Phase II Trial of LBH589 (panobinostat) in relapsed or relapsed and refractory Waldenstrom's Macroglobulinemia

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List of abbreviations

AE	**adverse event**
ALT	**alanine aminotransferase/glutamic pyruvic transaminase/GPT**
ANC	**absolute neutrophil count**
APL	**acute promyelocytic leukemia**
ASCO	**American Society of Clinical Oncologists**
AST	**aspartate aminotransferase/glutamic oxaloacetic transaminase/GOT**
ATRA	**all trans-retinoic acid**
AUC	**area under the curve**
BCR-ABL	**a fusion gene of the BCR and ABL genes**
BUN	**blood urea nitrogen**
CIS	**carcinoma in-situ**
Cmax	**maximum concentration of drug**
CML	**chronic myelogenous leukemia**
CNS	**central nervous system**
CR	**complete response/remission**
CS&E	**clinical safety and epidemiology**
CTCAE	**NCI common terminology criteria for adverse events (version 3.0)**
CTCL	**cutaneous T-cell lymphoma**
CV	**coefficient of variation**
DLT	**dose-limiting toxicity**
DNA	**deoxyribose nucleic acid**
ECG	**12 lead electrocardiogram**
ECOG	**Eastern Cooperative Oncology Group**
eRT	**eResearchTechnology**
FACT	**functional assessment of cancer therapy**
FDA	**food and drug administration**
G-CSF	**granulocyte colony-stimulating factor (e.g. filgrastim)**
GM-CSF	**granulocyte-macrophage colony-stimulating factor (e.g. sargramostim)**
H3, H4	**histones H3, H4**
HAT	**histone acetyltransferase**
HDAC	**histone deacetylase**
HDACi	**histone deacetylase inhibitor**
hERG	**human ether-a-go-go related gene**
HIV	**human immunodeficiency virus**
i.v.	**intravenous(ly)**
ICH	**international conference on harmonization**

IEC	**independent ethics committee**
IRB	**institutional review board**
LLN	**lower limit of normal**
LVEF	**left ventricular ejection fraction**
mg/m2	**milligrams per square meter**
MTD	**maximum tolerated dose**
MUGA	**multiple uptake gated acquisition scan**
MWF	**monday, wednesday, friday**
NCI	**national cancer institute**
NHL	**non-hodgkin's lymphoma**
NIH	**national institutes of health**
PD	**pharmacodynamic**
P-gp	**p-glycoprotein**
PK	**pharmacokinetic**
PLT	**platelet**
PR	**partial response**
REB	**research ethics board**
SAE	**serious adverse event**
SAHA	**suberoylanilide hydroxamic acid**
SD	**stable disease**
SOP	**standard operating procedure**
T4	**thyroxine**
TSH	**thyroid stimulating hormone**
ULN	**upper limit of normal**
WBC	**white blood cell**
WNL	**within normal limits**
WOCBP	**women of childbearing potential**

1 Introduction

1.1 Overview of Waldenstrom Macroglobulinemia

WM is a distinct B-cell lymphoproliferative disorder characterized primarily by BM infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy (Dimopoulos, Panayiotidis et al. 2000; Owen, Treon et al. 2003; Ghobrial and Witzig 2004; Dimopoulos, Kyle et al. 2005). This condition is classified as a lymphoplasmacytic lymphoma according to the REAL and WHO systems(Owen, Treon et al. 2003; Dimopoulos, Kyle et al. 2005). The overall incidence of WM is about 3 per million persons per year, with 1,500 new cases diagnosed per year in the US and a median age of diagnosis of 60 years(Herrinton 1993; Jemal, Murray et al. 2005). Unlike multiple myeloma (MM), WM is more common in Caucasians than in African Americans(Jemal, Murray et al. 2005). The median overall survival of patients with WM is 5-6 years; however a recent study in 337 patients with symptomatic WM, showed a median disease specific survival of 11.2 years(Ghobrial, Fonseca et al. 2006). Because the outcome of patients with WM varies widely, an international prognostic scoring system (IPSS) was defined using a series of 587 patients. This IPSS staging system is widely accepted as the prognostic staging system for WM. The scoring system based on the 5 risk factors as well as the survival of patients at 5 years is shown in table 1 below, showing that patients with low risk disease had a 5-year survival of 87%, while only 36% of patients with high-risk disease had a 5-year survival. .

Table 1: IPSS scoring system

Risk	Low	Intermediate	High	
Age > 65 years	-	X or	> 2 factors	
Hb ≤ 11.5 g/dL **Platelet ≤ 100 x10^9/L** **B2M > 3 mg/L** **IgM > 7 g/dL**	≤ 1 factor	2 factors		
N (%)	158 (27%)	223 (38%)	206 (35%)	
Survival at 5 years	**87%**	**68%**	**36%**	P<0.001

Hb : hemoglobin; B2M : beta2-microglobulin; N : number of patients; % : percentage

Limitations of current therapy in WM: Despite continuing advances in the therapy of WM, the disease remains incurable, thereby necessitating the development and evaluation of novel therapeutics(Ghobrial, Gertz et al. 2003; Kyle, Treon et al. 2003; Dimopoulos, Kyle et al. 2005). Most treatment options were originally derived from other lymphoproliferative diseases including multiple myeloma and chronic lymphocytic leukemia (CLL)(Vijay and Gertz 2007). Current therapies used in the upfront or relapsed settings include alkylator agents (e.g. chlorambucil), nucleoside analogues (cladribine or fludarabine), and the monoclonal antibody rituximab(Dimopoulos, O'Brien et al. 1993; Gertz, Anagnostopoulos et al. 2003;

Treon, Emmanouilides et al. 2005; Treon, Morel et al. 2005). The overall response rates (ORR including CR, PR and MR) in the upfront setting is in the range of 30-70% with complete response (CR) rates of less than 10%, and median durations of response averaging 2-3 years(Weber, Dimopoulos et al. 2003; Treon, Morel et al. 2005). In the salvage setting, the ORR is in the range of 30-40%, with a median response duration of 1 year or less(Dimopoulos, Weber et al. 1995; Treon, Morel et al. 2005). The use of fludarabine or alkylating agents in combination therapy in these patients induces high responses, but leads to significant toxicities in these elderly patients(McLaughlin, Estey et al. 2005; Treon, Gertz et al. 2006). Rituximab is the most widely used therapeutic agent in WM. It regulates the PI3K, NF-kB as well as the ERK signaling pathways(Bonavida 2007). Standard rituximab (4 weekly infusions of 375 mg/m2) or four weekly rituximab treatments repeated at 3 months (extended rituximab) triggered response rates of 35-48%(Dimopoulos, Zervas et al. 2002; Dimopoulos, Zervas et al. 2002; Gertz, Rue et al. 2004; Treon, Emmanouilides et al. 2005). However, all these studies included rituximab naïve patients. Most patients receive rituximab re-treatment after prior exposure to rituximab either alone or in combination with other therapies. In addition, the IgM level may initially increase in response to rituximab, a phenomenon termed IgM flare that occurs in about in 54% of patients(Ghobrial 2004; Treon 2004). These levels may persist for up to 3-4 months and do not indicate treatment failure.

Novel therapeutic agents that have demonstrated efficacy in WM include thalidomide, bortezomib and alemtuzumab(Dimopoulos, Zomas et al. 2001; Hunter 2004; Treon 2005; Treon, Morel et al. 2005). The ORR to these agents ranges between 25-80%(Dimopoulos, Zomas et al. 2001; Hunter 2004; Treon 2005; Treon, Morel et al. 2005). Unfortunately, some of these agents have a high toxicity profile such as Alemtuzumab therapy in WM(Hunter 2006; Chen, Kouroukis et al. 2007; Treon, Hunter et al. 2007). The use of bortezomib as a single agent in WM has been tested in two phase II clinical trials in relapsed WM. The agent was used in the standard dose of 1.3 mg/m^2 twice a week on days 1, 4, 8 and 11. Chen et al(Chen, Kouroukis et al. 2007) treated 27 patients with bortezomib in both untreated (44%) and previously treated (56%) patients with WM. The overall response rate to bortezomib was 78%, with major responses (PR or better) observed in 44% of patients, however, sensory neuropathy occurred in 20/27 patients, 5 with grade >3, and occurred following 2-4 cycles of therapy. However, there were no complete responses observed on these studies. Due to the significantly high risk of peripheral neuropathy in these patients, subsequent trials of bortezomib used the treatment schedule of once a week at 1.6 mg/m^2.

