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TITLE: A Phase II study of Vorinostat (Suberoylanilide Hydroxamic Acid) plus Rituximab in Indolent Non-Hodgkin's Lymphoma.

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DISEASE SITE: **Acute NHL**

STAGE

MODALITY(IES)

TYPE Phase II

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TITLE: **A Phase 2 Study of Vorinostat (Suberoylanilide Hydroxamic Acid) plus Rituximab in Indolent Non-Hodgkin's Lymphoma.**

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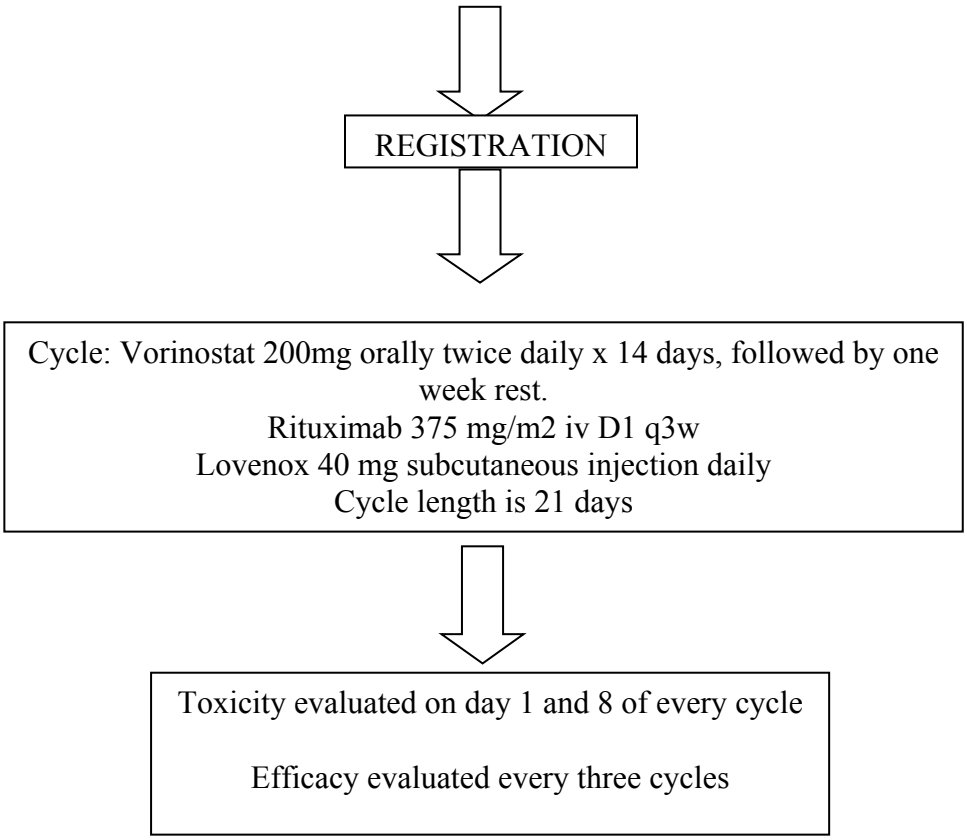
Merck Supplied Agent:	Suberoylanilide Hydroxamic Acid (VORINOSTAT); NSC 701852

SCHEMA

Indolent Non Hodgkin's Lymphoma newly diagnosed or with relapsed/refractory disease



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1. OBJECTIVES

1.1. To evaluate the anti-tumor activity of VORINOSTAT plus Rituximab as assessed by the objective response rate, time to progression and survival in subjects with indolent lymphoma.

1.2. To assess the toxicity profile of VORINOSTAT plus Rituximab in this patient population.

2. BACKGROUND

2.1 Current Status of Lymphoma Care

Despite thirty years of clinical trials, little progress has been made in the treatment of low grade lymphoma (Horning, 2003). Patients with low grade lymphomas, as classified by the Working Formulation classification, tend to respond initially to approaches as disparate as "watchful waiting", anthracycline based chemotherapy (in conjunction with cyclophosphamide (Dana, et al, 1993) or fludarabine (Klasa, et al, 2002; Velasquez, et al, 2003), or stem cell transplant (Bierman, et al, 2003; van Besien, et al, 2003), but invariably the lymphoma recurs in over 50% of patients within 5 years. There is as such no consensus on upfront therapy that can be designated as "standard".

Upon recurrence, remissions can be achieved with further chemotherapy, but the disease free intervals tend to be shorter with each line of treatment (Dana, et al, 1993). Allogeneic transplant has been successful in selected patients, but with greater treatment related mortality (van Besien, et al, 2003), while autologous high dose therapy, with or without the addition of high dose radio-labeled antibodies has not been curative (Gopal 2003). In recent years, the additional of Rituxan, a targeted antibody,has shown improved outcome and survival in single agent and combination chemotherapy regimens, suggesting that aside from its single agent, it acts as a chemosensitizer in lymphoma treatment (Czuczman 2003, Czuczman 2004, Forstpointner 2004). Thus, newer, more effective agents are necessary.

2.2 Vorinostat (Suberoylanilide Hydroxamic Acid (VORINOSTAT))

Vorinostat, (Zolinza, Suberoylanilide hydroxamic acid; NSC 701852)) is a small molecule inhibitor of histone deacetylase (HDAC) that binds directly in the enzyme's active site in the presence of a zinc ion (Finnin *et al*., 1999). Because aberrant HDAC activity has been implicated in a variety of cancers, development of HDAC inhibitors is a rational approach to the design of targeted anticancer therapeutics. Several HDAC inhibitors from multiple chemical classes have been developed and are currently in clinical trials. Trichostatin and butyric acid were among the first HDAC inhibitors to be administered to patients, but these were found to be clinically unsuitable due to potency and formulation issues (Gilbert *et al*., 2001; Gore *et al*., 2002). Depsipeptide was originally selected for clinical study based on its antiproliferative effects; subsequently it was discovered to antagonize HDACs (Sausville, 2003) and was the first HDAC inhibitor to demonstrate clinical efficacy (Piekarz *et al*., 2001). Of the three classes of HDACs, VORINOSTAT targets most human Class 1 (related to the yeast transcriptional regulator Rpd3) and Class 2 (similar to the yeast Hda1) enzymes (Marks *et al*., 2001a; Kelly *et al*., 2002); the third class of HDACs (homologues of yeast sir2) requires NAD+ for activity and is not inhibited by VORINOSTAT. Among those currently in clinical trials, VORINOSTAT is the most potent HDAC inhibitor that can be administered orally with excellent bioavailability. It received FDA approval for treatment in patients with Cutaneous T Cell Lymphoma on October 6, 2006. Promising activity is being seen in a current CTEP trial for indolent lymphoma, with reports pending on several responses, CR and PR, in refractory indolent lymphoma.

2.3 Rationale

2.3.1 Mechanism of Action

The HDACs exert their targeted action during post-translational acetylation of core nucleosomal histones, which affects chromatin structure, thereby regulating gene expression. DNA that is wrapped around condensed, non-acetylated histones is transcriptionally inactive, whereas acetylation of N-terminal histone lysine residues exposes DNA to important transcription factors that promote transcriptional activity (Workman and Kingston, 1998; Arts *et al*., 2003). The dynamic equilibrium between histone acetylation and deacetylation is regulated by histone acetyltransferases (HATs) and HDACs. The action of HDACs on nucleosomal histones leads to tight coiling of chromatin and silencing of expression of various genes, including those implicated in the regulation of cell survival, proliferation, differentiation, and apoptosis (Jones and Baylin, 2002). The effects of HDACs are not limited to histone deacetylation. HDACs also act as members of a protein complex to recruit transcription factors to the promoter region of genes, including those of tumor suppressors, and they affect the acetylation status of specific cell cycle regulatory proteins (Arts *et al*., 2003).

2.3.2 Nonclinical Activity

VORINOSTAT was identified originally by its ability to induce differentiation of murine erythroleukemia cells at micromolar concentrations (Richon *et al*., 1996; Richon *et al*., 1998). Subsequently, it was found to induce differentiation or arrest growth of a wide variety of human carcinoma cells. To date, VORINOSTAT activity has been reported in transformed hematopoietic cells, such as multiple myeloma (MM) (Feinman *et al*., 2002; Mitsiades *et al*., 2002; Mitsiades, N. *et al*., 2003), acute promyelocytic leukemia (APL) (Amin *et al*., 2001), acute lymphocytic leukemia (Guo *et al*., 2002), chronic myelogenous leukemia (Nimmanapalli *et al*., 2003; Yu *et al*., 2003), Waldenstrom's macroglobulinemia (Mitsiades, C. *et al*., 2003), and cutaneous T-cell lymphoma (CTCL) (Zhang *et al*., 2003). Activity has also been reported in cell lines representing other tumor types including bladder transitional cell carcinoma (Richon *et al.*, 2000), breast cancer (Huang *et al.*, 2000; Munster *et al.*, 2001; Said *et al.*, 2001), prostate cancer (Butler *et al.*, 2000), head and neck squamous carcinoma (Gillenwater *et al.*, 2002), and colon carcinoma (Peart *et al.*, 2003).

The antitumor activity of VORINOSTAT was demonstrated in several *in vivo* models of cancer, including a xenograft model of human CWR22 prostate cancer cells (Butler *et al.*, 2000), a mouse model of APL containing the promyelocytic leukemia zinc-finger-retinoic acid receptor α fusion gene (PLZF-RARα) (He *et al.*, 2001), and an *N*-methylnitrosourea-induced mammary tumor model in rodents (Cohen *et al.*, 1999). VORINOSTAT has also showed activity when administered daily by intraperitoneal (IP) injections in the CWR22 and PLZF-RARα models and by oral (PO) administration in the carcinogen-induced mammary tumor model.

2.3.3 VORINOSTAT Combination Studies

Accumulating evidence has demonstrated the effectiveness of HDAC inhibitors in combination with several other agents *in vitro*. The combination of VORINOSTAT and DNA hypomethylating agents (5-azacytidine or decitabine) acts synergistically to induce apoptosis, differentiation, and/or cell growth arrest in various cancer cell lines (Tabe *et al.*, 2002; Zhu and Otterson, 2003). When VORINOSTAT was combined with the anti-metabolite 5-fluorouracil, a supra-additive to additive antiproliferative effect in wild type and mutant-p53 colorectal cancer cells was observed (Di Gennaro *et al.*, 2003). VORINOSTAT with imatinib mesylate (Gleevec®) may be effective in chronic myelogenous leukemia (CML) cells that resist imatinib mesylate through increased Bcr-Abl expression (Nimmanapalli *et al.*, 2003; Yu *et al.*, 2003). Minimally toxic concentrations of the proteasome inhibitor bortezimib combined with VORINOSTAT resulted in increased apoptosis in human leukemia cells (Yu *et al.*, 2003). In cells from RARα-PLZF/RARα-PLZF transgenic mice and in cells harboring t(15;17) (RARα-PML fusion genes), VORINOSTAT induced significant apoptosis and growth inhibition, effects that were increased by adding all-*trans* retinoic acid (He *et al.*, 2001). Pre-treating four human cancer cell lines (including a brain tumor line) with VORINOSTAT increased the killing efficiency of etoposide, ellipticine, doxorubicin, or cisplatin, but not of the topoisomerase I inhibitor camptothecin (Kim *et al*., 2003). However, treating cells in the reverse order (anticancer drug followed by VORINOSTAT) was no more cytotoxic than the anticancer drug alone. Finally, overexpression of Bcl-2 or Bcl-XL in leukemia and MM cell lines abolished VORINOSTAT-

induced apoptosis but did not affect its differentiation or cell cycle regulatory effects (Vrana *et al.*, 1999; Mitsiades, N. *et al.*, 2003; Peart *et al.*, 2003). This suggests that agents blocking Bcl-2 expression or function could be effectively combined with VORINOSTAT. Studies done with other HDACs have suggested that a consequence of HDAC inhibitor-induced heat shock protein 90 (Hsp 90) acetylation is depletion of the Hsp 90 client protein Her-2 and increased apoptosis of breast cancer cell lines induced by taxotere, trastuzumab, epothilone B, and gemcitabine (Fuino *et al.*, 2003; Yu *et al.*, 2002). In addition to these potentially additive or synergistic interactions between VORINOSTAT or other HDACs and various anticancer drugs, VORINOSTAT has shown synergistic activity when combined with radiotherapy in prostate cancer cell spheroids (Sgouros *et al.,* 2002).

2.3.4 Phase 1 Clinical Experience

A phase 1 study evaluated VORINOSTAT administered intravenously (IV) to patients with advanced solid tumors and hematologic malignancies (Kelly *et al.*, 2003). VORINOSTAT was administered using two schedules: 2-hour IV infusion daily X 3 q21d, or daily X 5 for 1 to 3 weeks. No dose-limiting toxicities (DLTs) were observed in eight patients administered VORINOSTAT daily X 3 q21d at doses of 75, 150, 300, 600, and 900 mg/m²/day. One solid tumor patient given 900 mg/m² on the daily X 5 schedule for 3 weeks developed acute respiratory distress and grade 3 hypotension. Among five other patients at this dose, no additional DLTs were observed. Among 12 hematologic and 17 solid tumor patients enrolled on the daily X 5 schedule (300, 600, and 900 mg/m²/day), therapy was delayed >1 week for grade 3/4 leukopenia and/or thrombocytopenia in two of five patients with hematologic malignancies given 600 mg/m² for 3 weeks. The maximum tolerated dose (MTD) for hematologic malignancy patients was 300 mg/m² daily X 5 for 3 weeks. An MTD for solid tumors was not determined because the study was terminated when an oral formulation became available. The mean terminal half-life ($t_{1/2}$) ranged from 21 - 58 minutes, and the dose was linearly proportional to the area under the concentration versus time curve (AUC). Acetylated histones were detected in peripheral blood mononuclear cells (PBMCs) up to 4 hours post-infusion at higher dose levels. This observation was confirmed by immunohistochemical analyses of post-therapy tumor biopsies. Four patients, including two with lymphoma and two with bladder cancer, experienced objective tumor regression with clinical improvement in tumor-related symptoms.

