP Inducers
digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, elacridar, erythromycin, felodipine, (GF120918), itraconazole,	rifampin, St John's wort

PgP Substrates	PgP Inhibitors in vivo	PgP Inducers
	ketocoanzole, lopinavir, (LY335979), mibefradil, nifedipine, nitrendipine, (PSC833), quinidine, ranolazine, ritonavir, talinolol, valspodar, verapamil	

Reference:

Internal Clinical Pharmacology Drug-drug interaction (DDI) memo, updated Dec. 2, 2009, which summarizes DDI data from three sources including the FDA's "Guidance for Industry, Drug Interaction Studies, the University of Washington's Drug Interaction Database, and Indiana University School of Medicine's Drug Interaction Table.

Appendix V
Drugs that are generally accepted by the QTdrugs.org Advisory Board of the Arizona CERT to have a risk of causing torsades de pointes. Updated June 2011.

Generic Name	Brand Name	Class/Clinical Use	Comments
Amiodarone	Cordarone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Amiodarone	Pacerone®	Anti-arrhythmic / abnormal heart rhythm	Females>Males,TdP risk regarded as low
Arsenic trioxide	Trisenox®	Anti-cancer / Leukemia	
Astemizole	Hismanal®	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Bepridil	Vascor®	Anti-anginal / heart pain	Females>Males
Chloroquine	Aralen®	Anti-malarial / malaria infection	
Chlorpromazine	Thorazine®	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	Propulsid®	GI stimulant / heartburn	Restricted availability; Females>Males.
Clarithromycin	Biaxin®	Antibiotic / bacterial infection	
Disopyramide	Norpace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Dofetilide	Tikosyn®	Anti-arrhythmic / abnormal	

		heart rhythm	
Domperidone	Motilium®	Anti-nausea / nausea	Not available in the U.S.
Droperidol	Inapsine®	Sedative;Anti-nausea / anesthesia adjunct, nausea	
Erythromycin	Erythrocin®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Erythromycin	E.E.S.®	Antibiotic;GI stimulant / bacterial infection; increase GI motility	Females>Males
Halofantrine	Halfan®	Anti-malarial / malaria infection	Females>Males
Haloperidol	Haldol®	Anti-psychotic / schizophrenia, agitation	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Corvert®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Levomethadyl	Orlaam®	Opiate agonist / pain control, narcotic dependence	
Mesoridazine	Serentil®	Anti-psychotic / schizophrenia	
Methadone	Methadose®	Opiate agonist / pain control, narcotic dependence	Females>Males
Methadone	Dolophine®	Opiate agonist / pain control, narcotic dependence	Females>Males
Moxifloxacin	Avelox®	Antibiotic / bacterial infection	
Pentamidine	Pentam®	Anti-infective / pneumocystis pneumonia	Females>Males
Pentamidine	NebuPent®	Anti-infective / pneumocystis pneumonia	Females>Males
Pimozide	Orap®	Anti-psychotic / Tourette's tics	Females>Males
Probucol	Lorelco®	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Pronestyl®	Anti-arrhythmic / abnormal	

		heart rhythm	
Procainamide	Procan®	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Cardioquin®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Quinidine	Quinaglute®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sotalol	Betapace®	Anti-arrhythmic / abnormal heart rhythm	Females>Males
Sparfloxacin	Zagam®	Antibiotic / bacterial infection	
Terfenadine	Seldane®	Antihistamine / Allergic rhinitis	No longer available in U.S.
Thioridazine	Mellaril®	Anti-psychotic / schizophrenia	
Vandetanib	Zactima®	Anti-cancer / Thyroid cancer	"Zactima®" is the

APPENDIX VI

Barbara Ann KARMANOS Cancer Institute: Protocol Specific Data and Safety Monitoring Report

PROTOCOL #: _____ **REPORT DATE:** _____

PROTOCOL TITLE		
ATTENDANCE		

PROTOCOL ACTIVITY SINCE LAST REPORT			
Accrual Goal:	Eligible:		Total number of AE's to date:
Accrual to Date:	Ineligible (provide reason):		
Accrual Since Last Monthly Report:			

Specifically for Phase I Trial &/or Dose Escalating Trials:	
Dose Level	**Accrual**
1	
2	
3	

Record all Grade 3, 4, and 5 Adverse Events (AE). Group by category of AE. record the date OF the occurrence, attribution and if reportable to the IRB. Shade the rows of the AE's that have occurred for this Report. attach the HIC UP report form for these reportable events that occurred on this report.

Pt. ID#	Category and type of adverse reaction	Date of Occurrence	Grade[1]	Attribution[2]	Reportable to IRB (Y/N) Yes with date

1. Grade: 1-Mild, 2-Moderate, 3- Severe, 4-Life-threatening, or 5- Death.
2. Attribution: 1-unrelated, 2 - unlikely, 3 - possibly, 4 - probably, or 5 - definitely

OFF TREATMENT □ Provide reason [progression, death, toxicity, completed therapy, etc].

PROTOCOL VIOLATIONS □ Deviations from protocol treatment, monitoring, or study calendar.			
PROTOCOL AMENDMENTS □ Include date submitted to regulatory bodies and date approved.			
OTHER COMMENTS			
Investigator Signature:		**Data Manager Signature:**	

Appendix VII

A) Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk *1 877 778 9739*

Investigator contact details:
Name: _____
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Suspected/Unknown

B) Interventional Clinical Trial SAE Fax Cover Sheet

To: Local Novartis Drug Safety and Epidemiology Safety Desk *1 877 778 9739*

Investigator contact details:
Name: _____
Fax number : _____
Phone number : _____

Study Name	
Centre Number	
Patient Number	

Relationship between study treatment and event(s) is:

Not Suspected

Appendix VIII
Revised SOM230 Abnormal liver function management

Hepatic-related patient management for all ongoing studies
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.

SOM230 LFT Management Algorithm (s.c. and LAR studies)

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