We recently tested the activity of LBH589 on WM cells and cell lines in vitro. LBH589 induced a significant decrease of proliferation and triggered cytotoxicity in all cell lines tested and primary CD19+ WM cells (IC50 of 20-40nM), even in the presence of BMSC, IL-6 and IGF-1, which induce resistance to conventional therapies. Importantly, LBH589 did not induce cytotoxicity in healthy donor peripheral blood mononuclear cells. LBH589 induced both intrinsic and extrinsic apoptotic pathways, with caspase-9, caspase-8, caspase-3, and PARP cleavage in a dose-dependent manner. We also demonstrated significant upregulation of the pro-apoptotic transcription factor p53 and down-regulation of the anti-apoptotic proteins Bcl-xL, Mcl-1 and c-myc. We then demonstrated that LBH589 induced apoptosis in WM cells in a caspase-independent manner through induction of autophagy, as shown by upregulation of LC3B and Rab7 expression. We further determined the mechanism of action of LBH589 in WM, investigating the effect of LBH589 on histone acetylation and NF-kB pathways. We found that LBH589 induced a dose-dependent increase in histone H3-H4 acetylation; and inhibited both canonical and non-

canonical pathways of NF-kB, as shown by western blot and immunofluorescence. In addition, LBH589 augmented rituximab, fludarabine, bortezomib and perifosine-induced cytotoxicity in WM cells

1.2 Overview of LBH589

1.2.1 Anticancer activity of DAC inhibitors

Alterations in chromosome structure play critical roles in the control of gene transcription. These epigenetic alterations include modification of histones and others proteins by acetylation and/or phosphorylation. Normally, these modifications are balanced finely and are highly reversible in normal tissues, but they may be imbalanced and heritable in tumor cells. DAC inhibitors increase histone acetylation, thereby modulating the expression of a subset of genes in a coordinated fashion. Several tumors suppressor genes associated with the malignant phenotype are repressed by epigenetic mechanisms in sporadic cancers. Thus therapy with DAC inhibitors may alter tumor phenotype and inhibit growth in such tumors.

Multiple hallmarks of cancer are regulated by acetylation/deacetylation:

- DAC inhibition targets both histone and nonhistone proteins. Targeting the acetylation status of nonhistone, tumor-associated proteins that mediate proliferation may be the underlying antitumor mechanism of DAC inhibitors (Marks et al 2001).
- Nonhistone proteins regulated by acetylation include α-tubulin, p53, HIF-1α, and HSP90. These proteins are substrates of DACs (Glozak et al 2005).
- The ability of a single agent to target multiple molecular features of tumor cells may result in good efficacy against a range of different tumor types.

HSP90 is involved in protein stability and degradation; the inhibition of HSP90 affects protein turnover in diseases such as multiple myeloma and B-cell malignancies (Aoyagi and Archer 2005).

- Acetylated HIF-1α is degraded and can no longer act as a tumor growth factor. Class II DAC inhibitors target histone deacetylase (HDAC or DAC) 6, resulting in increased acetylation of HIF-1α and decreased vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis (Diaz-Gonzalez et al 2005).
- Both acetylation and ubiquitylation often occur on the same lysine residue, but these processes cannot occur simultaneously. Acetylation allows for increased stability, and ubiquitylation leads to protein degradation. Therefore, DACs decrease the half-life of a protein by exposing the lysine residue for ubiquitylation (Walsh Garneau-Tsodikova and Gatto 2005).

1.2.2 Panobinostat (LBH589)

Panobinostat (LBH589) is a deacetylase inhibitor (DACi) belonging to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor (pan-DACi) that has shown anti-tumor activity in pre-clinical models and cancer patients. Deacetylases (DAC) target lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, HSP90 and Rb. Panobinostat is formulated as an oral capsule and a solution for intravenous (i.v.) injection. Both the oral and i.v. formulations are currently being investigated in ongoing Phase I and Phase II studies in advanced solid tumors and hematological malignancies.

Inhibition of DAC provides a novel approach for cancer treatment. Histones are part of the core proteins of nucleosomes, and acetylation and deacetylation of these proteins play a role in the regulation of gene expression. Highly charged deacetylated histones bind tightly to the phosphate backbone of DNA, inhibiting transcription, presumably, by limiting access of transcription factors and RNA polymerases to DNA. Acetylation neutralizes the charge of histones and generates a more open DNA conformation. This conformation allows transcription factors and associated transcription apparatus access to the DNA, promoting expression of the corresponding genes. The opposing activities of two groups of enzymes, histone acetyltransferase (HAT) and DAC control the amount of acetylation. In normal cells a balance exists between HAT and DAC activity that leads to cell specific patterns of gene expression. Perturbation of the balance produces changes in gene expression.

Several lines of evidence suggest that aberrant recruitment of DAC and the resulting modification of chromatin structure may play a role in changing the gene expression seen in transformed cells. For example, silencing of tumor suppressor genes at the level of chromatin is common in human tumors (Herman 1994, Pratt 1994, Szyf 1994, Herman 1995, Merlo 1995, Herman 1996, Herman 1998, Cameron 1999) and DAC complexes have been shown to be crucial to the activity of the AML-specific fusion proteins PLZF-RAR-α, PML-RAR-α, and AML1/ETO (Gelmetti 1998, Grignani 1998, Lin 1998, Redner 1999). DAC inhibitors (DACi) have been shown to induce differentiation, cell cycle arrest or apoptosis in cultured tumor cells, and to inhibit the growth of tumors in animal models (Yoshida 1987, Yoshida 1988, Itazaki 1990, Yoshida 1990, Sugita 1992, Yoshida 1992, Medina 1997). In addition, DACi have been shown to induce expression of p21, a key mediator of cell cycle arrest in G1 phase and cellular differentiation (Biggs 1996, Nakano 1997, Sowa 1997, Sambucetti 1999).

Tumor growth inhibition and apoptosis in response to DACi treatment may also be mediated through changes in acetylation of non-histone proteins (e.g., HSP90, p53, HIF-1α, α-tubulin). For example, the chaperone protein HSP90 has been shown to be acetylated in cells treated with DACi (Yu 2002, Fuino 2003, Nimmanapalli 2003). Acetylation of HSP90 inhibits its ability to bind newly synthesized client proteins, thus preventing proper client protein folding and function. In the absence of HSP90 function, misfolded proteins are targeted for degradation in the proteasome. Many proteins that require HSP90 association are critical to cancer cell growth, including ErbB1, ErbB2, AKT, Raf, KDR, and BCR-ABL. Acetylation of HSP90 in cells treated with DACi inhibits the chaperone function of HSP90, leading to degradation of the client proteins and eventual cell death.

The potential clinical utility of the use of DACi in cancer therapy was first suggested by the activity of the DACi, sodium phenylbutyrate, against acute promyelocytic leukemia (APL). An adolescent female patient with relapsed APL, who no longer responded to all trans-retinoic acid (ATRA) alone, achieved a complete clinical remission after treatment with a combination of ATRA and the DACi sodium phenylbutyrate (Warrell et al 1998). Recent evidence suggests that there is activity in a variety of solid and hematological tumors with Vorinostat (Zolinza™), an orally administered, structurally-related DACi. Vorinostat has been reported to have single-agent activity in cutaneous T-cell lymphoma (CTCL), diffuse large cell lymphoma, and head and neck cancer (Heaney 2003, Kelly 2003). Similar activity has been reported in clinical studies with other DACi, including i.v. romidepsin (Kim et al 2007 ASH abstract). Vorinostat was approved by the FDA for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma for patients who have progressive, persistent or recurrent disease on or following two systemic therapies in October 2006 (Mann et al 2007).

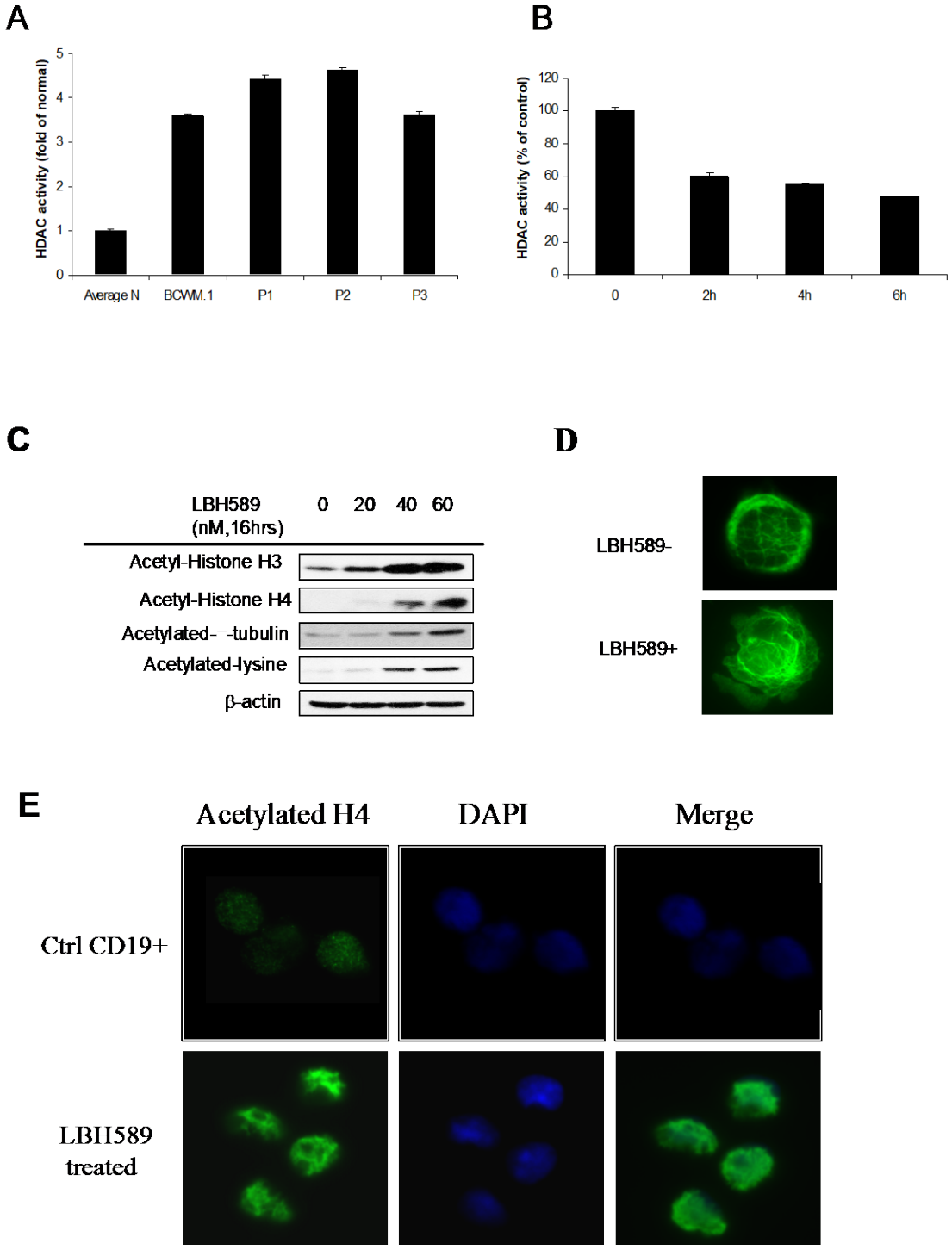
1.2.3 Preclinical data of LBH59 in Waldenstrom's Macroglobulinemia