As of June 2004, VORINOSTAT capsules have been administered to 143 patients with advanced solid tumors or hematologic malignancies in three phase 1 trials and three phase 2 trials (Investigator's Brochure, 2004) at total daily doses ranging from 200 to 900 mg. The MTD of continuous dosing (no rest period) of oral VORINOSTAT is 400 mg q.d. or 200 mg b.i.d. When the agent is given intermittently, the MTD is 300 mg b.i.d. daily × 3 days per week or 250 mg t.i.d. x 14 days followed by 7 days of rest. The DLTs are non-hematologic (anorexia, dehydration, diarrhea, and fatigue). The most common hematologic adverse events are anemia and thrombocytopenia, which are rapidly reversible after study drug interruption. Pharmacokinetic analysis of 26 patients has indicated that the bioavailability of oral VORINOSTAT is approximately 46%. VORINOSTAT doses in the range of 200 - 600 mg produced maximum concentration (C_{max}) and drug exposure (AUC) curves that were linearly proportional. The $t_{1/2}$ of oral VORINOSTAT ranges from 92 to 150 minutes, and preliminary data suggest that administration of VORINOSTAT with food does not appear to substantially alter the rate or extent of absorption. Inhibition of HDAC activity was achieved in PBMCs at the 200 mg dose level. At dose levels of 400 and 600 mg, the duration of HDAC inhibition lasted $\geq$10 hours.

Significant antitumor activity has been observed among members of the above patient population. In the ongoing phase 1 study of oral VORINOSTAT, seven patients with heavily pre-treated diffuse large B-cell lymphoma were entered. Among these patients, one complete response (CR) and one partial response (PR) were observed. In addition, one patient has had a significant PET scan response. The PR lasted 5 months, the PET scan response lasted 6 months, and the CR is ongoing with a duration >12 months. Decrease in tumor mass, pleural effusion, and improvement of tumor-related pain or shortness of breath have also been observed in patients with mesothelioma. In an ongoing phase 2 study of VORINOSTAT in patients with heavily pretreated CTCL or peripheral T-cell lymphoma, objective responses have been observed (including PRs in 5 of 13 patients), and 8 of

10 patients reported decreased pruritus. In the published Phase I study of VORINOSTAT, the MTD was identified as 200 mg PO bid for continuous dosing and 300 mg PO bid for three-day-per-week dosing (Kelly WK, et al 2005)

Based on the data from these clinical studies, the recommended doses and schedules of oral VORINOSTAT administration for phase 2 trials are 400 mg q.d., 200 mg b.i.d., or 300 mg b.i.d. daily × 3 days per week in patients with either solid tumors or hematologic malignancies.

2.3.5 Potential for Drug Interactions

In laboratory studies using cultured human hepatocytes, statistically significant and concentration-dependent suppression of the P450 isoenzymes CYP2B6, 2C9, and 2C19 was seen at concentrations exceeding the levels achieved following oral administration (10 to 50 μM) of VORINOSTAT, while CYP3A4 suppression was observed at clinically relevant (2 μM) concentrations of the agent (Investigator's Brochure, 2004). These effects could be the result of VORINOSTAT-induced changes in the cellular machinery that generates these enzymes or VORINOSTAT metabolites. These observations suggest that the potential exists for interactions between VORINOSTAT and concurrently administered drugs, over-the-counter medication, or alternative therapies. For this reason, caution should be observed when treating patients taking any agent found in Appendix C, a list of drugs or substances known to affect or with the potential to affect selected P450 isoenzymes.

2.3.6 Use of VORINOSTAT in Lymphoma

There is good preclinical evidence to support the use of HDAC inhibitors in lymphoid malignancies. Increased histone acetylation has been shown to regulate terminal B cell differentiation, as well as to cause apoptosis via upregulation of $p21^{waf\text{-}1/cip1}$. .Several natural agents have been shown to have HDAC inhibitory activity, however the orally bioavailable synthetic compound, suberoylanilide hydroxamic acid, has to been shown to effectively bring about increased histone acetylation in B cell malignancies. VORINOSTAT induces growth arrest and apoptosis in B cell tumor lines,at least in part via upregulation of $p21^{waf\text{-}1/cip1}$, in a caspase independent manner. B cell tumor lines were more sensitive to VORINOSTAT than solid tumor lines in vitro (Mitsiades, et al 2003).

In clinical trials as well, responses among patients with lymphoid malignancies were prominent. In the initial phase I study using IV VORINOSTAT, of the four responders, two were lymphoma patients (Kelly, et al, 2003) In the ongoing phase I studies, there were two responders among the seven lymphoma patients, one CR and one PR. In a Phase II trial of VORINOSTAT in cutaneous T cell lymphoma presented at this year's ASH meeting, five out of 13 patients were partial responders, and in a Phase I study presented at last year's meeting reduction in tumor size was seen in six out of 21 heavily pretreated patients with NHL and Hodgkin's lymphoma. In our ongoing phase II study of vorinostat alone in relapsed or refractory indolent lymphoma patients, at the first stage evaluation point, 4 CR, 2 PR, and several patients with prolonged stable disease were seen; the trial is currently accruing to the second stage. Thus, a combination trial with rituxan in upfront, relapsed, and refractory patients is indicated.

2.3.7 Rituximab (IDEC-C2B8, Rituxan)

Rituximab is a chimeric IgG1 monoclonal antibody targeting the CD20 surface antigen present on both normal lymphocytes and B-cell lymphomas. The activity of this agent is multifaceted, in that it leads to direct lysis by complement activation as well as antibody dependant cell mediated cytotoxicity, triggers apoptosis, and may lead to various signaling pathway changes in targeted cells (reviewed in Cartron 2004). Aside from its direct effect, it appears to also act as a chemosensitizer by blocking IL-10 binding, leading to decreased intracellular bcl-2 , and a pro-apoptotic environment (Demidem, 1997, Alas D 2001). This suggests that rituximab may synergise with vorinostat's pro-apoptotic activity. It is thus reasonable to combine the two agents, vorinostat and rituximab, in indolent lymphomas.

Given the activity seen in relapsed and refractory patients with vorinostat alone, we propose a Phase II study of vorinostat at 200 mg PO b.i.d. on a two week on, one week off schedule in patients with low grade lymphomas in combination with rituximab, at 375 mg/m2 given every three weeks on day 1 of the cycle along with vorinostat. Included in this cohort are patients with low-grade lymphomas according to the Working Formulation classification, newly diagnosed or who have recurred after rituxan and/or chemotherapy.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically or cytologically confirmed indolent Non-Hodgkin's Lymphoma (Included in this category are newly diagnosed or relapsed/refractory follicular center lymphomas grade I, II, III, relapsed /refractory marginal zone B-cell lymphoma (nodal and extranodal), relapsed/refractory mantle cell lymphoma).

3.1.2 Patients must have measurable disease by CT scan. PET scan evaluations are desirable but not mandatory, so that patients with negative PET scans but measurable disease by CT are eligible.

3.1.3 Patients may have had up to four prior chemotherapeutic regimens. Steroids alone and local radiation do not count as regimens (Radiotherapy must have been completed at least 14 days prior to starting vorinostat). Rituxan alone does not count as a regimen, however, Bexxar or Zevalin do. For treated patients, the most recent therapy must have failed to induce a complete response (i.e. there is persistent disease by CT or PET), or there must be disease progression or recurrence after the most recent therapy.

3.1.4 Patients may be enrolled who relapse after autologous stem cell transplant if they are at least three months after transplant, and after allogeneic transplant if they are at least six months posttransplant. To be eligible after either type of transplant, patients should have no active related infections (i.e. fungal or viral). In the case of allogeneic transplant relapse, there should be no active acute graft versus host disease (GvHD) of any grade, and no chronic Graft versus Host disease other than mild skin, oral, or ocular GvHD not requiring systemic immunosuppression.

3.1.5 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of VORINOSTAT in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric single-agent trials, if applicable.

3.1.6 Life expectancy of greater than 3 months.

3.1.7 ECOG performance status 2 (Karnofsky ≥60%; see Appendix A).

3.1.8 Patients must have normal organ and marrow function as defined below:

- Absolute Neutrophil Count ≥1,000/mcL
- platelets ≥100,000/mcL
- total bilirubin within normal institutional limits; patients with elevation of unconjugated bilirubin alone, as in Gilbert's Disease, are eligible.
- AST(SGOT)/ALT(SGPT) ≤2.5 X institutional upper limit of normal creatinine up to and including 2 mg/dl

3.1.9 Pre-menopausal women must have a negative serum pregnancy test prior to entry on this study. The effects of VORINOSTAT on the developing human fetus at the recommended therapeutic dose are unknown. For this reason and because HDAC inhibitors are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy within 4 weeks, or radiotherapy within 2 weeks or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier are excluded. This does not include use of steroids, which may continue until two days prior to enrollment. Low dose chlorambucil should be stopped two weeks prior to beginning VORINOSTAT. Valproic acid should be stopped at least two weeks prior to enrollment. Nitrosureas and mitomycin should be stopped 6 weeks prior to enrollment.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with known brain metastases are excluded from this clinical trial unless the metastases are controlled after therapy and have not been treated with steroids within the past two months.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to VORINOSTAT.

3.2.5 There must be no plans for the patient to receive concurrent hormonal, biological or radiation therapy.

3.2.6 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because VORINOSTAT is a HDAC inhibitor agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with VORINOSTAT, breastfeeding should be discontinued if the mother is treated with VORINOSTAT.

3.2.8 HIV-positive patients receiving combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with VORINOSTAT. In addition, HIV patients not receiving combination antiretroviral therapy are also ineligible as these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy.

3.2.9 Patients with other active malignancies are ineligible for this study.

3.2.10 Patients with preexisting or previous coagulation issues are not excluded from study as long as 1) previous pulmonary embolism or deep vein thrombosis have been adequately treated or 2) if they are actively receiving Coumadin or lovenox for anticoagulation. Patients who are already on Coumadin or Lovenox do not need to take additional 40 mg subcutaneous injections daily.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4. TREATMENT PLAN

4.1 Suberoylanilide Hydroxamic Acid (VORINOSTAT) Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications for VORINOSTAT are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

A cycle of therapy will consist of VORINOSTAT 200mg twice daily administered orally for 14 days followed by a seven day break on a 21 day cycle for the first cycle. If tolerated, the dose may be increased after the 2nd cycle to 200 mg TID x 14/21 days. If necessary, dose de-escalation may be instituted by reducing one of the daily doses by 100 mg; so, for example, patients might receive an am dose of 300 mg and a pm dose of 200 mg. Rituximab will be infused on day 1 of each cycle at the standard dose of 375 mg/m2 Radiological assessment by CT and/or PET scan will take place at baseline and after every three cycles (every 3 months). Response will be assessed by standard criteria (Cheson BD, *et al* 1999). Toxicity will be assessed on days 1 and 8 of every cycle, and graded using the NCI CTCAE version 3.0. Patients with measurable response or stable disease may continue receiving VORINOSTAT until progression. Patients who achieve CR will receive two further cycles of VORINOSTAT plus rituximab and then discontinue drug. Patients who achieve complete response may be restarted on drug in the event of relapse six months or greater from the time of initial CR, given the chronic relapsing nature of indolent lymphomas. Compliance with treatment will be monitored by use of drug diaries.

Because many drugs including antineoplastic agents are metabolized by the cytochrome P450 system, there is a potential for interaction of VORINOSTAT with concomitantly administered drugs. The case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies.

Patient compliance will be monitored using drug diaries, which will be reviewed on day 1 of each cycle after cycle 1.

4.2 Rituximab Administration

Rituximab will be administered at a dose of 375 mg/m2 on day 1 of every cycle, every three weeks. The initial dose rate should be 50 mg/hour IV for the first hour. If no toxicity is seen, the dose rate may be escalated gradually to a maximum of 400 mg/hour. Subsequent doses have required much less infusion time. If the first dose of rituximab is well tolerated, the starting flow rate for subsequent doses is 100 mg/hour, then increased gradually (100 mg/hour increments at 30-minute intervals) not to exceed 400 mg/hour.

Patients may experience transient fever and rigors with infusion. When these occur, the antibody infusion should be temporarily discontinued or slowed. When symptoms improve, the infusion should be resumed, initially at half the previous rate. Following the antibody infusion, the intravenous line should be kept open for medications, as needed. If there are no complications, the intravenous line may be discontinued after one hour of observation.

Oral premedication (acetaminophen and diphenhydramine hydrochloride) may be administered 30 to 60 minutes prior to starting each infusion of rituximab.

Lovenox Administration

Lovenox (enoxaparin) will be administered at a dose of 40 mg subcutaneously daily. Patients will be educated by nursing staff on how to perform daily injections. Administration should be alternated between left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and the forefinger. The skin fold should be held throughout the injection.