Epigenetic regulation of gene expression including histone acetylation is commonly deregulated in many malignancies leading to aberrant transcription. We sought to examine the role of histone acetylation in WM, and determine the activity of histone deacetylase inhibitors in this disease. We showed that WM cells aberrantly expressed a high level of HDAC activity compared to control B cells. We then identified the activity of the potent HDAC inhibitor LBH589 on the acetylation of H3 and H4 histones in cell lines and patient samples and the effect of HDAC inhibition on genes regulated by histone modification in WM cells using gene expression profiling, and demonstrated that HDAC inhibition led to upregulation of p53 and decreased expression of c-myc, Bcl-2 and BCl-xL.

To determine whether the imbalance of HDAC/HAT activity occurs in WM, we first examined the level HDAC activity in CD19+ selected WM cells from patients and BCWM.1 cells, compared it to control CD19+ cells from healthy subjects. As shown in Figure 1A, the level of HDAC activity was significantly higher in all the WM patient samples and BCWM.1 compared to the average of 3 normal controls, indicating that indeed in WM cells, HDAC/HAT activity is elevated. We then determined the effect of the HDAC inhibitor LBH589 on HDAC activity in BCWM.1. Figure 1B shows that HDAC activity was significantly inhibited by LBH589 (40nM) within 2 hours of incubation (p= 0.04). We next investigated the effect of LBH589 on specific histone acetylation in WM cells. BCWM.1 cells were incubated with LBH589 (20-60nM for 16 hours), and whole-cell extracts were then analyzed by immunoblotting. LBH589 induced a dose-dependent increase in histone H3 and H4 acetylation (Figure 1C). In addition, LBH589 induced α-tubulin and lysine hyperacetylation in a dose-dependent fashion. We next confirmed LBH589-induced hyperacetylation in BCWM.1 cells by immunofluorescence. BCWM.1 cells were treated with medium or LBH589 (40nM for 16 hours). LBH589-treated cells showed a hyperacetylated segmented α-tubulin, in contrast with untreated cells where a reticulated pattern of acetyl-α-tubulin, forming a latticed network was observed (Figure. 1D). Finally, we confirmed that patient CD19+ cells expressed low levels of acetylated Histone H4 levels using immunofluorescence staining, while treatment of these cells with LBH589 (40nM for 16 hours) led to a significant increase in the expression of acetylated Histone H4 in the nuclei of these cells, as confirmed by DAPI blue staining for nuclei (Figure 1E).

We further showed that HDAC inhibition leads to a significant reduction of both the canonical and non-canonical NF*k*B pathways in WM. Based on these studies, we showed that LBH589 induced significant cytotoxicity, cell cycle arrest, and apoptosis with an IC50 of 20-40nM, even in the presence of bone marrow stromal cells, IL-6 and IGF-1, which induce resistance to conventional therapies. LBH589 induced both intrinsic and extrinsic apoptotic pathways. In addition, LBH589 induced apoptosis in WM cells in a caspase-independent manner through induction of autophagy, as shown by upregulation of LC3B and Rab7 expression. Finally, we demonstrated that LBH589 augmented rituximab, fludarabine, and bortezomib-induced cyotoxicity in WM cells, providing the scientific rationale for studying this agent in clinical trials in WM (data not shown)**.**

Fig. 1


A
HDAC activity (fold of normal)
0
1
2
3
4
5
Average N
BCWM.1
P1
P2
P3
B
HDAC activity (% of control)
0
20
40
60
80
100
120
0
2h
4h
6h
C
LBH589 (nM,16hrs)
0
20
40
60
Acetyl-Histone H3
Acetyl-Histone H4
Acetylated- -tubulin
Acetylated-lysine
β-actin
D
LBH589-
LBH589+
E
Acetylated H4
DAPI
Merge
Ctrl CD19+
LBH589 treated

1.2.4 Preclinical pharmacology

1.2.4.1 *In vitro* pharmacology

LBH589 was devised through iterative design and combinatorial approach using in vitro histone deacetylase inhibition assays, activation of the p21 promoter and inhibition of the proliferation of tumor cell lines in monolayer as selection criteria. LBH589 is active as an inhibitor of histone deacetylase activity purified from H1299 lung carcinoma cell lines (IC_{50} = 0.03 μM) and, in nanomolar concentrations, transcriptionally activates a p21 promoter luciferase construct transiently transfected into H1299 cells.

Consistent with the proposed mechanism of action for LBH589, tumor cells exposed to LBH589 for 2 hours or more demonstrated increased levels of histone-H3 and -H4 acetylation, and the increased histone acetylation levels persisted for up to 24 hours. LBH589 induced cell death in transformed cells while, under similar conditions, induced growth arrest in normal cells. Exposure of tumor cells to low nanomolar concentrations of LBH589 for 16 hours or longer resulted in significant cell death. Exposure of normal dermal human fibroblasts to similar concentrations of LBH589 for similar durations induced growth arrest but not cell death. Similarly, treatment of SV40-T antigen and telomerase transformed bronchial epithelial cells with LBH589 induced apoptosis as assessed by annexin V staining. However, similar treatment of normal bronchial epithelial cells with higher concentrations of LBH589 did not induce apoptosis.

1.2.4.2 Effects of panobinostat on solid tumor cell lines *in vitro*

LBH589 exhibits potent antiproliferative activity against a broad range of tumor cell lines including HCT116 colon carcinoma cells (IC50 = 0.005 μM), H1299 lung carcinoma cells (IC50 = 0.069 μM), DU145 prostrate cancer cells (IC50 = 0.016 μM) and PC-3 prostate cancer cells (IC50 = 0.022 μM). Antiproliferative activity in the tumor cell lines is accompanied by increased histone acetylation, suggesting that LBH589 modulates the intended target. Further, LBH589 demonstrates antiproliferative activity against tumor cell lines resistant to paclitaxel due to over-expression of P-gp.

1.2.4.3 *In vivo* pharmacology and *in vivo* anti-tumor activity

The activity of LBH589 was assessed in two different in vivo anti-tumor models using two different human tumor cell lines; HCT116 (colon adenocarcinoma) and PC3-M2AC6 (prostate adenocarcinoma). Since the oral bioavailability of LBH589 is < 5% in nude mice, all efficacy studies in vivo were performed with the intravenous formulation.

Following intravenous administration to tumor bearing mice, LBH589 was rapidly absorbed by tumor cells with concentrations in tumor higher than plasma. The LBH589 tumor concentration at 16 hours in mice bearing HCT116 xenographs was 0.71 μM, which is 142 times the IC50 and 41 times the LD90 observed in the HCT116 cell line.

The levels of histone-H3 and -H4 acetylation were examined in LBH589-treated mice bearing either HCT116 subcutaneous tumors or PC-3M2AC6 orthotopic tumors. IV administration of LBH589 to the tumor-bearing mice resulted in consistent increases in histone H3 and H4 acetylation in the tumor. In the HCT116 model, histone acetylation was seen after doses as low as 1.25 mg/kg, the lowest dose that induced significant tumor growth inhibition. Increased levels of histone acetylation persisted post-dose for at least 48 hours in the PC-3M2AC6 model and 24 hours in the HCT116 model

In the HCT116 subcutaneous human tumor xenograft, i.v administration of LBH589 induced regressions at doses of 20 and 40 mg/kg administered once daily 5x/wk for 3 weeks. Intravenous LBH589 treatment resulted in tumor stasis in the human orthotopic PC3-M2AC6 bone metastases model.

The effects of dose scheduling on the efficacy and tolerability of LBH589 were evaluated in the HCT 116 human tumor xenograft model. The number of i.v doses (1, 3 or 5) per week was varied, while the total amount of compound administered per week was kept constant at 40 mg/kg per week and the duration of treatment was kept constant at 3 weeks. There was no significant difference in efficacy when LBH589 was administered for 5 consecutive days (8 mg/kg/day) followed by 2 days without treatment (12% tumor/control [T/C]) and when LBH589 was administered for 3 consecutive days (13.3 mg/kg/day) followed by 4 days without treatment (20% T/C) as compared to controls. Although a regimen of a total weekly dose of 40 mg/kg administered 1 day per week was less efficacious than when the same dose was split over 3 or 5 days, this dosing schedule produced statistically significant efficacy (48% T/C) as compared to controls.

1.2.5 Animal pharmacokinetics and drug metabolism

The absolute oral bioavailability of panobinostat in rats was found to be ~6%; however, absolute oral bioavailability in dogs following a 1.5 mg/kg dose was ~50%. The oral bioavailability of panobinostat in humans was estimated to be ~31% (23-40%), similar to that in dogs.