4.3 Supportive Care Guidelines

4.3.1 Antiemetics

Individualization of antiemetic treatment for patients receiving VORINOSTAT is required, as some patients require no antiemetic therapy, while others may require more intense therapy. Recommended antiemetics include: ondansetron, prochlorperazine, metoclopramide, lorazepan, or diphenhydramine. It is recommended that steroids not be used for anti-emesis.

4.3.2 Chemotherapy

Concurrent chemotherapy is not allowed in this study.

4.3.3 Complimentary or Alternative medications

Patients may not take CAM medications while on protocol. Routine vitamin supplementation is allowed.

4.3.4 Growth Factors

Patients already on erythropoeitin or aranesp for lymphoma related anemia may continue to use these agents. Use of G-CSF or erythropoeitin is allowed after the first cycle.

4.3.5 Radiation Therapy

Patients who require localized external beam radiotherapy at the time of protocol screening should receive it prior to study entry.

Patients who require localized external beam radiotherapy during study will be considered to have progression of lymphoma and will be removed from study.

4.3.6 Diarrhea

Treat diarrhea promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever.

4.3.7 Oral Intake and Hydration

Care should be taken to ensure adequate hydration during and after treatment. Popsicles and Gatorade have been found to be useful in this setting.

4.3.8 Anticoagulation prophylaxis

Patient will need to take Lovenox 40 mg subcutaneously daily when patients are getting active treatment with vorinostat and rituxan. Five research participants on this study have developed either pulmonary embolism or deep vein thrombosis. These have been without symptoms and found on CT scans. Lovenox (40 mg) subcutaneously will be taken starting from Cycle 1 Day 1 of study to prevent pulmonary embolus and deep vein thrombosis. Lovenox will continue for at least 28 days status post last dose of vorinostat or rituximab. For patients with creatinine clearance less than 30 ml/min, lovenox dose will be 30 mg subcutaneously daily. Elderly patients with creatinine clearance less than 50 ml/min should also be dosed at 30 mg subcutaneously daily.

4.4 Duration of Therapy

Patients who achieve CR as defined in section 9 will receive two further cycles of VORINOSTAT plus rituximab and then discontinue drug. Radiologic studies will be continued every three months for the first year, and at a minimum of every six months for the next two years.
In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.5 Duration of Follow Up

Patients will be followed until disease progression is noted or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

5. DOSING DELAYS/DOSE MODIFICATIONS

5.1 Vorinostat Dose Reductions for Toxicity:

Treatment will be administered at 100 mg daily less than their previous dose for patients who present to treatment and are found to have ANC≥ 500, but ≤ 1000, or platelet counts ≥50K but ≤75K. This dose reduction is reversible with normalization of counts.

Treatment will be held for patients who present with:

1. non-hematologic toxicity of grade 3 or 4, until toxicity resolves to below grade 2. These patients will restart at 100 mg daily less than their previous dose. If this dose leads to recurrence of the toxicity at grade 3 or greater, the patient will come off study.
2. hematologic toxicity of ANC <500, or platelet count <50K. Should dose need to be held for greater than two weeks, upon recovery of ANC >1000 or platelet count >50 patient may restart at 100 mg daily less than their previous dose. If this dose also leads to ANC<500 or platelet count <50, then patient should come off study.

Treatment will be discontinued in patients who experience toxicity of grade 3 or greater that does not resolve within 3 weeks. Requirement for more than two dose reductions mandates removal from the study. Delay of protocol treatment for more than four weeks from date of scheduled treatment mandates removal from protocol treatment, unless there are extenuating circumstances and approved by the principal investigator.

Lovenox Dose Reductions for Toxicity:
Hematologic Toxicity: If platelet count drops to <50K, lovenox should be held until platelets recover.

5.2 Treatment Delays and Schedule Modification

Brief interruptions and delays in the 21-day cycle may occasionally be required due to travel delays, airport closure, inclement weather, family responsibilities, security alerts, government holidays, etc. This can also extend to complications of disease or unrelated medical illness not related to disease progression. These delays will not be considered protocol violations.

6. PHARMACEUTICAL INFORMATION

6.1 Suberoylanilide Hydroxamic Acid (NSC 701852)

Chemical Name: N-hydroxy-N'-phenyl-octane-1,8-diotic acid diamide;
N-hydroxyl-N'-phenyl (9CI) octanediamide

Other Names: VORINOSTAT, L-001079038, WIN 64652, MSK390, AP390

Classification: Antineoplastic

CAS Registry Number: 149647-78-9

Molecular Formula: $C_{14}H_{20}N_2O_3$ **M.W.:** 264

Approximate Solubility: Water $\leq$ 5 mg/mL

Description: Histone deacetylase (HDAC) inhibitor

Mode of Action: Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones.

Suberoylanilide hydroxamic acid, a potent inhibitor of HDAC activity, binds directly to the catalytic pocket of HDAC enzymes. VORINOSTAT causes G1 or G2 phase cell-cycle arrest, apoptosis, or differentiation in cultured transformed cells.

How Supplied: Suberoylanilide hydroxamic acid is supplied by Merck and Co., Inc. Suberoylanilide hydroxamic acid is supplied in the following strengths:

1. a white, opaque gelatin capsule containing 100 mg (size 3 capsule) of suberoylanilide hydroxamic acid
2. a white, opaque gelatin capsule containing 200 mg (size 1 capsule) of suberoylanilide hydroxamic acid.

The inactive ingredients contained in each capsule are microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

Suberoylanilide hydroxamic acid 100 mg capsules are supplied in bottles of 120 capsules and 200 mg capsules are supplied in bottles of 100 capsules.

Storage: Store suberoylanilide hydroxamic acid capsules at room temperature, 15 to 30 ºC (59 to 86 ºF). Transient temperature spikes up to 40 ºC (104 ºF) for up to 24 hours are permissible.

Stability: Shelf life stability studies of the intact bottles are ongoing.

Route of Administration: Orally

Method of Administration: Unless otherwise stated in the protocol, suberoylanilide hydroxamic acid capsules must be administered whole. The absolute bioavailability of suberoylanilide hydroxamic acid under fasted or fed conditions is approximately 46%. Oral administration with food does not appear to substantially alter the rate or extent of absorption.

Potential Drug Interactions: In cultured human hepatocytes, suberoylanilide hydroxamic acid was shown to inhibit CYP2B6, CYP2C9, CYP2C19, and CYP3A4 isoenzymes. Therefore, it is possible that suberoylanilide hydroxamic acid may interact with drugs that are metabolized by the P450 CYP isoenzymes. Caution should be exercised when combining the study agent with medications that are metabolized by these isoenzymes.

Special Handling: VORINOSTAT is an anticancer drug. Powder spills from VORINOSTAT capsules due to damaged or broken capsules should be cleaned up carefully so as to minimize inhalation. The affected area must be washed at least 3 times with ethyl alcohol, followed by water.

Patient Care Implications: Because VORINOSTAT's dose limiting toxicities are anorexia, dehydration, diarrhea, and fatigue, patients should maintain adequate fluid and food intake. Encourage patients to seek a nutritional consult.

Comprehensive Adverse Events and Potential Risks List (CAEPR):

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/reporting/adeers.html for further clarification. *Frequency is provided based on 299 patients*. Below

is the CAEPR for VORINOSTAT (vorinostat).

Version 2.3, November 30, 2006[1]

Adverse Events with Possible Relationship to VORINOSTAT (Vorinostat) (CTCAE v3.0 Term) [n=299 patients]			**'Agent Specific Adverse Event List' (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD/BONE MARROW			
Hemoglobin			***Hemoglobin***
Leukocytes (total WBC)			***Leukocytes***
	Lymphopenia		***Lymphopenia***
Neutrophils/granulocytes (ANC/AGC)			***Neutrophils/granulocytes (ANC/AGC)***
Platelets			***Platelets***
CARDIAC ARRYTHMIA			
	Prolonged QTc interval		
COAGULATION			
	INR (International Normalized Ratio of prothrombin time		
CONSTITUTIONAL SYMPTOMS			
Fatigue (asthenia, lethargy, malaise)			***Fatigue (asthenia, lethargy, malaise)***
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)		
	Rigors/chills		
Weight loss			***Weight loss***
DERMATOLOGY/SKIN			
	Hair loss/alopecia (scalp or body)		
		Dermatology/Skin – Other: skin necrosis	
GASTROINTESTINAL			
Anorexia			***Anorexia***
	Constipation		
	Dehydration		***Dehydration***
Diarrhea			***Diarrhea***
	Dry mouth/salivary gland (xerostomia)		
	Heartburn/dyspepsia		
Nausea			***Nausea***
	Taste alteration (dysgeusia)		
Vomiting			***Vomiting***
INFECTION			

	Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection)(ANC <1.0 x 10e9/L, fever >=38.5 degrees C)		
	Infection with normal ANC or Grade 1 or 2 neutrophils - Select		
	Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L - Select		
LYMPHATICS			
	Edema: limb		
METABOLIC/LABORATORY			
	Albumin, serum-low (hypoalbuminemia)		
	Alkaline phosphatase		
	ALT, SGPT (serum glutamic pyruvic transaminase)		
	AST, SGOT (serum glutamic oxaloacetic transaminase)		
	Bilirubin (hyperbilirubinemia)		
	Calcium, serum-low (hypocalcemia)		
Creatinine			
Glucose, serum-high (hyperglycemia)			***Glucose, serum-high(hyperglycemia)***
	Magnesium, serum-high (hypermagnesemia)		
	Phosphate, serum-low (hypophosphatemia)		
	Potassium, serum-low (hypokalemia)		
	Sodium, serum-low (hyponatremia)		
MUSCULOSKELETAL/SOFT TISSUE			
	Musculoskeletal/Soft Tissue - Other (muscle spasms)		
	Muscle weakness, generalized or specific area (not due to neuropathy) - Select		
NEUROLOGY			
	Dizziness		
	Neuropathy: sensory		

PAIN			
	Pain - abdomen NOS		
	Pain - head/headache		
PULMONARY/UPPER RESPIRATORY			
	Cough		
	Dyspnea (shortness of breath)		
VASCULAR			
	Thrombosis/thrombus/embolism		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting ADEERSMD@tech-res.com. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on VORINOSTAT (vorinostat) trials but with the relationship to VORINOSTAT (vorinostat) still undetermined:
ALLERGY/IMMUNOLOGY - vasculitis
CARDIAC ARRHYTHMIA - atrial fibrillation; palpitations; ventricular fibrillation
CARDIAC GENERAL - cardiac ischemia/infarction; hypertension; hypotension
COAGULATION - PTT
CONSTITUTIONAL SYMPTOMS - insomnia; sweating
DEATH – death NOS
DERMATOLOGY/SKIN –nail changes; pruritus; rash; ecchymosis
GASTROINTESTINAL - dysphagia; esophagitis; flatulence; gastritis; mucositis/stomatitis
HEMORRHAGE/BLEEDING - epistaxis; hematuria; hemoptysis; petechiae
INFECTION – infection – NOS
METABOLIC/LABORATORY – hypercalcemia; hyperkalemia; hypernatremia; hypoglycemia; hypomagnesemia; proteinuria
MUSCULOSKELETAL/SOFT TISSUE - gait/walking
NEUROLOGY - confusion
PAIN - back pain; chest/thorax pain; flank pain; gingival pain; joint pain; limb pain; muscle pain; pharyngolaryngeal pain
PULMONARY/UPPER RESPIRATORY - sinus congestion
RENAL/GENITOURINARY – urinary incontinence; urinary retention
VASCULAR - deep vein thrombosis

Note: VORINOSTAT (vorinostat) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Availability

VORINOSTAT is an investigational agent supplied to investigators by Merck and Co. Inc.

6.2 Rituximab

Other names
IDEC-C2B8, Rituxan.
Classification
Monoclonal antibody.
Mode of action
This chimeric mouse/human anti-CD20 antibody binds human complement and causes lysis of B-cells. It has significant activity in assays for antibody dependent cellular cytotoxicity.
Storage and stability
Stored at 2-8^0 C. Reconstituted antibody is stable for 24 hours upon refrigeration followed by 12 hours at room temperature.
Preparation
Diluted with normal saline to a concentration of 1 - 4 mg/mL. Shaking can cause aggregation and precipitation of the antibody and should be avoided.

Route of Administration: Intravenous

AVAILABILITY AND ACCOUNTABILITY

Rituximab is commercially available in 10 mL (100 mg) and 50 mL (500 mg) single-use vials at a concentration of 10 mg /mL. Use of rituximab is considered standard care for this indication, and will not be provided by Merck.

Incompatibilities

Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

Side effects

1. Infusion related symptoms: Fevers, chills, rigors, hypotension, anaphylaxis or hypersensitivity reactions, arrhythmia, dyspnea, bronchospasm, angioedema. In rare cases, severe and fatal cardiopulmonary events, including hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, and cardiogenic shock, have occurred (4-7/10,000 patients or 0.04-0.07%.) Nearly all fatal infusion-related events occurred in association with the first infusion. Patients with preexisting cardiac conditions, including arrhythmia and angina, have had recurrences of these cardiac events during rituximab infusions.

2. Gastrointestinal: Nausea, vomiting.

3. Hematologic: Leukopenia, anemia, thrombocytopenia. In clinical trials, NCI CTC Grade 3 and 4 cytopenias were reported in 48% of patients treated with rituximab; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following rituximab therapy were reported.