After a single intravenous dose of radiolabeled LBH589, the drug is cleared rapidly from blood and extensively distributed into the organs and tissues with concentration in many tissues exceeding those in blood. In rats at 5 minutes post dose, the highest tissue radioactivity concentrations were measured in the kidney. Numerous other tissues and organs (i.e., adrenal cortex, adrenal medulla, brown fat, heart, liver, pancreas, salivary gland, spleen, glandular stomach, and thyroid gland) had radioactivity levels that were at least five times higher than those in blood. Despite the nearly complete recovery of radiolabeled material at 96 hours post dose, relatively low amounts of radioactivity were observed in most tissues and organs, with the highest levels observed in the adrenal medulla, skin of pigmented animals, and the uveal tract of pigmented animals. The latter observation indicates that LBH589 and/or its metabolites are bound to melanin.

LBH589 was moderately bound to plasma proteins and binding was independent of concentrations over the 0.1 to 100 µg/mL test range in the mouse, rat, dog, and human. At 37°C, the average bound fraction in dogs, mice, rats, and humans measured 78.7%, 82.8%, 88.9%, and 89.6% respectively. Elimination of panobinostat in the rat and dog was primarily by metabolism as recovery of panobinostat in the excreta after oral or i.v. administration was 8.6 and 6.1- 9.8 % of the dose in rat, and ~2% and ~3% of the dose in the dog, respectively. Excretion of [^{14}C] panobinostat and drug-related material occurred primarily via the fecal route, with urinary excretion accounting for 12.5% (rat) and ~33% (dog) and fecal excretion accounting for 81% (rat) and 49% (dog) of the administered intravenous dose. Data from the rat bile study indicated that excretion of drug related material was primarily by the biliary route. The metabolism of [^{14}C]- panobinostat following i.v. or oral administration in the rat and dog was extensive and involved many types of biotransformation reactions including reduction, oxidation, hydrolysis, and glucuronidation (rat only). Metabolites M34.4 (glucuronide) and M36.9 (carboxylic acid metabolite) were major components following an oral dose in the rat and M36.9 was the predominant metabolite in the dog, accounting for about half of the total exposure to panobinostat and its metabolites.

Incubation of human liver microsomes with selective probe substrates of the cytochrome P450 isoforms showed that panobinostat is a potent inhibitor of CYP2D6 but not CYP1A2, CYP2C8, CYP2C9, CYP2E1, CYP2C19, and CYP3A4. Therefore, if therapeutic concentrations of panobinostat are sufficiently high, drug-drug interactions may result from concomitant administration of panobinostat with drugs eliminated primarily by CYP2D6-dependent metabolism. Panobinostat was found to be metabolized in human liver, in part, by human cytochrome P450s CYP3A4, CYP2D6, and CYP2C19. CYP3A4 appears to be the main enzyme involved in the oxidative metabolism of panobinostat (70-98%) in human liver microsomes. It is possible that inhibitors of CYP3A would affect the clearance of panobinostat *in vivo*, however, the magnitude of interaction is dependent upon the actual fraction of the dose eliminated by this pathway. This information is pending the radiolabeled human ADME study. Panobinostat was determined not to be an *in vitro* inducer of CYP1A1/2, CYP2B6, CYP2C8/9/19, or CYP3A mRNA or activity in primary human hepatocytes. In addition, panobinostat was not an inducer of UGT1A1, ABCB1 (Pgp) or ABCC2 (MRP2) mRNAs. It is unlikely that panobinostat would act as an inducer of drug metabolizing enzymes and transporters *in vivo*.

1.2.6 Animal toxicology

Following oral administration of panobinostat using a 3-day/week (Monday, Wednesday, Friday) dosing schedule to rats and dogs in studies up to 26 (rats) or 39-weeks (dogs) in duration, the primary target organs were identified as the erythropoietic and myelopoietic systems, and lymphatic system. Reductions in peripheral red cell parameters, lymphocyte, eosinophil and basophil counts and lymphoid depletion in thymus and lymph nodes were present in rats and dogs. Platelet counts were decreased in rats but elevated in dogs. Bone marrow atrophy was characterized by maturation arrest of the granulocytic lineage, consisting of a decrease in the proportion of later stage granulocytic precursors and mature cells, and accompanied by decreases in the number of cells from the erythroid series and an increase in the proportion of cells from the eosinophilic series. Evidence of reversibility was observed for all white blood cell and red blood cell parameters, indicating that the bone marrow had not lost its regenerative capability.

Other target organs were the gastrointestinal (GI) tract, reproductive system, thyroid and bone. Diarrhea was observed at higher doses, as used in the oral rising-dose toxicity study in dogs. Gastrointestinal changes ranged from mild inflammatory changes to necrosis and ulceration and was associated with diarrhea in dogs at doses exceeding the maximal tolerated dose (MTD). Reproductive target organs included the prostate, testis and changes in estrus cycling was also noted. Thyroid changes, including thyroid follicular hypertrophy (rat and dog) and follicular adenoma (1 high dose (75 mg) recovery rat in 26-week study) were noted in both species. Histone deacetylases have been reported to be involved in the negative feedback regulation of thyroid hormone (T3) and in the secretion of thyroid stimulating hormone (TSH) (Sasaki et al 1999), and thyroid changes may have resulted from an over stimulation of the thyroid epithelium by excess circulating thyroid hormone. Hyperostosis was observed in rats at high doses of 100 mg/kg only at 13 weeks. This finding was not observed in longer term studies in rat and dog. All effects in repeated-dose toxicity studies are considered related to the pharmacology of panobinostat. While effects on the hematopoietic system showed clear signs of reversibility, histopathological changes in the thyroid and male reproductive organs were still present at the end of the 4-week recovery period.

Oral administration of panobinostat during gestation to rats and rabbits is associated with embryo-fetal toxicity including embryo-lethality, and an increase in skeletal variations/anomalies (i.e. ossification

changes, supernumerary vertebrae, sternabrae and ribs) at doses which also produced maternal toxicity in rats (doses ≥ 30 mg/kg/day) and rabbit (doses ≥ 40 mg/kg/day). No major malformations were observed. Fertility and early embryonic studies indicate an increase in early resorptions indicating embryo-lethality at doses which also produced maternal toxicity (doses ≥ 30 mg/kg/day). The No Observable Adverse Effect level (NOAEL) for both fertility study in rats and embryo-fetal toxicity studies in rats and rabbits is 10 mg/kg/day.

Panobinostat has a clear genotoxic potential in bacterial and eukaryotic systems (mutagenic and endoreduplication inducing effects). Safety pharmacology studies indicate that the compound has a low likelihood to interfere with vital functions of the respiratory and CNS systems. *In vitro* electrophysiology data from the hERG channel assay revealed an IC_{50} of 3.9 μM and the compound showed a prolongation of the action potential duration in the isolated rabbit heart at a concentration of 2 μM. There was no evidence of cardiovascular toxicity in the *in vivo* dog studies including telemetry study in animal.

Based upon the results of preclinical studies, hematology parameters, thyroid function, and cardiac function monitoring assessments are included in this trial. Panobinostat has a potential for genotoxicity and patients should be advised of the risk for developing secondary tumors. Furthermore, panobinostat poses a reproductive risk to men and women of child bearing potential, therefore use of adequate birth control methods is required in the study.

1.2.7 Clinical experience with LBH589 in humans

Overview of clinical experience

In clinical studies, both oral and i.v. formulations of panobinostat are being explored for further development. As of 31st December 2007, fifteen phase I and/or phase II studies have either been completed or are ongoing. Preliminary safety data have been reviewed for 462 patients who received panobinostat in these studies.

Most adverse events have been grade 1 or grade 2. The most common adverse events seen in the human studies concern the gastrointestinal tract (nausea, diarrhea) and the hematopoietic system (thrombocytopenia and neutropenia). The incidence of diarrhea is slightly more frequent in patients who received the oral formulation of panobinostat. The more commonly encountered grade 3 and grade 4 events, as anticipated from the preclinical studies, have included thrombocytopenia, neutropenia and fatigue. The occurrence of thrombocytopenia appears to be related to the underlying disease (incidence is higher in patients with malignancies that involved the bone marrow e.g., acute myeloid leukemia, chronic myeloid leukemia, multiple myeloma, myelodysplastic syndrome, etc.)

Since the dosing in this study will follow the three-times-per-week schedule, Table 1-1 below, provides a summary of adverse events that occurred in >15% of the patients at any dose using this schedule and the footnote to the table describes the grade 3 and grade 4 events that occurs in > 10% of the patients with solid tumors or lymphoma.

Table 1-1 **All grade adverse events (>15% incidence) regardless of causality, in patients receiving panobinostat three-times-per-week**

Preferred Term	Dose in mg/dose given three-times-per-week (N)					Total N = 129
	15 (7)	20 (102)	30 (13	40 (3)	60 (4)	
	n	n	n	n	n	N (%)
Diarrhea	**4**	**53**	**10**	**2**	**0**	**69 (53.5)**
Nausea	**4**	**50**	**5**	**2**	**1**	**62 (48.1)**
Fatigue	**2**	**41**	**7**	**2**	**2**	**54 (41.9)**
Thrombocytopenia	**2**	**39**	**8**	**1**	**3**	**52 (40.3)**
Anorexia	**2**	**35**	**6**	**1**	**0**	**44 (34.1)**
Vomiting	**3**	**22**	**4**	**0**	**0**	**29 (22.5)**
Dizziness	**2**	**20**	**3**	**0**	**1**	**26 (20.2)**
Weight decreased	**2**	**20**	**3**	**0**	**0**	**25 (19.4)**
Dysgeusia	**0**	**20**	**2**	**1**	**0**	**25 (19.4)**
Peripheral edema	**0**	**20**	**4**	**0**	**0**	**24 (18.6)**
Anemia	**1**	**14**	**6**	**0**	**0**	**21 (16.3)**
Headache	**0**	**17**	**4**	**0**	**0**	**21 (16.3)**
Pyrexia	**0**	**16**	**3**	**0**	**1**	**20 (15.5)**
Grade 3 and Grade 4 events: **Thrombocytopenia = 18.9%; neutropenia = 9%; diarrhea = 5%; anemia = 4 %; dyspnea = 4%; ECG QTc prolongation = 4%**						

In the first human study, panobinostat was administered intravenously on consecutive days and a prolongation of QTc interval on ECG was noted in a few patients. One patient also suffered with Torsade de pointes. Although comorbidities and concomitant medications could have contributed to these events, it was decided to discontinue the daily dosing schedule. The most common ECG findings reported have included clinically non-signifcant changes in T-waves (inverted, flat, or biphasic). Sporadic APCs and VPCs have also been reported.

The most frequently encountered laboratory abnormalities include thrombocytopenia, neutropenia, some degree of anemia, and fluctuations in electrolytes that may not be clinically significant. Thyroid function, as monitored by the measurement of TSH and free T4 have revealed fluctuations in the values of TSH, mostly within normal limits, and not clinically overt hyper-or hypo-thyroidism has been reported.

Phase I clinical experience with oral panobinostat

Phase I study of panobinostat in patients with advanced solid tumors and NHL

[CLBH589B2101] is a first-in-human, multi-arm, multi-center, dose-escalation study of oral panobinostat in adult patients with advanced solid tumors or non-Hodgkin's lymphoma including cutaneous T-cell lymphoma. In this study, panobinostat is administered orally on three dose schedules. Arms 1, 3 and 5 explore different dosing schedules; either Monday-Wednesday-Friday (MWF) every week (Arm 1) or MWF every other week (Arm 3), or Monday-Thursday (MTh) every week (Arm 5). Arm 2 has not been opened. The MTD determined in Arm 1, 20 mg/day on MWF every week, was expanded into 2 separate cohorts of patients with melanoma or CTCL without prior systemic therapy (Arm 4 and 6, respectively). Arm 1, 20 mg/day on MWF every week, was also expanded to include a pilot food effect study in 14 patients. This study is primarily designed to determine the maximal tolerated dose (MTD) based upon the dose limiting toxicity (DLT) of panobinostat as a single agent, and to characterize the safety, tolerability, biologic activity, preliminary efficacy and pharmacokinetic profile of panobinostat. As of Feb 2008, a total of 94 patients have been enrolled, 89 patients have discontinued and 5 patients are on-going as follows: 1 patient in Arm 1, 1 patient in Arm 3, and 3 patients in Arm 5. In Arm 4 (patients with melanoma), 2 patients were treated with 20 mg/day on the MWF every week schedule.

In Arm 1, 3 patients were treated at 15 mg/day on MWF, 10 patients were treated at 30 mg/day on MWF and 19 patients have been treated at 20 mg/day on MWF [most common tumor types: CTCL (10 pts), melanoma (6 pts), renal (6 pts), prostate (4 pts), rhabdomyosarcoma (1 pt), mesothelioma (1 pt), colon (1 pt), hepatic (1 pt), parotid gland (1 pt) and bladder (1 pt)]. DLT was observed in 2 patients at the 30 mg dose level: one grade 3 diarrhea (1pt) and one grade 4 thrombocytopenia (1 pt). The third case of DLT in Arm 1 occurred at the 20 mg dose level with grade 3 fatigue. Based upon these clinical findings, 30 mg was determined to be the DLT dose level and 20 mg was determined to be the MTD dose level for the MWF every week schedule.

In Arm 3, 21 patients were treated at 30 mg, 2 patients were treated at 45 mg on the MWF every other week schedule [most common tumor types: CTCL (9 pts), colon (2 pts), lung (2 pts), NHL (2 pts), melanoma (1 pt), vulva (1 pt), breast (1 pt), mesothelioma (1 pt), prostate (1 pt), ovarian (1 pt), and hepatocellular carcinoma (2 pts)]. DLT was observed in 2 patients at the 45 mg dose level (grade 4 thrombocytopenia) and 1 patient at the 30 mg dose level (grade 4 thrombocytopenia). Based upon these clinical findings, 45 mg was determined to be the DLT dose level and 30 mg was determined the MTD dose level for the MWF every other week schedule.

In Arm 5, 3 patients were treated at 30 mg, 4 patients at 60 mg, and 15 patients at 45 mg on the MTh every week schedule. No DLTs were observed at 30 mg and one DLT was observed at the 60 mg dose level as grade 4 thrombocytopenia, and 3 DLTs were observed at 45mg as follows: grade 3 fatigue, grade 3 QTc prolongation, and grade 4 thrombocytopenia. The patient who experienced grade 3 fatigue at 45mg only received 3 doses of panobinostat.

Preliminary pharmacodynamic analysis in study [CLBH589B2101] of histones from normal PBMCs reveal increased acetylation at doses of 20 mg and above, and duration of effect for at least 72 hours in 50% of patients post last dose at doses of 20 mg and 30 mg in both arms 1 and 3.

Although efficacy is not the primary endpoint of study [CLBH589B2101], 32 patients were enrolled in Arm 1 on the MWF schedule; including 10 patients with CTCL. Of the CTCL patients, 2 patients have achieved a complete response (CR), 4 patients have achieved a partial response (PR), 2 patients have met the criteria for stable disease (SD), and 2 patients have progressive disease (PD). In non-CTCL tumor types, the best response has been SD, with 6 of 22 patients having met the SD criteria (RCC [2 pts], prostate cancer [1 pt], melanoma [1 pt], mesothelioma [1 pt], and parotid gland cancer [1 pt]). This information pertains to Arm 1 (MWF every week) only and also excludes the food effect cohort of Arm 1.

Phase I/II study of panobinostat in patients with hematological malignancies

The safety and tolerability of panobinostat is being explored in a multi-arm, multi-center, Phase I/II study [CLBH589B2102] in patients with hematological malignancies, including Hodgkin's Lymphoma (HL). This study is evaluating 2 schedules of panobinostat administration:

Arm 1 - MWF every week

Arm 2 - MWF every other week

Within each schedule (arm) patients are assigned to one of two subgroups based upon the type of hematologic malignancy that they have. Patients with leukemia, MDS and other hematologic malignancies characterized by severe thrombocytopenia are included in one subgroup (X), while patients with lymphoma or myeloma are included in another subgroup (Y). The subgroups differ with respect to the definition of hematological dose limiting toxicity (DLT); in general, neutropenia and thrombocytopenia are considered a DLT only in the Y subgroup.

As of October 2008, a total of 146 patients (Arm 1 - 90 total, 64 X subgroup, 26 Y subgroup; Arm 2 - 56 total, 33 X subgroup, 23 Y subgroup) have been enrolled in the study.

Clinical safety in study [CLBH589B2102]

In Arm 1 subgroup X, doses of 20 or 30 mg (n=16), 40 (n=10), 60 mg (n=16), and 80 mg (n=11) have been evaluated with DLTs of grade 3 fatigue noted at the 40 mg dose level (two patients) and 60 mg dose level (1 patient). At the 80 mg dose level, DLTs comprised of grade 3 QTcF prolongation (2 patients), grade 3 fatigue (2 patients), and grade 3 cardiac insufficiency (1 patient). In Arm 1 subgroup Y, doses of 20 or 30 mg (n=5), 40 (n=16), and 60 mg (n=5) have been evaluated, and DLT of grade 4 thrombocytopenia has been observed in four patients each at the 40 and 60 mg dose levels.

In Arm 2 subgroup X, doses of 30, 45, and 60 mg (n=24) have been evaluated with no cycle 1 DLTs noted. At the 80 mg dose level (n=9), DLTs noted include grade 3 QTcF prolongation, atrial fibrillation, fatigue, and increase in bilirubin in one patient each. In Arm 2 subgroup Y, at doses of 30 and 45 mg (n=8)no DLT has been reported. At the 60 mg dose level (n=5) 1 patient each had a grade 3 increase in troponin and grade 3 thrombocytopenia; additionally, 1 patient had grade 4 thrombocytopenia, grade 3 fatigue, and grade 3 congestive heart failure.

Across both arms, the most common adverse events, regardless of grade or causality, have included nausea, diarrhea, fatigue, anorexia, vomiting, and thrombocytopenia.

As of October 2008, central review of a total of 4,834 post-dose ECGs from the 146 patients has been performed. A dose-dependent increase in mean change from baseline QTcF has not been observed. Five

patients (3%) experienced QTcF >500 msec. However, all five patients were among the 76 patients (7%) treated at dose levels ≥ 60 mg.

Clinical activity in patients with Hodgkin's Lymphoma in study [CLBH589B2102]

Encouraging preliminary efficacy has been seen in the 28 patients enrolled to study [CLBH589B2102] with a primary diagnosis of HL. As shown in Table 1-2 below, more than 80% of the patients had been treated with stem cell transplant. These patients were heavily pre-treated with antineoplastic therapies consisting of chemotherapeutic agents and radiotherapy.