   In addition, there have been a limited number of postmarketing reports of prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia (defined as occurring 40 days after the last dose of rituximab) in patients with hematologic malignancies. In reported cases of late onset neutropenia (NCI-CTC Grade 3 and 4), the median duration of neutropenia was 10 days (range 3 to 148 days). Documented resolution of the neutropenia was described in approximately one-half of the reported cases; of those with documented recovery, approximately half received growth factor support. In the remaining cases, information on resolution was not provided. More than half of the reported cases of delayed onset neutropenia occurred in patients who had undergone a prior autologous bone marrow transplantation. In an adequately designed, controlled, clinical trial, the reported incidence of NCI-CTC Grade 3 and 4 neutropenia was higher in patients receiving rituximab in combination with fludarabine as compared to those receiving fludarabine alone (76% [39/51] vs. 39% [21/53]).[33]

4. Dermatologic: Rash, pruritus, urticaria, and rarely severe mucocutaneous reactions.

5. Infectious: Reactivation of hepatitis B; reactivation of other viral infections or increased susceptibility to other infections. Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with rituximab. The majority of patients received rituximab in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately four months after the initiation of rituximab and approximately one month after the last dose.

6. Renal and electrolyte: Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^2) or high tumor burden who experience tumor lysis syndrome. Although rare, tumor

lysis syndrome has been reported in postmarketing studies and is characterized in patients with a high number of circulating malignant cells (>25,000 ul) by rapid reduction in tumor volume, renal insufficiency, hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia

7. Other: Headache, asthenia. The following immune serious adverse events have been reported to occur rarely (<0.1%) in patients following completion of rituximab infusions: arthritis, disorders of blood vessels (vasculitis, serum sickness and lupus-like syndrome), lung disorders including pleuritis and scarring of the lung (bronchiolitis obliterans), eye disorders (uveitis and optic neuritis), and severe bullous skin reactions (including toxic epidermal necrolysis and pemphigus) that may result in fatal outcomes. Patients may have these symptoms alone or in combination with rash and polyarthritis. Five patients have developed deep vein thrombosis or pulmonary embolism as well. These were asymptomatic and found incidentally on CT scans.

Nursing implications

1. Monitor vital signs prior to Rituximab and if the patient has clinical deterioration during the infusion.

2. Have epinephrine for subcutaneous injections, diphenhydramine for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions available.

3. Monitor and alter infusion rates in the presence of toxicities.

4. Prolonged pancytopenia and bone marrow hypoplasia have been submitted as postmarketing reports. Patients should be monitored closely.

5. Prophylaxis for tumor lysis syndrome should be used in patients with high tumor burden, particularly with markedly elevated numbers of circulating malignant cells. Precautionary hospitalization should be made available for patients who experience severe infusion symptoms, which do not resolve after discontinuation or completion of the infusion.

6. Observe the patient for mucositis with sore throat or mouth ulcers followed by a diffuse skin rash. Skin reactions can be life threatening and lead to fatal Stevens-Johnson syndrome or toxic epidermic necrolysis. Patients should be instructed to be observant for signs and symptoms of skin reaction. Patients who develop a sore throat, mucositis should be evaluated and monitored very closely for development of skin reaction, and hospitalized and treated with corticosteroids if indicated. Patients who develop evidence of significant skin rash, oral pharyngeal mucositis that are thought to be related to rituximab should be taken off the study.

6.3 Lovenox

LOVENOX® Prescribing Information

(enoxaparin sodium injection) for subcutaneous and intravenous use **Rx only**

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Lovenox safely and effectively. See full prescribing information for Lovenox.

Lovenox® (enoxaparin sodium injection) for subcutaneous and intravenous use
Initial U.S. Approval: 1993

WARNING: SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH) or heparinoids and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- Use of indwelling epidural catheters
- Concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- A history of traumatic or repeated epidural or spinal punctures
- A history of spinal deformity or spinal surgery.

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis [see ***Warnings and Precautions (5.1)*** and ***Drug Interactions (7)***].

RECENT MAJOR CHANGES

Administration (2.4) (04/2011)

INDICATIONS AND USAGE

Lovenox is a low molecular weight heparin [LMWH] indicated for:

- Prophylaxis of deep vein thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness (1.1)
- Inpatient treatment of acute DVT with or without pulmonary embolism (1.2)
- Outpatient treatment of acute DVT without pulmonary embolism. (1.2)
- Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction [MI] (1.3)
- Treatment of acute ST-segment elevation myocardial infarction [STEMI] managed medically or with subsequent percutaneous coronary intervention [PCI] (1.4)

DOSAGE AND ADMINISTRATION

Indication Dose	
DVT prophylaxis in abdominal surgery	40 mg SC once daily
DVT prophylaxis in knee replacement surgery	30 mg SC every 12 hours
DVT prophylaxis in hip replacement surgery	30 mg SC every 12 hours or 40 mg SC once daily
DVT prophylaxis in medical patients	40 mg SC once daily
Inpatient treatment of acute DVT with or without pulmonary embolism	1 mg/kg SC every 12 hours or 1.5 mg/kg SC once daily *
Outpatient treatment of acute DVT without pulmonary embolism	1 mg/kg SC every 12 hours *
Unstable angina and non-Q-wave MI	1 mg/kg SC every 12 hours (with aspirin)
Acute STEMI in patients <75 years of age [For dosing in subsequent PCI, see *Dosage and Administration (2.1)*]	30 mg single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg SC every 12 hours (with aspirin)
Acute STEMI in patients ≥75 years of age	0.75 mg/kg SC every 12 hours (no bolus) (with aspirin)

- See recommended durations for Lovenox therapy (2.1)
- *See recommendations regarding transitioning to warfarin therapy (2.1)
- Adjust the dose for patients with severe renal impairment (2.2, 8.7)

DOSAGE FORMS AND STRENGTHS

100 mg/mL concentration (3.1):

- Prefilled syringes: 30 mg/0.3 mL, 40 mg/0.4 mL
- Graduated prefilled syringes: 60 mg/0.6 mL, 80 mg/0.8 mL,100 mg/1 mL
- Multiple-dose vial: 300 mg/3 mL

150 mg/mL concentration (3.2):

- Graduated prefilled syringes: 120 mg/0.8 mL, 150 mg/1 mL

CONTRAINDICATIONS

- Active major bleeding (4)
- Thrombocytopenia with a positive in vitro test for anti-platelet antibody in the presence of enoxaparin sodium (4)
- Hypersensitivity to enoxaparin sodium (4)
- Hypersensitivity to heparin or pork products (4)
- Hypersensitivity to benzyl alcohol [for multi-dose formulation only] (4)

WARNINGS AND PRECAUTIONS

- Increased risk of hemorrhage: Use with caution in patients at risk (5.1)
- Percutaneous coronary revascularization: Obtain hemostasis at the puncture site before sheath removal (5.2)
- Concomitant medical conditions: Use with caution in patients with bleeding diathesis, uncontrolled arterial hypertension or history of recent gastrointestinal ulceration, diabetic retinopathy, renal dysfunction, or hemorrhage (5.3)
- History of heparin-induced thrombocytopenia: Use with caution (5.4)
- Thrombocytopenia: Monitor thrombocytopenia closely (5.5)
- Interchangeability with other heparins: Do not exchange with heparin or other LMWHs (5.6)
- Pregnant women with mechanical prosthetic heart valves and their fetuses, may be at increased risk and may need more frequent monitoring and dosage adjustment (5.7)

ADVERSE REACTIONS

Most common adverse reactions (>1%) were bleeding, anemia, thrombocytopenia, elevation of serum aminotransferase, diarrhea, and nausea (6.1)

DRUG INTERACTIONS

Discontinue agents which may enhance hemorrhage risk prior to initiation of Lovenox or conduct close clinical and laboratory monitoring (5.9, 7)

USE IN SPECIFIC POPULATIONS

- Severe Renal Impairment: Adjust dose for patients with creatinine clearance <30mL/min (2.2, 8.7)
- Geriatric Patients: Monitor for increased risk of bleeding (8.5)
- Patients with mechanical heart valves: Not adequately studied (8.6)
- Hepatic Impairment: Use with caution. (8.8)
- Low-Weight Patients: Observe for signs of bleeding (8.9)

7. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to administration of protocol therapy. Scans and x-rays must be done within 4 weeks prior to the start of therapy. For subsequent weeks, the studies may be performed within ± 2 days of the indicated dates.

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12+ [g]	Off Study
VORINOSTAT[a, g]		X	X		X	X		X	X		X	X		
Rituximab		X			X			X			X			
Lovenox		X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X													
Demographics	X													
Medical history	X													
Height	X													
B-HCG [b]	X													
Record concurrent medications	X	X----------X												
Physical exam	X	X			X			X			X			X
Vital signs	X	X			X			X			X			X
Weight	X	X			X			X			X			X
Performance status	X	X			X			X			X			X
CBC w/diff, plts	X	X			X			X			X			X
Serum chemistry [c]	X	X			X			X			X			X
Correlatives[i]	X		X											
Adverse event evaluation		X----------X												X
Tumor measurements	X	Tumor measurements are repeated every 3 cycles (~9 weeks)[j]. Bone marrow assessment should be done within 4 weeks of starting therapy, and repeated every 3 cycles if the initial marrow shows involvement by lymphoma. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X [d]
Radiologic evaluation	X	CT scans are repeated every 3 cycles (~9 weeks)[j]. Follow up PET scans for patients with PET positive disease is optional, but suggested.												X [d]
Bone marrow	X[h]									X				

a: VORINOSTAT: Starting dose 200mg orally twice daily for 2 weeks, followed by 1 week of rest (21 day cycle).
b: Serum pregnancy test (women of childbearing potential).
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
d: Off-study evaluation.
g. Patients with partial response or stable disease may continue to receive VORINOSTAT until progression. Patients who achieve CR will receive two further cycles of VORINOSTAT and then discontinue drug. Follow up radiological studies will continue every three months for one year, then every six months for the next two years.
h. Bone Marrow aspiration and biopsy may be performed up to four weeks prior to starting study drug, and if positive should be repeated every three cycles.
i. For details see section 11.
j. After one year of treatment, if the patient achieved two consecutive PR based on prior CT scans or PET, the radiological assessment can be done after every 4 cycles instead of 3 cycles. If patients achieved CR, follow up radiological studies will continue every 3 months for one year, then every six months for the next two years.

8. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be reevaluated for response every three cycles (~ 9 weeks) by radiological and marrow studies as described in the study calendar (section 8). After one year of treatment, if the patient achieved two consecutive PR based on prior CT scans or PET, the radiological assessment can be done after every 4 cycles instead of 3 cycles. If patients achieved CR, follow up radiological studies will continue every 3 months for one year, then every six months for the next two years.

8.1 Response Criteria

(as per Cheson BD, et al. J Clin Oncol. 2007 Feb 10;25(5):579-86.)Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measuable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET		

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

CR:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before

therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

2b. Variably FDG-avid lymphomas/FDG avidity unknown: in patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size (≤ 1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to ≤1.0 cm in their short axis after treatment.

3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

Cru

The use of the above definition for CR and that below for PR eliminates the category of CRu.

PR

The designation of PR requires all of the following:

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by ≥50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (eg, large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.
   When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used.

In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease

Stable disease (SD) is defined as the following:

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.

3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes ≤1.0 x ≤1.0 cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (eg, splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by ≥50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

9. REGULATORY AND REPORTING REQUIREMENTS

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 3.0. A list of adverse events that have occurred or might occur (Comprehensive Adverse Events and Potential Risks list) can be found in Section 6 (Pharmaceutical Information). *A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).*

9.1 Expedited Adverse Event Reporting

We agree to provide Merck (Attn: Worldwide Product Safety; FAX 215 993-1220) with copies of all serious adverse experiences within two working days. Additionally, we agree to report any pregnancy occurring in association with use of a Merck Product to Merck (Attn: Worldwide Product Safety; FAX 215 993-1220). A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators by the investigator. We agree to cross reference this submission according to local regulations, to the Merck Investigational Compound number (IND, CSA, etc) at the time of submission. Additionally we agree to submit a copy of these reports to Merck (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to the appropriate regulatory agency.

Notes:

* In studies involving human subjects, serious adverse experience means any experience that suggest a significant hazard, contraindication, side effect or precaution. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or is a congenital anomaly, cancer, or overdose.

Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the subject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

9.1.2 Expedited Adverse Event Reporting Exclusions

None

9.2 Registration Guidelines

Once the signed informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study. To register a patient, the research nurse or data manager must complete the Eligibility Checklist and FAX a copy of this and the informed consent including the Bill of Rights to the Coordinator at the City of Hope (FAX #626-256-8654). The research nurse or data manager will call the Coordinator at 626-256-HOPE (4673) extension 65928, and after verifying the eligibility, the Coordinator will register the patient onto the study and assign a patient accession number

Protocol waivers and/or treatment deviations are not allowed other than in the case of delay as described in sections 5.1 and 5.2.

9.3 COH DSMB Data Reporting

A) Definition of Risk Level

This is a Risk Level 3 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx because it is a Phase 2 clinical trial where the risks are at least balanced by the potential benefit to subjects and the importance of the knowledge that may result.

B) Monitoring and Personnel Responsible for Monitoring

The Protocol Management Team (PMT) consisting of the PI, Collaborating Investigator, CRA, protocol nurse, and statistician is responsible for monitoring the data and safety of this study, including implementation of any stopping rules for safety and efficacy.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS
3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

Data and safety will be reported to the COH DSMC using the PMT report and submitted according to the timelines in Table 1 above. Protocol specific data collection will include the following items:. hematologic response and toxicities of treatment.

C) Definitions

Adverse event (AE) - An adverse event is any untoward medical experience or change of an existing condition that occurs during or after treatment, whether or not it is considered to be related to the protocol intervention.

Unexpected Adverse Event [21 CFR 312.32 (a) – An adverse event is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event.

Expected Adverse Event - Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the adverse event

Serious Adverse Event (SAE) [21 CFR 312.32] is defined as *any expected or unexpected adverse event* that results in any of the following outcomes:

- Death
- Is life-threatening experience (places the subject at immediate risk of death from the event as it occurred)
- Unplanned hospitalization (equal to or greater than 24 hours) or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Secondary Malignancy
- Any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

Unanticipated problem (UP) – Any incident, experience, or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

D. Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at

http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting electronically in iRIS (http://iris.coh.org).

Serious Adverse Events - All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the protocol continuation reports and PMT report (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

Externally Sponsored Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED[1]**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	
Unlikely, Unrelated		
	Grades 1 and 2	
Possibly, Probably, Definitely	No DSMC reporting required - IRB reporting may be necessary	

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

9.4 RECORDS TO BE KEPT AND DATA SUBMISSION SCHEDULE

9.4.1 Confidentiality of Records: The original data collection forms will be stored in secure cabinets at the originating institution. Copies of these forms will also be maintained in secure cabinets at the Data Coordinating Center.

9.4.2 Patient Consent Form: At the time of registration, three signed and dated copies of the patient Informed Consent form must be available. Non-COH institutions will FAX a copy of a signed informed consent to COH (see registration procedures in Appendix E) at the time of registration.

9.4.3 Registration Eligibility Worksheet: At the time of registration, the information requested on the On-Study/Eligibility Form will be submitted to the protocol coordinator at COH.

9.4.4 Data Collection Forms and Submission Schedule
All data will be collected using COH Biostatistics Information Tracking System (BITS) data collection forms. Copies of the completed forms will be submitted to City of Hope Department of Biostatistics, the data coordinating center, c/o the Consortium Manager for data entry and stored in a secure location. The original data collection forms will reside at the originating institution in secure location.

9.4.5 The data manager will complete the Eligibility Checklist Worksheet at the time of registration.

9.4.6 Within two weeks of registration, the data manager will complete the On-

Study Form (Form OS).

9.4.7 Within four weeks of completion of each course of treatment, the data manager must complete the following:

- Treatment and Adverse Event Form
- Supplemental Data Form (if applicable)
- Flow Sheets (These are to be submitted along with each treatment form.)

9.4.8 Each time a patient is evaluated for response and/or new follow-up information is obtained the data manager will complete the Response/Off-Study Follow-Up Form.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

Response rate (CR+PR) will be the primary endpoint. An underlying 20% response rate will be regarded as not sufficiently active, and the trial is designed to have little chance of missing a 40% response rate. A two-stage design will be used. In the first stage, 17 patients will be enrolled. If 4 or more respond, accrual will continue to a total of 33 patients, with 10 or more responses regarded as evidence of sufficient activity to warrant further investigation. If the true response rate is 20%, the proposed design has a 90% chance of declaring vorinostat plus rituximab insufficiently active, and a 55% chance of stopping early. If the true response rate is 40%, there is a 89% chance of concluding VORINOSTAT is sufficiently active. All patients beginning VORINOSTAT therapy will be included in response rates calculations, which will include exact binomial confidence intervals.

All reportable adverse events will be monitored by the PI and CRA, and reported as described in section 10. Reportable and non-reportable adverse events are routinely tabulated for phase II consortium trials as the reports arrive. The time to progression and overall survival will be estimated using the product-limit method of Kaplan and Meier. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity. Baseline information (e.g. the extent of prior therapy, extent of disease) and demographic information will be presented, as well, to describe the patients treated in this Phase II study.

10.2 Sample Size/Accrual Rate

Estimated monthly accrual: 3 patients
Proposed sample size: 17 to 33 patients as outlined in section 11.1

10.3 Stratification Factors

None planned.

10.4 Reporting and Exclusions

10.5 Evaluation of toxicity. All patients will be evaluable for toxicity from the time of their first treatment with vorinostat.

10.5.1 Evaluation of response. All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: complete response, partial response, stable disease, progressive disease, early death from malignant disease, early death from toxicity, early death because of other cause, or unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the main analysis of the response rate. Patients in any response categories other than complete response, partial response or stable disease will be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions will be based on all eligible patients, with possible exploratory analysis of subset of patients in the event of early death due to other reasons, early discontinuation of treatment, major protocol violations, or similar circumstances requiring an assessment of the sensitivity of results. However, such subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis will be clearly reported. Exact binomial 95% confidence intervals will be provided for response rates.

11. Correlative Studies:

Cytokine analysis

We have recently demonstrated (Li, et al PNAS, 2008) that even low doses of vorinostat dramatically decrease pro-inflammatory cytokines such as IL-2, IFN-γ, TNF-α, and IL-6. This suppression of cytokines may be of importance to the clinical effect of histone deacetylase inhibition on symptoms such as itching or the B symptoms of lymphoma, as well as potentially impacting upon lymphoma growth.

The effects of treatment on systemic levels of immune cytokines will be evaluated by cytokine bead array analysis using Luminex X-MAP bead array technology. This technology platform allows for the simultaneous measurement and quantification of multiple cytokines and other secreted factors from very small (10-50 μl) samples. This analysis is sensitive (generally single pictogram level), reproducible, and accurate. The Clinical Immunobiology Correlative Studies Laboratory (CICSL) at COH is equipped with two Bioplex HTF units for these analyses.

Preassembled multiplex panels are available commercially that allow for the simultaneous evaluation of the following 30 pro- and anti-inflammatory cytokine and immune factors:
IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40/p70, IL-13, IL-15, IL-17, TNF-α, IFN-α, IFN-γ, GM-CSF, MIP-1α, MIP-1β, IP-10, MIG, Eotaxin, RANTES, MCP-1, VEGF, G-

CSF, EGF, FGF-basic, and HGF.
For these analyses, 2 ml peripheral blood will be collected prior to starting therapy, and on day 14. Whole blood will be collected in red-top tubes (Becton Dickinson) that are completely free of anti-coagulant reagents. Sample tubes should be set in an upright position at room temperature may be processed for up to 24 hours.

To process serum:

i. Allow whole blood samples to clot for 1 – 2 hours at room temperature.
ii. Centrifuge at 1000 x g at 4°C for 15 minutes, max brake.
iii. Using a micropipettor, collect the serum without disturbing the red cell pellet at the bottom of the tube and transfer to a flip-top microfuge tube or a 15-mL centrifuge tube (depending on the total volume).
iv. Freeze and store at -80ºC in 100 ìL aliquots.

Luminex analysis on serum samples will be performed in bulk. Each sample will be evaluated in duplicate with the average value recorded. Quantitative values will only be determined for samples with values that fall within the 80% observed/expected range for the standard curve.

Samples should be sent to:

Clinical Immunobiology Correlative Studies Laboratory
Attn. Vivi Tran
1042 Shapiro
City of Hope,
Duarte, CA 91010

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Model Informed Consent

A Phase II Study of Suberoylanilide Hydroxamic Acid (VORINOSTAT) (NSC 701852) plus Rituximab in Indolent Non-Hodgkin's Lymphoma

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

You are being asked to take part in this study because you have slow growing Non-Hodgkin's Lymphoma (NHL) or low-grade lymphoma that has returned.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, vorinostat (Suberoylanilide Hydroxamic Acid (VORINOSTAT)) plus rituximab has on you and your lymphoma.

This research is being done because lymphoma responds initially to chemotherapy but usually comes back within 5 years. The disease free interval between treatments becomes shorter and shorter. Better and new methods of therapy are needed to treat low-grade lymphoma.

How many people will take part in the study?

About 37 people will take part in this study.

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

Treatment:

If you are eligible and decide to take part in this treatment, you will take a drug called vorinostat, an drug approved by the Food and Drug Administration (FDA) in a different type of lymphoma, but experimental in this form of lymphoma. VORINOSTAT is an oral drug that will be given to you in capsule form that you will take by mouth two times a day, every day for two weeks followed by one week of rest (no drug). Each 3 weeks, or 21 days, is considered one cycle of therapy. You will continue to take VORINOSTAT for a total of 12 cycles or until your cancer begins to grow or you have side effects that are unmanageable. You will also receive a drug called rituximab, which is FDA approved for treatment of this type of lymphoma.

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical history and physical examination
- Blood tests (about one tablespoon of blood) to look at the cellular and chemical make up of your blood
- Scans and/or X-rays to evaluate the extent of your disease
- You will also have your bone marrow examined (called "bone marrow aspiration and biopsy") at the start of this study, and at the end of the treatment period if the first bone marrow test indicates presence of lymphoma. Your skin over your hipbone will be numbed by a shot of local anesthetic (lidocaine) given just under your skin. A needle will be inserted through the numbed skin and into the hipbone. The bone marrow will be removed by using suction and a twisting motion of the needle. You may feel pain, and minor infection is also possible. Rarely allergic reactions to the anesthetic may occur. These are routine tests for many patients with lymphoma. The bone marrow will be looked at to find out if any lymphoma cells are present. This will be repeated every 3 cycles.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care**.**

You will be asked to keep track of your study medication by recording the date and time you take the study medication, any symptoms you experience and any questions you may have in a study diary. You will be asked to bring the study diary with you each time you come in to see your doctor.

- Physical examinations every week for the first cycle, and every three weeks after that
- Blood tests every week for the first four weeks, and every three weeks after that (appropriate amount of blood collected per test will be 2 - 3 teaspoons)
- Scans and/or X-rays every nine weeks
  - If your tumor shrinks and stays that way for 2 sets of scans, you may be able to go 12 weeks between scans

When I am finished taking VORINOSTAT:

After you complete treatment, your medical condition will be followed until your disease returns.

Study Chart

You will receive VORINOSTAT twice a day every day for 14 days in this study followed by a 7 day rest period. This 21 day period of time is called a cycle. The cycle will be repeated up to 12 times. Each cycle is numbered in order. The chart below shows what will happen to you during Cycle 1 and future treatment cycles as explained previously. The left-hand column shows the day in the cycle and the right-hand column tells you what to do on that day.

Cycle 1

Day	**What you do**
One week before beginning study	• Physical examination, blood tests (routine and research), EKG, pregnancy test (if you are a women of child bearing age), Scans and/or X-rays (may be done up to 28 days before treatment)
Day 1	• Get physical examination, and routine blood tests. • Begin taking VORINOSTAT twice a day. Keep taking VORINOSTAT for two weeks (14 days), unless told to stop by your health care team.

	• Receive the first dose of rituximab intravenously.
Day 8	• Get routine blood tests and physical examination.
Day 15	• Stop taking VORINOSTAT for one week. • Get routine blood tests and physical examination
Day 22	• Get routine blood tests. • Return to your doctor's office for your next exam and to begin the next cycle.

Future cycles

Day **What you do**

Days 1-21	• Keep taking VORINOSTAT twice a day for 14 days if you have no bad side effects and cancer is not getting worse. Call the doctor at (626) 256-HOPE (4673) ext. 63974 if you do not know what to do. • Keep receiving rituximab by intravenous infusion every three weeks. • Get routine X-rays, CT scans, or MRIs every other cycle (more if your doctor tells you to).
Day 22	• Get routine blood tests (on day 22 of cycle 2, get research blood test too) • Return to your doctor's office for your next exam and to begin the next cycle.

How long will I be in the study?

You will be asked to take VORINOSTAT plus rituximab for up to 12 cycles (36 weeks) or until your disease worsens, or you have unmanageable side effects. After you are finished taking VORINOSTAT, the study doctor will keep track of your medical condition until your disease returns.

Can I stop being in the study?

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

It is important to tell the study doctor if you are thinking about stopping so any risks from the VORINOSTAT can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

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

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

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

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

Likely

- **Nausea,** which is temporary and may require additional medication
- **Diarrhea,** which is temporary and may require additional medication and/or a delay in your treatment
- **Anemia:** (low red blood cell count), which may make you feel tired and short of breath. If this happens, you may be started on a drug to increase your red blood cell count. Severe anemia may require a transfusion of red blood cells
- **Decreased platelet count,** which increases the risk of easy bleeding and/or bruising. This could result in the need for a platelet transfusion.
- **Fatigue,** which is temporary and should get better when treatment is stopped
- **Loss of appetite,** which is temporary and should get better when treatment is stopped
-
- **High creatinine,** which is temporary, seen on blood tests and is without symptoms. It should return to normal when treatment is stopped.
- **High blood sugar**, which is temporary and may require additional medication.
- **Neutropenia,**
- **Weight loss,**
- **Vomiting**, which is temporary and may require additional medication

Less Likely

- **Changes in taste**, which is temporary and should get better when treatment is stopped
- **Low blood calcium**, which is temporary and may require additional medication
- **Low potassium,** which is temporary, seen on blood tests and may require potassium supplements
- **Abdominal pain,** which is temporary and may require additional medication
- **Low lymphocyte counts,** a change in the number of lymphocytes in the blood, which doesn't cause symptoms, is temporary and should get better when treatment is stopped.
- **Prolonged QTc interval,** which may cause increased risk for heart rhythm changes, which is temporary and should resolve when drug is stopped.
- **Increased INR**, which implies increased blocking of blood clotting when on coumadin, this may require decrease of your coumadin therapy and more frequent monitoring of your clotting profile.
- **Fever,** in the absence of low white blood counts or other signs of infection. If caused by the drug, it should go away when drug is stopped.
- **Shakes and chills,** which is temporary and should go away when drug is stopped.
- **Hair loss,** which is temporary and tends to stop over time.
- **Constipation,** which is temporary and can be treated with standard anti-constipation medicines.
- **Dry mouth,** which is temporary and should go away when the drug is stopped.
- **Heartburn,** or a feeling of "stomach ache", which is temporary and can be treated with standard heartburn medications.
- **Increased risk of infection,** even with normal blood counts, which may be related to the drug's effect on immune cells, which are defective already in lymphoma.
- **Edema,** swelling of the lower limbs, which is temporary and should go away when drug is stopped.
- **Changes in liver function tests (AST, ALT, , Alkaline Phosphatase, Bilirubin)** which are temporary and should go away when drug is stopped.
- **Hypocalcemia, which means low calcium on blood tests, which is temporary, should resolve when drug is**

stopped, and can be replaced with supplements.