Table 1-2 Demography and disease characteristics for HL patients enrolled in study [CLBH589B2102]

Parameter	Arm 1 Panobinostat dosed three times per week *every week*	Arm 2 Panobinostat dosed three times per week *every other week*
Number of patients treated[a]	18	10
Female/male	6 (33%) / 12 (67%)	2 (20%) / 8 (80%)
Median age, years [range]	34 [16-52]	31 [19-45]
Prior antineoplastic medication regimens [range]	5 [0-15]	5 [0-14]
Prior antineoplastic radiation regimens [range]	2 [0-7]	3 [0-12]
Number of patients with prior stem cell transplantation	15 (83%)	8 (80%)

a Data cut-off: October 17, 2008

More specifically, most patients received doxorobucin, bleomycin, vinblastine, dacarbazine (ABVD) at their first treatment.

Due to its significance in defining the entry criteria for this Phase II study, the use of gemcitabine-, or vinorelbine-, or vinblastine-containing regimens as part of prior treatments has been further assessed with regards to the timing of their use and for patients who achieved a response with panobinostat treatment.

Twenty-two of the 28 patients received a vinka-alkaloid in the first-line setting; seven patients received one of these agents in the second-line setting and 15 patients received these drugs after second relapse (third-line setting) or beyond. Only 4 patients received any of these drugs as a single agent at any time.

Responses, as assessed by CT scan and PET scan are shown in Table 1-3.

Table 1-3 CT and PET responses by dose and use of prior therapy with gemcitabine or vinorelbine or vinblastine at any time in patients with HL enrolled in study [CLBH589B2102]

Arm	Dose Level (mg)	Prior therapy with G/V/V N (%)	Number of Responders by CT N (%)	Number of Responders by PET N (%)
Arm 1	30 mg (n = 2)	1 (50.0)[a]	1 (50.0)	2 (100.0)
	40 mg (n = 11)	8 (73.0)[b]	5 (45.0)	8 (73.0)
	60 mg (n = 5)	5 (100.0)	1 (20.0)	1 (20.0)
Total-Arm 1	**n = 18**	**14 (77.8)**	**7 (38.9)**	**11 (61.1)**
Arm 2	45 mg (n = 3)	2 (67.0)[c]	1 (33.0)	1 (33.0)[e]
	60 mg (n = 7)	4 (57.0)[d]	0 (0.0)	3 (43.0)[e]
Total-Arm 2	**n = 10**	**6 (60.0)**	**1 (10.0)**	**4 (40.0)**
TOTAL PATIENTS	**N = 28**	**20 (71.4)**	**8 (28.6)**	**15 (53.6)**

Abbreviations: CT = computerized tomography; G = gemcitabine, PET = positron emission tomography; V = vinblastine or vinorelbine

a None of the 2 patients at the 30 mg dose level in Arm 1 received G/V/V after the 1st line treatment and 1 patient had a CT response

b Two patients at the 40 mg dose level in Arm 1 did not received G/V/V after the 1st line treatment and 1 of these 2 patients had a CT response

c Two patients at the 45 mg dose level in Arm 2 did not received G/V/V after the 1st line treatment and 1 of these 2 patients had a CT response

d Two patients at the 60 mg dose level in Arm 1 did not received G/V/V after the 1st line treatment and 2 of these patients had a CT response

In Arm 1 (MWF every week) at dose levels of 30 mg, 40 mg, or 60 mg, 11 of 18 patients (2 patients at 30 mg, 8 patients at 40 mg, and 1 patient at 60 mg) achieved a metabolic partial response (PR) as measured by positron emission tomography (PET) scan, and 7 of these 18 patients also achieved a PR as assessed by CT scan (1 patient at 30 mg, 5 patients at 40 mg and 1 patient at 60 mg). These 18 patients have completed a median of 4 cycles of treatment (range 1-18, 28 days/cycle), and 5 of 18 patients remain on study.

In Arm 2 (MWF every other week) 10 patients with relapsed/refractory HL have been enrolled to dose levels of 45 mg and 60 mg, and 4 have achieved a metabolic PR or CR (1 patient had a PR at 45 mg and 3 patients had a PR at 60 mg). One patient at the 45 mg dose had a PR by CT evaluation. In Arm 2, patients with Hodgkin's lymphoma have completed a median of 5.5 cycles of treatment (range 2-18) with 5 of 10 patients remaining on study (Ottmann, et al 2008).

As shown in Table 1-3, the use of gemcitabine, vinorelbine, or vinblastine-containing regimens as prior treatment did not seem to make a difference in the patients who achieved a response. Three of the 8 responders did not receive prior treatment with these specific drugs beyond 1st line treatment for HL. The number of prior chemotherapy regimens did not seem to make a difference for achieving response.

Phase I study of panobinostat in patients with hormone refractory prostate cancer

Study [CLBH589B2105] is a two-arm dose-escalating phase IA/IB study of oral panobinostat with and without docetaxel in patients with hormone refractory prostate cancer. In Arm I, single agent panobinostat was administered at 20 mg/day on days 1, 3, and 5 every week for two weeks followed by one week off. Eight patients were enrolled on this Arm. One AE was reported that met criteria for DLT (grade 3 dyspnea). In Arm 2, panobinostat dosing started at 15 mg/day on days 1, 3, and 5 every week for two weeks on/one week off in combination with docetaxel 75 mg/m^2 i.v. once every 21 days and prednisone 5 mg p.o. twice daily. Of the 8 patients treated on this Arm, 7 were considered eligible for MTD evaluation per protocol. One patient experienced a DLT (grade 3 neutropenia lasting > 7 days). One patient was discontinued from study treatment for febrile neutropenia, 1 patient had disease progression, 3 patients had stable disease, and 3 patients achieved partial response with 2 remaining on treatment as of March 2008. This study is now closed to enrollment in order to focus on development of the i.v. formulation of panobinostat in prostate cancer.

Phase I clinical experience with IV panobinostat

Two phase I, dose-escalation, single agent studies of panobinostat, administered as a 30-minute i.v. infusion examining various dose schedules of administration, were initiated.

[CLBH589A2101] is a first-in-human, multi-arm, dose-escalation phase I study in patients with advanced solid tumors or NHL. As of December 2007, 77 patients with a wide spectrum of solid tumors received i.v. panobinostat on three schedules of administration. Twenty-three patients were treated on Arm 1 [dosing on days 1-3, days 8-10 q21 days] at the following dose levels (mg/m^2/day): 1.2 (2 pts), 2.4 (3 pts), 4.8 (3 pts), 7.2 (7 pts), and 9 (8 pts). Seven patients were treated on Arm 2 [dosing on days 1-3, days 15-17 q28 days] at the following dose levels (mg/m^2/day): 2.4 (1 pt), 4.8 (1 pt), 9.6 (1 pt), 15 (3 pts), and 20 (1 pt). Forty-seven patients are treated on Arm 3 [dosing on days 1, 8, and 15 q28 days] at dose levels: 10 (8 pts), 15 (8 pts), and 20 (31 pts).

In [CLBH589A2101] Arm 1, DLT was observed in 1 patient at the 7.2 mg/m^2/day dose level (grade 2 thrombocytopenia). Four of 8 patients at the 9 mg/m^2/day dose level experienced DLT, grade 3/4 thrombocytopenia (3 pts) and grade 4 neutropenia (1 pt). The myelosuppression observed was transient and reversible. Due to myelosuppression, 9 mg/m^2/day was determined to be the DLT dose level, and 7.2 mg/m^2/day was determined the MTD dose level for Arm 1.

For [CLBH589A2101] Arm 2, no significant toxicity was observed at dose levels $\leq$ 9.6 mg/m^2/day. A patient treated at the 20 mg/m^2/day dose level had a prolonged QT interval, grade 3 sinus bradycardia, grade 4 neutropenia, grade 3 thrombocytopenia, grade 2 anemia, and grade 3 transaminitis. In addition, this patient had a temporary pacemaker placement and a 13 beat episode of Torsades de Pointes which was transient and did not cause hemodynamic compromise. When this episode occurred, 36 hours after the second dose of panobinostat, the patient had significant co-morbidities including prolonged QTc at baseline, hypokalaemia, bradycardia, and co-administration of medications that have been shown to be associated with prolonged QTc (i.e. granisetron, citalopram, and prochlorperazine). It was the judgment of the treating physicians that hematologic toxicity and transaminitis were related to panobinostat administration and a contribution of panobinostat to the cardiac events could not be ruled out. Enrollment was completed at a decreased dose of 15 mg/m^2/day for 3 patients and no toxicity was observed at this

dose level. For both arms, all other adverse events were not unexpected for a patient population with advanced cancers. No responses (CR or PR) have been reported.

In [CLBH589A2101] Arm 3 panobinostat was given once a week for 3 consecutive weeks and one week off. The dosing frequency was reduced from a 3-day consecutive dose to a weekly dose in effort to: 1) determine if the QTc prolongation is due to a drug accumulation effect; 2) reduce adverse events; and 3) improve drug tolerability. All patients in Arm 3 tolerated the lower dose levels. No DLTs were observed in the 10 or 15 mg/m^2 dose. Two patients on 15mg/m^2 experienced thrombocytopenia (grade 3) prior to receiving the day 15 dose. Thrombocytopenia was transient and reversible in ≤ 4 days. In the 20 mg/m^2 dose, six of the 31 enrolled patients have experienced grade 3/4 thrombocytopenia (lasting > 7 days) and five (grade 3) anemia. In addition, patients experienced (grade 3) dyspnea, cardiac failure, atypical dermatitis, fatigue, hypotension, and/or leucopenia while on study. In this study arm, 11 patients with prostate cancer were treated; one patient, treated weekly at the 20 mg/m^2 dose, had a PR per RECIST and a > 50% decrease in PSA (ongoing response after 9 treatment cycles).