- **Muscle spasms,** which are temporary and should resolve over time.
- **Muscle weakness,** which is temporary and should resolve when drug is stopped.
- **Headches,** which are temporary and can be treated with additional medication
- **Cough,** which is temporary and should resolve when drug is stopped
- **Shortness of breath,** which is temporary and should resolve when drug is stopped.
- **Blood clots,** which may appear in the legs or lungs, and would necessitate further medical therapy such as anti-clotting medicines.
- **Hypermagnesemia,**
- **Hypophosphatemia,**
- **Hyponatremia,**
- **Dizziness**
- **Sensory neuropathy,**
- **Dehydration,** which is temporary and may require additional fluids, either by mouth or by IV (intravenous, through a tube in your arm) infusion

The following side effects have been reported by subjects on other studies with VORINOSTAT, but the relationship to VORINOSTAT is not known

ALLERGY/IMMUNOLOGY – **vasculitis**- swelling around blood vessels which should resolve with stopping the drug if not due to underlying disease.
CARDIAC ARRHYTHMIA - atrial fibrillation; palpitations; ventricular fibrillation- serious heart beat changes which may require additional medications.
CARDIAC GENERAL - cardiac ischemia/infarction- "heart attacks", which may be serious and require further medical treatment; **hypertension; hypotension-** changes in blood pressure which may require additional medicines for control, and should resolve with stopping drug if not related to underlying disease.
COAGULATION – PTT- changes in blood clotting profile which may return to normal after stopping drug.
CONSTITUTIONAL SYMPTOMS – insomnia- sleeplessness; **sweating**- both of which may be temporary and disappear with stopping of medication if not due to underlying disease.
DEATH – unexplained death of uncertain relationship to study drug
DERMATOLOGY/SKIN –nail changes; **pruritus**- itching; **rash-** these changes may disappear with stopping of drug; **ecchymosis**- bleeding into skin, which should heal over time.
GASTROINTESTINAL – dysphagia- difficulty in swallowing; **esophagitis-** pain upon swallowing; **flatulence**- excess gas; **gastritis**- burning sensation in the stomach; **mucositis/stomatitis-** pain due to changes in the cells lining the mouth and throat; all of these should improve with stopping the drug.
HEMORRHAGE/BLEEDING – epistaxis-nosebleed; **hematuria**- blood in the urine; **hemoptysis**- bloody cough; **petechiae-**tiny bleeds in the skin. These may improve when drug is stopped if not related to the underlying disease.
INFECTION – infection – these may require the addition of further medications such as antibiotics.
METABOLIC/LABORATORY – hypercalcemia- high blood levels of calcium, which may require additional medications; **hyperkalemia**- high blood levels of potassium, treated with additional medications; **hypernatremia-** high blood sodium, usually treated with intravenous fluid; **hypoglycemia**- low blood sugar treated with sugar supplements; **hypomagnesemia-** low blood magnesium, treated with magnesium supplements; **proteinuria-** protein in the urine, which may resolve with stopping of the drug.
MUSCULOSKELETAL/SOFT TISSUE - gait/walking- changes in ability to walk which may get better with stopping of drug if not related to the underlying disease.
NEUROLOGY – confusion- which may resolve with stopping of drug if not related to underlying disease.
PAIN - back pain; chest/thorax pain; flank pain; gingival (gum) pain; joint pain; limb pain; muscle pain; pharyngolaryngeal pain- all these may disappear with stopping of drug if not due to underlying disease.
PULMONARY/UPPER RESPIRATORY - sinus congestion- may resolve with stopping of drug if not due to underlying disease.

RENAL/GENITOURINARY – urinary incontinence; urinary retention- difficulty controlling urination or difficulty in passing urine, both may disappear with stopping drug if not due to underlying disease.
VASCULAR - deep vein thrombosis- blood clots in the arms, legs, or lungs, which may require anti-clotting medications for prevention of further abnormal clots.

Biopsy and blood tests: The biopsies and blood tests that will be done as a part of this study may cause pain at the site where the needle enters the skin, bleeding, or infection. Pain lasting several days may also result after the biopsies. This side effect may be treated with pain medication.

Bone Marrow Aspiration and Biopsy: The local anesthesia used to numb the hip area may initially cause a burning sensation in the skin and bone surface lasting several seconds. During the actual procedure, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your physician for additional local anesthesia or a medication to ease your stress. After the procedure is completed, you may bleed, have a bruise, and may experience soreness in the area for a few days. Rarely an infection can develop.

Reproductive risks: You should not become pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope VORINOSTAT will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about VORINOSTAT as a treatment for cancer. This information could help future cancer patients.

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

Your other choices may include:

- Getting treatment or care for your cancer without being in a study, including other chemotherapy,
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

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

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

- The City of Hope Medical Group, Pasadena, t
- Merck and Co., Inc, the maker of VORINOSTAT
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

What are the costs of taking part in this study?

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

Merck and Co, Inc, will provide you with the investigational agent, VORINOSTAT, free of charge for this study and with rituximab. Every effort has been made to ensure adequate supplies of the investigational agent(s), free of charge, for all participants. If, however, the investigational agent(s) become(s) commercially available while you are being treated, there is a possibility that you would be asked to purchase subsequent supplies.

You and/or your insurance carrier will be responsible for the other costs of treatment and diagnostic or laboratory procedures. You and/or your insurance carrier will be billed in the same way as if you were not in a research study. However, you and your insurance carrier will not be asked to bear the costs of any tests or procedures done solely for research purposes.

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

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

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

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

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

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

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

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

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

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

Who can answer my questions about the study?

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

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

Where can I get more information?

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

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

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

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

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

Signature

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

Participant _____

Date _____

APPENDIX A

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 C

Drugs Known To Be Metabolized By Selected CYP450 Isoenzymes

Potential Cytochrome P450 (CYP) Drug Interactions – CYP2A6

	Generic Name	Trade Names	Substrate [1]	Inhibitor[2]	Inducer[3]
CYP2A6	Amiodarone	CORDARONE, PACERONE		++	
	Amlodipine	NORVASC		±	
	Amobarbital	AMYTAL SODIUM			Y
	Buprenorphine	BUPRENEX		±	
	Clofibrate			±	
	Clotrimazole	GYNE-LOTRIMIN, LOTRIMIN, MYCELEX		±	
	Desipramine	NORPRAMIN, PERTOFRANE		++	
	Dexmedetomidine	PRECEDEX	Y		
	Disulfiram	ANTABUSE	N	±	
	Entacapone	COMTAN		±	
	Isoniazid	INH, NYDRAZID, PMS-ISONIAZID		++	
	Ketoconazole	NIZORAL		++	
	Letrozole	FEMARA	N	±	
	Methimazole	TAPAZOLE		±	
	Methoxsalen	8-MOP, OXSORALEN, OXSORALEN-ULTRA, UVADEX	N	+++	
	Metyrapone	METOPIRONE		±	
	Miconazole	LOTRIMIN, MICATIN, MICONAZOLE 7, MONISTAT		+++	
	Modafinil	PROVIGIL		±	
	Nicotine	CLEAR NICODERM CQ, HABITROL, NICOTROL	N	±	
	Orphenadrine	FLEXOR, NORFLEX		±	
	Pentobarbital	NEMBUTAL SODIUM			Y
	Phenobarbital	LUMINAL			Y
	Pilocarpine	ISOPTO CARPINE, OCUSERT PILO, PILOCAR, PILOPINE HS, SALAGEN		±	
	Rifampin	RIFADIN, RIMACTANE	Y		Y
	Secobarbital	SECONAL			Y
	Selegiline	ELDEPRYL	N	±	
	Sulconazole	EXELDERM		±	
	Tioconazole	MONISTAT 1, VAGISTAT-1		±	
	Tranylcypromine	PARNATE		+++	

Adapted from Lacy *et al*. "Drug Information Handbook", 12th edition, 2004

[1] **Substrates**

Yes (Y): Enzyme plays a clinically significant role (≥ 30%) in drug metabolism. Therefore, competitive inhibition may occur resulting in increased serum levels of the drug and/or study agent.

No (N): Enzyme plays clinically insignificant role (<30%) in drug metabolism. Therefore, competitive inhibition is unlikely to occur.

[2] **Inhibitors**

Degree of inhibition was determined by evaluating Ki values set in a ratio with achievable serum drug concentrations under normal dosing conditions (C_{max}). The following parameters for predicting clinical relevance of competitive CYP inhibition were employed:

+++: likely, $C_{max}/Ki \geq 1$. Clinically relevant inhibition will likely result in increased serum levels of the study agent.

++: possible, $C_{max}/Ki = 0.1\text{-}1$. Clinically relevant inhibition may possibly result in increased serum levels of the study agent.

±: remote, $C_{max}/Ki < 0.1$. Clinically relevant inhibition is remotely possible.

[3] **Inducers**

Yes (Y): Enzyme was effectively induced by drug. Therefore, lowered serum levels of the study agent may occur.

No (N): Enzyme was not effectively induced by drug. Therefore, serum levels of the study agent are not expected to be altered.

Potential Cytochrome P450 (CYP) Drug Interactions – CYP2C8/9

	Generic Name	Trade Names	Substrate[1]	Inhibitor[2]	Inducer[3]
CYP2C8/9	Alosetron	LOTRONEX	Y		
	Amiodarone	CORDARONE, PACERONE	Y	++	
	Amitriptyline	ELAVIL	N	±	
	Amlodipine	NORVASC		±	
	Anastrozole	ARIMIDEX		±	
	Aprepitant	EMEND		±	N
	Atazanavir	REYATAZ		±	
	Azelastine	ASTELIN, OPTIVAR, RHINOLAST		±	
	Bortezomib	VELCADE	N	±	
	Bosentan	TRACLEER	Y		N
	Candesartan	ATACAND	N	±	
	Carbamazepine	CARBATROL, TEGRETOL	N		Y
	Carvedilol	COREG	Y		
	Chloramphenicol	CHLOROMYCETIN, CHLOROPTIC SOP, OCU-CHLOR		±	
	Cholecalciferol/ vitamin D_3	CALEL-D, CALTRATE PLUS, CLOCREAM, DELTA-D		±	
	Cimetidine	TAGAMET		±	
	Clopidogrel	PLAVIX		±	
	Clotrimazole	GYNE-LOTRIMIN, LOTRIMIN, MYCELEX		±	
	Clozapine	CLOZARIL	N	±	
	Cyclosporine	GENGRAF, NEORAL, RESTASIS, SANDIMMUNE		±	
	Delavirdine	RESCRIPTOR		+++	
	Dexmedetomidine	PRECEDEX		±	
	Diclofenac	CATAFLAM, VOLTAREN	N	±	
	Diltiazem	CARDIZEM, DILACOR XR, TIAZAC	N	±	
	Dimethyl sulfoxide	RIMSO-50		±	
	Disulfiram	ANTABUSE		±	
	Drospirenone	YASMIN (w/ethinyl estradiol)		±	
	Efavirenz	SUSTIVA		±	
	Entacapone	COMTAN		±	
	Eprosartan	TEVETEN		±	
	Etoposide	ETOPOPHOS, VEPESID		±	
	Felodipine	PLENDIL		±	
	Fluconazole	DIFLUCAN		+++	
	Fluoxetine	PROZAC, SARAFEM	Y	±	
	Fluphenazine	PROLIXIN		±	
	Flurbiprofen	ANSAID, OCUFEN	N	+++	
	Fluvastatin	LESCOL	N	++	
	Fluvoxamine	LUVOX		±	
	Fosphenytoin	CEREBYX	Y		Y
	Gemfibrozil	LOPID		+++	

	Glimepiride	AMARYL	Y		
	Glipizide	GLUCOTROL	Y		
	Ibuprofen	ADVIL, MOTRIN, NUPRIN, RUFEN	N	+++	
	Imatinib	GLEEVEC	N	±	
	Indinavir	CRIXIVAN		±	
	Indomethacin	INDOCIN	N	+++	
	Irbesartan	AVAPRO	N	++	
	Isoniazid	INH, NYDRAZID, PMS-ISONIAZID		++	
	Ketamine	KETALAR	Y		
	Ketoconazole	NIZORAL		+++	
	Ketoprofen	ORUDIS, ORUVAIL		±	
	Lansoprazole	PREVACID	N	±	
	Leflunomide	ARAVA		±	
	Losartan	COZAAR	Y	++	
	Lovastatin	ALTOCOR, MEVACOR		±	
	Mefenamic acid	PONSTEL	N	+++	
	Meloxicam	MOBIC	N	±	
	Mephenytoin	MESANTOIN	Y		
	Mestranol	NECON 1/50, NORINYL 1/50, ORTHO-NOVUM 1/50 (w/ norethindrone)	Y		
	Methimazole	TAPAZOLE		±	
	Methoxsalen	8-MOP, OXSORALEN, UVADEX		±	
	Metronidazole	FLAGYL, METROGEL, NORITATE		±	
	Miconazole	LOTRIMIN, MICATIN, MICONAZOLE 7, MONISTAT		+++	
	Midazolam	VERSED		±	
	Modafinil	PROVIGIL		±	
	Montelukast	SINGULAIR	Y	±	
	Nateglinide	STARLIX	Y	±	
	Generic Name	**Trade Names**	**Substrate[1]**	**Inhibitor[2]**	**Inducer[3]**
	Nelfinavir	VIRACEPT	N	±	
	Nicardipine	CARDENE	N	+++	
	Nifedipine	ADALAT, PROCARDIA		±	
	Olanzapine	ZYPREXA, ZYPREXA ZYDIS		±	
	Omeprazole	PRILOSEC	N	++	
	Ondansetron	ZOFRAN	N	±	
	Orphenadrine	FLEXOR, NORFLEX		±	
	Paclitaxel	TAXOL	Y		
	Pantoprazole	PANTOLOC, PROTONIX		++	
	Paroxetine	PAXIL		±	
	Pentamidine	NEBUPENT, PENTAM 300		±	
	Phenobarbital	LUMINAL	N		Y
	Phenytoin	DILANTIN, PHENYTEK, PHENYTOIN SODIUM	Y		Y
	Pioglitazone	ACTOS	Y	+++	
	Piroxicam	FELDENE	N	+++	
	Pravastatin	PRAVACHOL		±	
	Primidone	MYSOLINE			Y

CYP2C8/ 9, continued	Progesterone	CRINONE, PROGESTASERT, PROMETRIUM	N	±	
	Propafenone	RYTHMOL		±	
	Propofol	DIPRIVAN	Y	±	
	Propoxyphene	DARVON		±	
	Pyrimethamine	DARAPRIM		++	
	Quinidine	QUINAGLUTE DURA, CARDIOQUIN, QUINIDEX	N	±	
	Quinine	LEGATRIN, QUINAMM		++	
	Rifampin	RIFADIN, RIMACTANE	Y		Y
	Rifapentine	PRIFTIN			Y
	Ritonavir	NORVIR		±	N
	Rosiglitazone	AVANDIA	Y	++	
	Saquinavir	INVIRASE, FORTOVASE		±	
	Secobarbital	SECONAL			Y
	Selegiline	ELDEPRYL	Y	±	
	Sertraline	ZOLOFT	Y	±	
	Sildenafil	VIAGRA	N	±	
	Simvastatin	ZOCOR		±	
	Sulconazole	EXELDERM		±	
	Sulfadiazine		Y	+++	
	Sulfamethoxazole	BACTRIM, SEPTRA, SULFATRIM (all w/Trimethropim)	Y	++	
	Sulfinpyrazone	ANTURANE	Y	++	
	Sulfisoxazole	GANTRISIN	Y	+++	
	Tamoxifen	NOLVADEX	Y	±	
	Teniposide	VUMON		±	
	Thioridazine	MELLARIL		±	
	Ticlopidine	TICLID		±	
	Tioconazole	MONISTAT 1, VAGISTAT-1		±	
	Tolbutamide	ORINASE	Y	+++	
	Tolcapone	TASMAR		±	
	Torsemide	DEMADEX	Y		
	Tranylcypromine	PARNATE		±	
	Tretinoin	AVITA, RENOVA, RETIN-A, VESANOID	N	±	
	Triazolam	HALCION		±	
	Trimethoprim	PRIMSOL, PROLOPRIM	Y	++	
	Valdecoxib	BEXTRA	N	±	
	Valproic acid	DEPAKENE	N	±	
	Valsartan	DIOVAN		±	
	Verapamil	CALAN, CHRONOVERA, COVERA-HS, ISOPTIN, VERELAN	N	±	
	Voriconazole	VFEND	Y	±	
	Warfarin	COUMADIN	Y	++	
	Zafirlukast	ACCOLATE	Y	++	
	Zopiclone	RTIO-ZOPICLONE	Y		

Potential Cytochrome P450 (CYP) Drug Interactions – CYP2C19

	Generic Name	Trade Names	Substrate[1]	Inhibitor[2]	Inducer[3]
CYP2C19	Amiodarone	CORDARONE, PACERONE	N	±	
	Aminoglutethimide	CYTADREN			Y
	Amitriptyline	ELAVIL	N	±	
	Amprenavir	AGENERASE		±	
	Azelastine	ASTELIN, OPTIVAR, RHINOLAST	N	±	
	Bortezomib	VELCADE	N	++	
	Buprenorphine	BUPRENEX		±	
	Carbamazepine	CARBATROL, TEGRETOL			Y
	Carisoprodol	SOMA	Y		
	Cholecalciferol/ vitamin D_3	CALEL-D, CALTRATE PLUS, CLOCREAM, DELTA-D		±	
	Cimetidine	TAGAMET		++	
	Citalopram	CELEXA	Y	±	
	Clomipramine	ANAFRANIL	Y		
	Clotrimazole	GYNE-LOTRIMIN, LOTRIMIN, MYCELEX		±	
	Clozapine	CLOZARIL	N	±	
	Delavirdine	RESCRIPTOR		+++	
	Desogestrel	CYCLESSA, DESOGEN, MIRCETTE, ORTHO-CEPT (w/ethinyl estradiol)	Y		
	Diazepam	DIASTAT, DIZAC, VALIUM	Y	±	
	Dimethyl sulfoxide	RIMSO-50		±	
	Drospirenone	YASMIN (w/ethinyl estradiol)		±	
	Efavirenz	SUSTIVA		±	
	Entacapone	COMTAN		±	
	Escitalopram	LEXAPRO	Y		
	Esomeprazole	NEXIUM	Y		
	Ethinyl estradiol	ESTINYL, ORTHO TRI-CYCLEN (w/norgestimate) TRI-LEVLEN, TRIPHASIL (w/levonorgestrel)		±	
	Ethotoin	PEGANONE		±	
	Felbamate	FELBATOL		±	
	Fluconazole	DIFLUCAN		+++	
	Fluoxetine	PROZAC, SARAFEM	N	++	
	Fluvoxamine	LUVOX		+++	
	Fosamprenavir	LEXIVA		±	
	Fosphenytoin	CEREBYX	Y		Y
	Gefitinib	IRESSA		±	
	Gemfibrozil	LOPID		+++	
	Imipramine	TOFRANIL	Y	±	
	Indinavir	CRIXIVAN		±	
	Indomethacin	INDOCIN	N	±	
	Isoniazid	INH, NYDRAZID, PMS-ISONIAZID		+++	
	Ketoconazole	NIZORAL		++	

	Lansoprazole	PREVACID	Y	++	
	Letrozole	FEMARA		±	
	Loratadine	CLARITIN		++	
	Losartan	COZAAR		±	
	Mephenytoin	MESANTOIN	Y		
	Mephobarbital	MEBARAL	Y	±	
	Mestranol	NECON 1/50, NORINYL 1/50, ORTHO-NOVUM 1/50 (w/ norethindrone)		±	
	Methimazole	TAPAZOLE		±	
	Methoxsalen	8-MOP, OXSORALEN, UVADEX		±	
	Methsuximide	CELONTIN	Y	±	
	Miconazole	LOTRIMIN, MICATIN, MICONAZOLE 7, MONISTAT		+++	
	Modafinil	PROVIGIL		+++	
	Nelfinavir	VIRACEPT	Y	±	
	Nicardipine	CARDENE		++	
	Nilutamide	NILANDRON	Y	±	
	Olanzapine	ZYPREXA, ZYPREXA ZYDIS		±	
	Omeprazole	PRILOSEC	Y	+++	
	Orphenadrine	FLEXOR, NORFLEX		±	
	Oxcarbazepine	TRILEPTAL		±	
	Pantoprazole	PANTOLOC, PROTONIX	Y		
	Paroxetine	PAXIL		±	
	Pentamidine	NEBUPENT, PENTAM 300	Y	±	
	Phenobarbital	LUMINAL	Y		
	Phenytoin	DILANTIN, PHENYTEK, PHENYTOIN SODIUM	Y		Y
	Pimozide	ORAP		±	
	Pioglitazone	ACTOS		±	
CYP2C19, continued	**Generic Name**	**Trade Names**	**Substrate[1]**	**Inhibitor[2]**	**Inducer[3]**
	Probenecid	BENEMID, PROBALAN		±	
	Progesterone	CRINONE, PROGESTASERT, PROMETRIUM	Y	±	
	Propofol	DIPRIVAN	N	++	
	Propranolol	INDERAL, INNOPRAN XL	Y		
	Rabeprazole	ACIPHEX	Y	++	
	Rifampin	RIFADIN, RIMACTANE			Y
	Ritonavir	NORVIR		±	
	Rosiglitazone	AVANDIA		±	
	Saquinavir	INVIRASE, FORTOVASE		±	
	Selegiline	ELDEPRYL		±	
	Sertraline	ZOLOFT	Y	++	
	Sildenafil	VIAGRA		±	
	Sulconazole	EXELDERM		±	
	Telmisartan	MICARDIS		±	
	Ticlopidine	TICLID		+++	
	Tioconazole	MONISTAT 1, VAGISTAT-1		±	
	Topiramate	TOPAMAX		±	
	Torsemide	DEMADEX		±	

	Tranylcypromine	PARNATE		++	
	Trimipramine	SURMONTIL	Y		
	Valdecoxib	BEXTRA		±	
	Valproic acid	DEPAKENE	N	±	
	Voriconazole	VFEND	Y	±	
	Warfarin	COUMADIN	N	±	
	Zafirlukast	ACCOLATE		±	

Potential Cytochrome P450 (CYP) Drug Interactions – CYP3A4

	Generic Name	Trade Names	Substrate[1]	Inhibitor[2]	Inducer[3]
CYP3A4	Acetaminophen	TYLENOL	N	±	
	Acetazolamide	DIAMOX		±	
	Albuterol	PROVENTIL, VENTOLIN, VOLMAX	Y		
	Alfentanil	ALFENTA	Y		
	Alprazolam	ALPRAZOLAM INTENSOL, XANAX	Y		
	Aminoglutethimide	CYTADREN			Y
	Amiodarone	CORDARONE, PACERONE	N	++	
	Amlodipine	NORVASC	Y	±	
	Amprenavir	AGENERASE	Y	+++	
	Anastrozole	ARIMIDEX		±	
	Aprepitant	EMEND	Y	±	N
	Aripiprazole	ABILIFY	Y		
	Atazanavir	REYATAZ	Y	+++	
	Atorvastatin	LIPITOR	Y	±	
	Azelastine	ASTELIN, OPTIVAR, RHINOLAST	N	±	
	Azithromycin	ZITHROMAX	N	±	
	Benzphetamine	DIDREX	Y		
	Betamethasone	CELESTONE, SOLUSPAN, DIPROSONE		±	
	Bisoprolol	ZEBETA	Y		
	Bortezomib	VELCADE	Y	±	
	Bosentan	TRACLEER	Y		N
	Bromazepam	LECTOPAM, LEXOTAN, LEXOTANIL	Y		
	Bromocriptine	PARLODEL	Y	±	
	Buprenorphine	BUPRENEX	Y		
	Buspirone	BUSPAR	Y		
	Busulfan	BUSULFEX, MYLERAN	Y		
	Caffeine		N	++	
	Carbamazepine	CARBATROL, TEGRETOL	Y		Y
	Cerivastatin	BAYCOL	Y	±	
	Chloramphenicol	CHLOROMYCETIN, CHLOROPTIC SOP, OCU-CHLOR		±	
	Chlordiazepoxide	LIBRITABS, LIBRIUM	Y		
	Chloroquine	ARALEN	Y		
	Chlorpheniramine	CHLOR-TRIMETON	Y		
	Chlorzoxazone	PARAFLEX	N	±	