When panobinostat is given IV once weekly the greatest increases in QTcF seems to occur after the first weekly dose. For reasons that are still not understood, QTcF interval prolongation substantially diminishes with subsequent weekly doses. The maximum increase in QTcF occurs approximately 26 hours after the first infusion has been given, and with the 20 mg/m^2 dose the QTcF increases from baseline by an average of 18 msec (95% CI = 11-25 msec) at this point in time. Mean increases in QTcF at points before and after are lower, and by 48 hours post-infusion there is no perceptible effect of the treatment on the QTcF interval. Of 1247 ECGs performed on 21 patients treated at the 20mg/m^2 dose, there were 3 QTc outliers; one ≥ 500msec and two > 60msec from baseline. This data suggests that there is not a strong QTc signal when panobinostat is administered on a day 1, 8, 15 of a 28-day schedule.

Study [CLBH589A2102] is a two-arm, dose-escalation phase IA/II study in patients with advanced hematologic malignancies examining two dose schedules of administration. In Arm 1 (dosing on days 1-7 q21 days), 15 patients were treated at the following dose levels (mg/m^2/day): 4.8 (3 pts), 7.2 (3 pts), 9.0 (1 pt), 11.5 (3 pts), 14.0 (5 pts). Four DLTs (grade 3 QTcF prolongation) have been observed, in 3 patients at 14.0 mg/m^2 and in 1 patient at 11.5 mg/mg^2. All patients with QTcF prolongation were asymptomatic and recovered upon discontinuation of panobinostat. One patient treated at 14.0 mg/m^2 died of pulmonary hemorrhage resulting from sepsis while on study. Treatment with panobinostat as well as the patient's underlying disease (MDS) were considered contributing factors to the sepsis. A white cell differentiation syndrome (which was successfully treated with high-dose steroids) was observed in 1 patient with refractory AML treated at 14.0 mg/m^2. Arm 2 was not opened to enrollment.

Human pharmacokinetics

Following a single oral dose administration, the PK profile of panobinostat was best described by a rapid absorption phase with a large volume of distribution followed by a biphasic distribution and elimination. Maximum plasma concentration (C_{max}) was reached within 1 hr (range 0.5-3 hrs) and a large volume of distribution was consistent with an extensive tissue distribution as seen in the animals (Figure 1-2). Panobinostat systemic exposure and C_{max} increased linearly with doses (10-80 mg) but with moderate inter-patient variability (CV% in AUC = 60%) (Table 1-3). Both C_{max} and AUC increased slightly after every MWF administrations of panobinostat with an AUC ratio (R value ~1.4) which was consistent with the terminal half-life and dosing interval. The mean terminal half-life was estimated to be 15.6 (± 5)

hours. Absolute bioavailability was estimated to be 31% (23-40%) with an inter-study comparison (CLBH589A2101, CLBH589B2101, and CLBH589B2102).

Food influence on panobinostat PK was evaluated in patients with advanced cancer who received 20 mg panobinostat twice a week and were randomized to receive 1 of 6 treatment sequences where PK was evaluated weekly under fasting, high fat, and normal breakfast conditions [CLBH589B2111]. The overall exposure and inter-patient variability (CV 59%) in 34 patients remained unchanged with or without food, whereas C_{max} was transiently reduced (<45%) by food (i.e., both normal and high fat breakfast). Since the overall extent of absorption was not altered by food, food is unlikely to significantly impact panobinostat's systemic exposure in cancer patients. It is recommended that panobinostat can be administered without regard to food in future studies.

Figure 1-1 Mean plasma concentrations of panobinostat following a single i.v or oral panobinostat administration

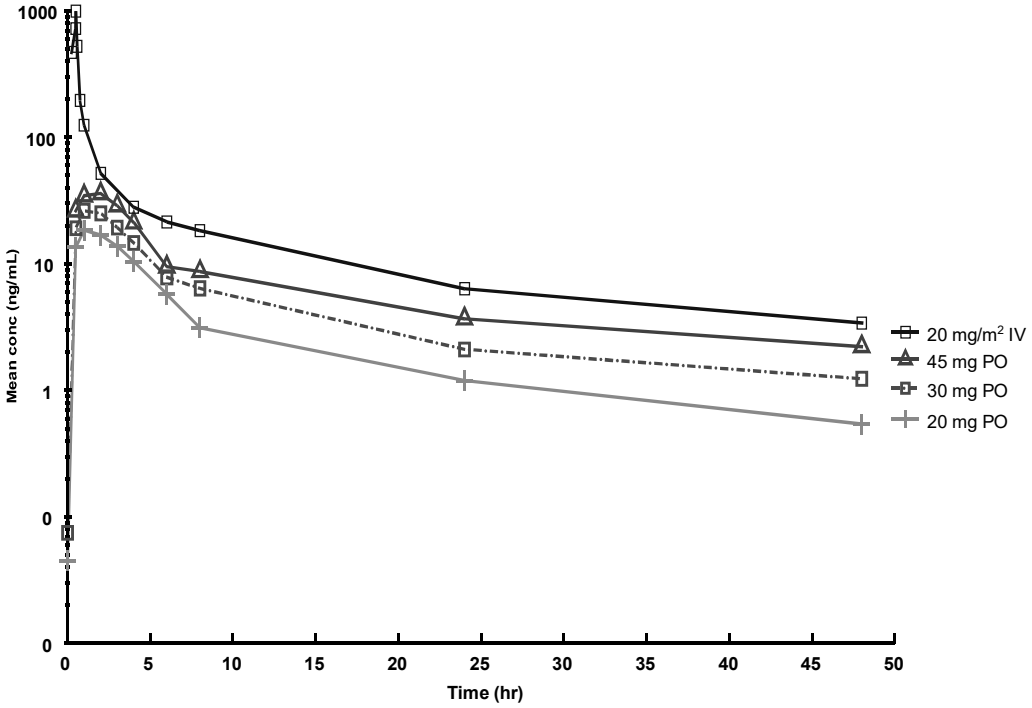


Table 1-4 Mean panobinostat PK parameters following i.v. or oral administration

Daily dose (No. of patients)	Median T_{max} (hr)	Mean [CV%] C_{max} (ng/mL)	Mean [CV%] $AUC_{0-\infty}$ (ng*hr/mL)
PO 20 mg (n=42)	1	23 [57]	183 [56]
PO 30 mg (n=40)	1	37 [55]	288 [51]
PO 40 mg (n=14)	0.7	48 [67]	235 [65]
IV 20 mg/m^2 (n=26)	0.48	836 [48]	922 [42]
Abbreviations: IV = intravenous, PO = oral			

Preliminary pharmacodynamic analysis evaluating acetylated histones status in peripheral blood mononuclear cells (PBMCs) revealed that acetylated histones were maintained over 72 hours in majority of the patients, supporting a three-times weekly schedule [CLBH589B2101].

Panobinostat underwent reduction, oxidative metabolism, hydrolysis, and glucorindation in human livers. The oxidative metabolism of panobinostat was found to be mediated by CYP3A4/5 and CYP2D6 in human liver microsomes, of which CYP3A contribution is major. Using results from clinical drug-drug interaction study [CLBH589B2110], it is predicted that panobinostat fraction metabolized by CYP3A is 37.5% (Ohno, et al 2008).

A clinical drug-drug interaction study between ketoconazole, a potent CYP3A inhibitor, and panobinostat was evaluated in 14 cancer patients in study [CLBH589B2110]. Single-dose panobinostat at 20 mg did not change ketoconazole concentrations. Multiple ketoconazole doses at 400 mg increased C_{max} and AUC of panobinostat by 1.6- and 1.7-fold, respectively, but with no change in T_{max}. The < 2-fold increase in panobinostat AUC upon co-administration suggests that CYP3A contribution to the total panobinostat clearance is low. The observed interaction is not considered clinically relevant, as panobinostat doses at least 2-fold greater than 20 mg (40 mg and 60 mg) have been safely administered in patients. CYP3A4 inhibitors should have no major impact on the exposure of panobinostat and may be co-administered when medically necessary.

Electrocardiographic experience with panobinostat

Panobinostat i.v.

A total of 3,272 pre- and post-dose ECGs have been collected from 47 patients who received intravenous panobinostat at various doses in 2 Phase I studies as shown in the table below.

Table 1-5 Studies and the number of patients evaluated for QTcF monitoring in the intravenous panobinostat studies

Study Number	Dose (mg/m^2)	Number of Patients	Number of ECGs
CLBH589A2101 (Dosing on Days 1, 8, and 15 every 28 days)	10.0	8	579
	15.0	8	656
	20.0	31	2037
CLBH589A2102 (Dosing on Days 1-7 every 21 days - a schedule that will not be further explored)	4.8	3	40
	7.2	3	25
	9.0	1	12
	11.5	3	30
	14.0	5	42

The maximum mean change of QTcF from baseline was noted to be 17.95 msec (range of QTcF change from baseline values = -64.66 msec: 126.83 msec). A delayed effect for maximal QTcF increase was noted at approximately 24 hours after dosing. However, at the highest dose (20 mg/m^2), similar elevations of approximately 10 msec – 18 msec were observed spanning from 4 hours post-1^{st} dose to day 2.