	Cimetidine	TAGAMET		++	
	Ciprofloxicin	CILOXAN, CIPRO		+++	
	Cisapride	PREPULSID, PROPULSID	Y	±	
	Citalopram	CELEXA	Y		
	Clarithromycin	BIAXIN	Y	+++	
	Clemastine	ALLERHIST, TAVIST		±	
	Clobazam	FRISIUM	Y		
	Clofazimine	LAMPRENE		±	
	Clonazepam	KLONOPIN	Y		
	Clorazepate	TRANXENE, T-TAB	Y		
	Clotrimazole	GYNE-LOTRIMIN, LOTRIMIN, MYCELEX		++	
	Clozapine	CLOZARIL	N	±	
	Cocaine		Y	±	
	Colchicine	COLBENEMID, COLSALIDE	Y		N
	Cyclophosphamide	CYTOXAN, NEOSAR	Y	±	
	Cyclosporine	GENGRAF, NEORAL, RESTASIS, SANDIMMUNE	Y	++	
	Danazol	DANOCRINE		±	
	Dantrolene	DANTRIUM	Y		
	Dapsone		Y		
	Delavirdine	RESCRIPTOR	Y	±	
	Desipramine	NORPRAMIN, PERTOFRANE		++	
	Dexmedetomidine	PRECEDEX		±	
	Diazepam	DIASTAT, DIZAC, VALIUM	Y	±	
	Diclofenac	CATAFLAM, VOLTAREN	N	+++	
	Digitoxin	CRYSTODIGIN	Y		
	Dihydroergotamine	D.H.E. 45, MIGRANAL	Y	±	
	Diltiazem	CARDIZEM, DILACOR XR, TIAZAC	Y	++	
	Disopyramide	NORPACE	Y		
	Disulfiram	ANTABUSE	N	±	
	Docetaxel	TAXOTERE	Y	±	
	Doxepin	ADAPIN, SINEQUAN, ZONALON	Y		
	Doxorubicin	ADRIAMYCIN	Y	±	
	Doxycycline	ADOXA, ATRIDOX, DORYX, MONODOX, PERIOSTAT, VIBRAMYCIN	Y	+++	
	Drospirenone	YASMIN (w/ethinyl estradiol)	N	±	
	Generic Name	**Trade Names**	**Substrate[1]**	**Inhibitor[2]**	**Inducer[3]**
	Efavirenz	SUSTIVA	Y	±	N
	Eletriptan	RELPAX	Y		
	Enalapril	VASOTEC	Y		
	Enoxacin	PENETREX		+++	
	Entacapone	COMTAN		±	
	Eplerenone	INSPRA	Y		
	Ergoloid mesylates	GERIMAL, HYDERGINE	Y		
	Ergonovine	ERGOTRATE	Y		
	Ergotamine	GENERGEN	Y	±	

CYP3A4, continued	Erythromycin	A/T/S, AKNE-MYCIN, EES, ERY-TAB, ERYC, ERYPED, ERYTHROCIN	Y	++	
	Escitalopram	LEXAPRO	Y		
	Estradiol	ALORA, CLIMARA, ESTRACE, ESTRADERM, ESTRING, FEMRING, VAGIFEM	Y		N
	Estrogens, conjugated A/synthetic	CENESTIN	Y		N
	Estrogens, conjugated equine	PREMARIN	Y		N
	Estrogens, conjugated esterified	MENEST	Y		
	Estrone	KESTRONE	Y		
	Estropipate	OGEN, ORTHO-EST	Y		
	Ethinyl estradiol	ESTINYL, ORTHO TRI-CYCLEN (w/norgestimate) TRI-LEVLEN, TRIPHASIL (w/levonorgestrel)	Y	±	
	Ethosuximide	ZARONTIN	Y		
	Etoposide	ETOPOPHOS, VEPESID	Y	±	
	Felbamate	FELBATOL	Y		N
	Felodipine	PLENDIL	Y	±	
	Fentanyl	ACTIQ, DURAGESIC, SUBLIMAZE	Y	±	
	Fluconazole	DIFLUCAN		++	
	Fluoxetine	PROZAC, SARAFEM	N	±	
	Flurazepam	DALMANE	Y		
	Flutamide	EULEXIN	Y		
	Fluvastatin	LESCOL	N	±	
	Fluvoxamine	LUVOX		±	
	Fosamprenavir	LEXIVA	Y	+++	
	Fosphenytoin	CEREBYX	N		Y
	Fulvestrant	FASLODEX	Y		
	Gefitinib	IRESSA	Y		
	Glyburide	DIABETA, GLYNASE PRESTAB, MICRONASE		±	
	Grapefruit juice			++	
	Halofantrine	HALFAN	Y		
	Haloperidol	HALDOL	Y	++	
	Hydralazine	APRESOLINE		±	
	Ifosfamide	IFEX	Y	±	
	Imatinib	GLEEVEC	Y	+++	
	Indinavir	CRIXIVAN	Y	+++	
	Irbesartan	AVAPRO		±	
	Irinotecan	CAMPTOSAR	Y		
	Isoniazid	INH, NYDRAZID, PMS-ISONIAZID		+++	
	Isosorbide dinitrate	DILATRATE, ISORDIL, SORBITRATE	Y		
	Isosorbide mononitrate	IMDUR, ISMO	Y		
	Isradipine	DYNACIRC	Y	±	

	Itraconazole	SPORANOX	Y	+++	
	Ketamine	KETALAR	Y		
	Ketoconazole	NIZORAL	Y	+++	
	Lansoprazole	PREVACID	Y	±	
	Letrozole	FEMARA	Y		
	Levomethadyl acetate hydrochloride	ORLAAM	Y		
	Levonorgestrel	MIRENA, PLAN B	Y		
	Lidocaine	XYLOCAINE	Y	++	
	Lomustine	CEENU		±	
	Losartan	COZAAR	Y	±	
	Lovastatin	ALTOCOR, MEVACOR	Y	±	
	Medroxyprogesterone	DEPO-PROVERA, PROVERA	Y		N
	Mefloquine	LARIAM	Y	±	
	Mestranol	NECON 1/50, NORINYL 1/50, ORTHO-NOVUM 1/50 (w/ norethindrone)	Y	±	
	Methadone	DISKETS, DOLOPHINE, METHADONE HYDROCHLORIDE INTENSOL	Y	±	
	Methimazole	TAPAZOLE		±	
	Generic Name	**Trade Names**	**Substrate[1]**	**Inhibitor[2]**	**Inducer[3]**
	Methoxsalen	8-MOP, OXSORALEN, UVADEX		±	
	Methylergonovine	METHERGINE	Y		
	Methylprednisolone	MEDROL, DEPO-MEDROL, A-METHAPRED, SOLU-MEDROL	N	±	
	Methysergide	SANSERT	Y		
	Metronizadole	FLAGYL, METROGEL, NORITATE		++	
	Miconazole	LOTRIMIN, MICATIN, MICONAZOLE 7, MONISTAT	Y	+++	
	Midazolam	VERSED	Y	±	
	Mifepristone	MIFEPREX	N	±	
	Miglustat	ZAVESCA	Y		
	Mirtazapine	REMERON	Y	±	
	Mitoxantrone	NOVANTRONE		±	
	Modafinil	PROVIGIL	Y	±	N
	Montelukast	SINGULAIR	Y		
	Moricizine	ETHMOZINE	Y		N
	Nafcillin	NAFCIL, NALLPEN			Y
	Nateglinide	STARLIX	Y		
	Nefazodone	SERZONE	Y	+++	
	Nelfinavir	VIRACEPT	Y	+++	
	Nevirapine	VIRAMUNE	Y	±	Y
	Nicardipine	CARDENE	Y	+++	
	Nifedipine	ADALAT, PROCARDIA	Y	±	
	Nimodipine	NIMOTOP	Y		
	Nisoldipine	SULAR	Y	±	
	Nitrendipine		Y	±	

CYP3A4, continued	Nizatidine	AXID		±	
	Norethindrone	AYGESTIN, NOR-QD, ORTHO MICRONOR	Y		
	Norfloxacin	NOROXIN		++	
	Norgestrel	LO/OVRAL, LO/OVRAL-28, OVRAL-21, OVRAL-28 (w/ethinyl estradiol)	Y		
	Olanzapine	ZYPREXA, ZYPREXA ZYDIS		±	
	Omeprazole	PRILOSEC	N	±	
	Ondansetron	ZOFRAN	Y		
	Orphenadrine	FLEXOR, NORFLEX	N	±	
	Oxcarbazepine	TRILEPTAL			Y
	Oxybutynin	OXYTROL, DITROPAN	N	±	
	Paclitaxel	TAXOL	Y		N
	Paroxetine	PAXIL		±	
	Pentamidine	NEBUPENT, PENTAM 300		±	
	Pentobarbital	NEMBUTAL SODIUM			Y
	Pergolide	PERMAX	Y	±	
	Phencyclidine		Y	±	
	Phenobarbital	LUMINAL			Y
	Phenytoin	DILANTIN, PHENYTEK, PHENYTOIN SODIUM	N		Y
	Pilocarpine	ISOPTO CARPINE, OCUSERT PILO, PILOCAR, PILOPINE HS, SALAGEN		±	
	Pimozide	ORAP	Y	±	
	Pioglitazone	ACTOS	Y		N
	Pravastatin	PRAVACHOL	N	±	
	Prednisolone	AK-PRED, ECONOPRED, INFLAMASE, ORAPRED, PEDIAPRED, PRED FORTE, PRED MILD, PRELONE	N	±	
	Primaquine		Y	±	
	Primidone	MYSOLINE			Y
	Progesterone	CRINONE, PROGESTASERT, PROMETRIUM	Y	±	
	Propofol	DIPRIVAN	N	+++	
	Propoxyphene	DARVON		±	
	Quetiapine	SEROQUEL	Y		
	Quinidine	QUINAGLUTE DURA, CARDIOQUIN, QUINIDEX	Y	+++	
	Quinine	LEGATRIN, QUINAMM	N	±	
	Quinupristin	SYNERCID (w/dalfopristin)		±	
	Rabeprazole	ACIPHEX	Y	±	
	Repaglinide	PRANDIN	Y		
	Rifabutin	MYCOBUTIN	Y		Y
	Rifampin	RIFADIN, RIMACTANE	Y		Y
	Rifapentine	PRIFTIN			Y
	Risperidone	RISPERDAL	N	±	
	Ritonavir	NORVIR	Y	+++	N
	Saquinavir	INVIRASE, FORTOVASE	Y	++	
	Selegiline	ELDEPRYL	N	±	
	Sertraline	ZOLOFT	Y	++	

	Sibutramine	MERIDIA	Y		
	Sildenafil	VIAGRA	Y	±	
CYP3A4, continued	**Generic Name**	**Trade Names**	**Substrate[1]**	**Inhibitor[2]**	**Inducer[3]**
	Simvastatin	ZOCOR	Y		
	Sirolimus	RAPAMUNE	Y	±	
	Sufentanil	SUFENTA	Y		
	Sulconazole	EXELDERM		±	
	Tacrolimus	PROGRAF, PROTOPIC	Y	±	
	Tamoxifen	NOLVADEX	Y	±	
	Tamsulosin	FLOMAX	Y		
	Telithromycin	KETEK	Y	+++	
	Teniposide	VUMON	Y	±	
	Terbinafine	DESENEX MAX, LAMISIL	Y		N
	Testosterone	ANDRODERM, ANDROGEL, TESTIM, TESTODERM	N	±	
	Tetracycline	SUMYCIN	Y	++	
	Theophylline	ELIXOPHYLLIN, SLO-BID, SLO-PHYLLIN, THEO-24, THEO-DUR, THEOCHRON, UNIPHYL	Y		
	Tiagabine	GABITRIL	Y		
	Ticlopidine	TICLID	Y	±	
	Tolterodine	DETROL	Y		
	Toremifene	FARESTON	Y		
	Tranylcypromine	PARNATE		±	
	Trazodone	DESYREL	Y	±	
	Triazolam	HALCION	Y		
	Trimethoprim	PRIMSOL, PROLOPRIM	Y		
	Trimipramine	SURMONTIL	Y		
	Troleandomycin	CYCLAMYCIN, TAO	Y	++	
	Valproic acid	DEPAKENE		±	
	Vardenafil	LEVITRA	Y		
	Venlafaxine	EFFEXOR	Y	±	
	Verapamil	CALAN, CHRONOVERA, COVERA-HS, ISOPTIN, VERELAN	Y	++	
	Vinblastine	VELBAN, VELBE	Y	±	
	Vincristine	ONCOVIN	Y	±	
	Vinorelbine	NAVELBINE	Y	±	
	Voriconazole	VFEND	N	++	
	Zafirlukast	ACCOLATE		±	
	Ziprasidone	GEODON	N	±	
	Zolpidem	AMBIEN	Y		
	Zonisamide	ZONEGRAN	Y		
	Zopiclone	RTIO-ZOPICLONE	Y		

Appendix D

City of Hope National Medical Center

NOTIFICATION OF TOXICITY

THIS FORM OR A COPY OF A SUBMITTED AdEERS REPORT MUST BE FAX'D (626-256-8654) TO THE CONSORTIUM COORDINATOR WITHIN 24 HOURS OF ONSET OF ADVERSE EVENT.

Consortium Protocol Number: PH___- _____ NCI # (if applicable): _____

Protocol Title: _____

Treating Institution (check one) ___COH ___USC ___UCD ___UOP ___Other_____

Reporter: _____ Phone #:_____

Email: _____

PATIENT INFORMATION

Patient Name_____ Pt Study ID: _____

ADVERSE EVENT INFORMATION

Adverse Event: _____ Start Date of AE: ____/____/____

If Phase I trial, is the adverse event considered dose-limiting? __ No __ Yes
Is toxicity reportable as defined by NCI Guidelines? __ No __ Yes

REPORTING INFORMATION

Has the event been reported to the following:

Institutional IRB __ No __ Yes Date: __ __ / __ __ / __ __

FDA __ No __ Yes Date: __ __ / __ __ / __ __

NCI Telephone __ No __ Yes Date: __ __ / __ __ / __ __ Ticket# _____

AdEERS __ No __ Yes Date: __ __ / __ __ / __ __ Ticket# _____

Report sent to DCC? __ No __ Yes Date: __ __ / __ __ / __ __