- Four patients had at least 1 ECG that was > 60 msec increase from baseline or absolute QTcF > 500 msec
  - Two of these patients had the ECG finding sometime in the first two days, but at least 4 hours post-dose.
  - The third patient experienced the >60 msec increase during cycle 3
  - The fourth patient had a QTcF value of 512 msec on day 2. This patient was the only one on the weekly IV schedule to experience QTcF > 500 msec.

All four patients experiencing either > 60 msec increase or QTcF > 500 msec were at the highest dose. In addition, in Arm 2 of [CLBH589A2101] there was one event of Torsades de Pointe in a patient treated at the 20 mg/m^2/day dose, 36 hours after 2 consecutive iv dosings, who entered the study with hypokalaemia, and at time of event was using drugs that are known to prolong QT (i.e. citalopram, prochlorperazine and granisetron) and presenting with bradycardia (see Section 1.2.6).

Additionally, 2,249 post-dose ECGs obtained from 55 patients enrolled to the [CLBH589A2101] and [CLBH589A2102] i.v. studies (where a daily x 3 schedule was used) were analyzed for changes in QTc interval duration. These schedules are no longer in use. For Arms 1 & 2, central tendency analysis (mean change from baseline) demonstrated no measurable change in QTc in the 24 hours after day 1 dosing. However, a dose related increase in QTc of < 20 msec was detected after day 3 of dosing. An analysis of outlier ECGs (ECGs with > 60 msec change from baseline and/or absolute QTcF > 500 msec) demonstrated that 10 of the 12 patients with at least 1 outlier ECG, had their initial outlier ECG on day 3 of dosing or later.

Together these data suggests that panobinostat has a delayed effect on QTc, and that the effect may require administration of consecutive doses. In Arm 3 of study [CLBH589A2101] where a weekly schedule was used, only two out of 47 patients experienced a QTcF change from baseline > 60 msec and one patient experienced a new absolute QTcF ≥ 500 msec. This data suggests that accumulation of panobinostat from the daily x 3 dosing may have contributed to the delayed effect on QTc while the QTc change is less apparent from the weekly dosing schedule.

Panobinostat oral

As of November 2007 a total of 5549 ECGs have been collected from 132 patients who received oral panobinostat at a dose of 20 mg three times every week in a 28 day cycles. Of the 132 patients, 44 patients were treated in the two phase I studies (CLBH589B2101 and CLBH589B2102) and 108 have been treated in four disease specific phase II studies enrolling patients with CTCL, multiple myeloma, chronic myelogenous leukemia (CML) or CML with blast crisis. Patients had received panobinostat for a mean number of 66 days (range 1-815 days; SD = 87 days).

Preliminary analysis of the data suggests that panobinostat is generally well tolerated with minimal effects on QTc interval following oral dosing.

The mean change of QTcF from baseline was less than 5 msec for time points at which data were available for more than 6 patients. The maximum change from baseline was seen in Cycle 1, Day 5, Hour 3 = 4.20 msec [range of QTcF change from baseline values = 26.83 : 70.83] and a slight delayed effect was noted.

A total of 8 patients have been considered as outliers (ECG findings of QTcF > 480 msec or change of > 60 msec from baseline):

- Number of patients with QTcF > 500 msec = 2
- Number of patients with QTcF > 480 msec but < 500 msec and a QTcF change from baseline > 60 msec = 2
- Number of patients with QTcF > 480 msec but < 500 msec and a QTcF change from baseline < 60 msec = 1
- Number of patients with only QTcF change from baseline > 60 msec = 3

In all patients with prolonged QTcF or with >60 msec change from baseline, confounding factors were present (e.g., hypokalaemia, severe bradycardia, pulmonary embolism, myocardial infiltration in context of hypereosinophilia, complete left bundle branch block, atrial fibrillation) and could have contributed to the prolongation. Additionally, continuation of dosing despite the finding of QTcF prolongation (after a break) did not worsen the observation and in most cases, the ECG reverted to baseline or normal.

The timing of the QTcF prolongation or observation of > 60 msec change from baseline in these studies have been:

- Day 1 of Cycle 1 - 1 patient
- Day 5 of Cycle 1 and on Day 113 - 1 patient
- Day 5 of Cycle 1 and Day 15 - 1 patient
- Day 5 of Cycle 1 - 3 patients
- Day 17 of Cycle 1 - 1 patient
- Day 26 of Cycle 1 - 1 patient

No patient dosed at the 20 mg/dose on MWF experienced prolongation of QTc in Cycle 2 or beyond except for the 1 patient (on Day 113 as stated above).

A review of the serious adverse events received by Novartis as recommended in the guideline ICH E14 (i.e. sudden death, ventricular arrhythmia, ventricular tachycardia, syncope, seizures) found 3 additional cases of QTc prolongation. These were reported as syncope. In these 3 cases confounding factors of vasovagal signs and hypotension were present.

In study [CLBH589B2102], 2,584 post-dose ECGs have been reviewed centrally on 77 patients who all received dose levels higher than 20 mg (i.e. 30 mg, 40 mg, 60 mg, and 80 mg) on various dosing schedules. Among those, 1384 post-dose ECGs have been centrally reviewed in 43 patients who all received doses on the MWF weekly schedule specifically. The following results were found:

- 30 mg dose: 391 ECGs in 12 patients - no event of QTcF > 500 msec or QTcF > 60 msec increase from baseline
- 40 mg dose: 540 ECGs in 16 patients - no event of QTcF > 500 msec or QTcF > 60 msec increase from baseline
- 60 mg dose: 370 ECGS in 12 patients, 1 patient with QTcF to >500 msec, and 2 patients with QTcF > 60 msec increase from baseline

- 80 mg dose: 83 ECGs in 3 patients, 1 patient with QTcF to >500 msec, and 2 patients with QTcF > 60 msec increase from baseline

In the phase I studies, cardiac troponin, creatinine phosphokinase (CK) and MB isoenzyme of CK (CK-MB) were tested at baseline and Day 8 of cycle 1, CK and CK-MB were slightly elevated in 2 patients but not clinically significant. Based upon the available data, panobinostat oral has demonstrated minimal clinically meaningful ECG changes to date.

Relationship between panobinostat plasma concentrations and QTcF

As presented in Figure 1-3 (i.v.) and Figure 1-4 (po) below, the maximum change of QTcF from baseline does not coincide with the peak plasma concentration-time course of panobinostat for either route of administrations suggesting a possible delayed effect.

It is noteworthy (as shown in Table 1-3) that the mean maximum concentration (C_{max}) and overall exposure (AUC) for the oral formulation is at least 30-fold and 5-fold, respectively lower than that has been seen with intravenous panobinostat. It does not appear that QTcF change is directly related to panobinostat plasma concentrations.

Figure 1-2 **QTcF change from baseline over time vs. panobinostat conc-time course following the first intravenous panobinostat weekly doses**

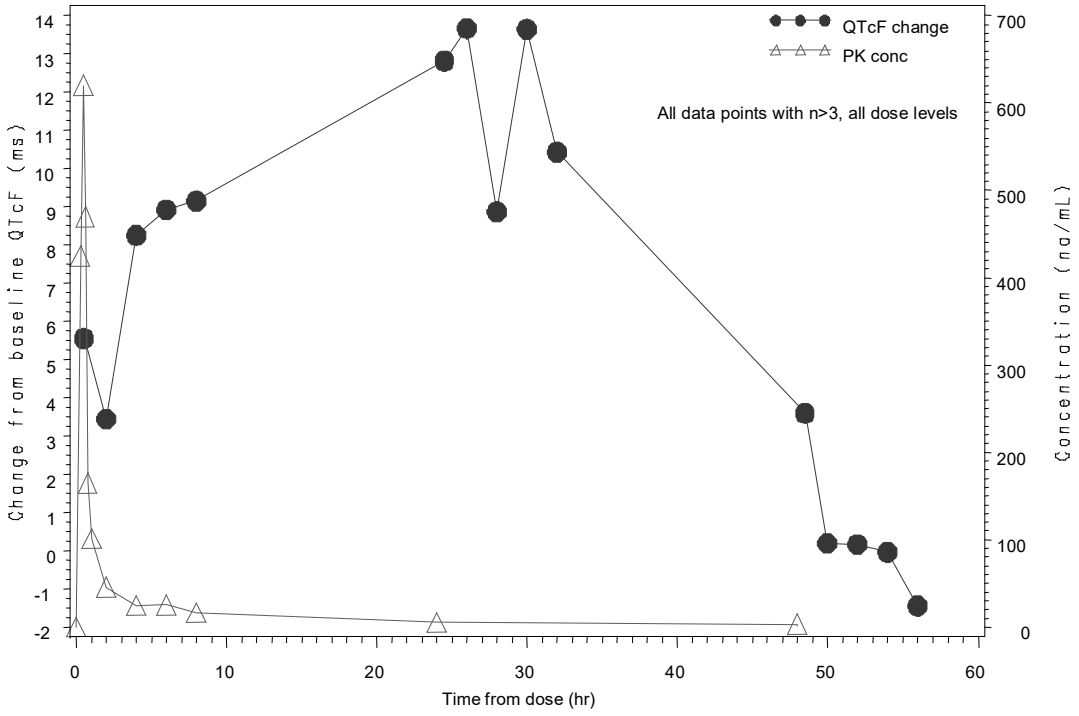
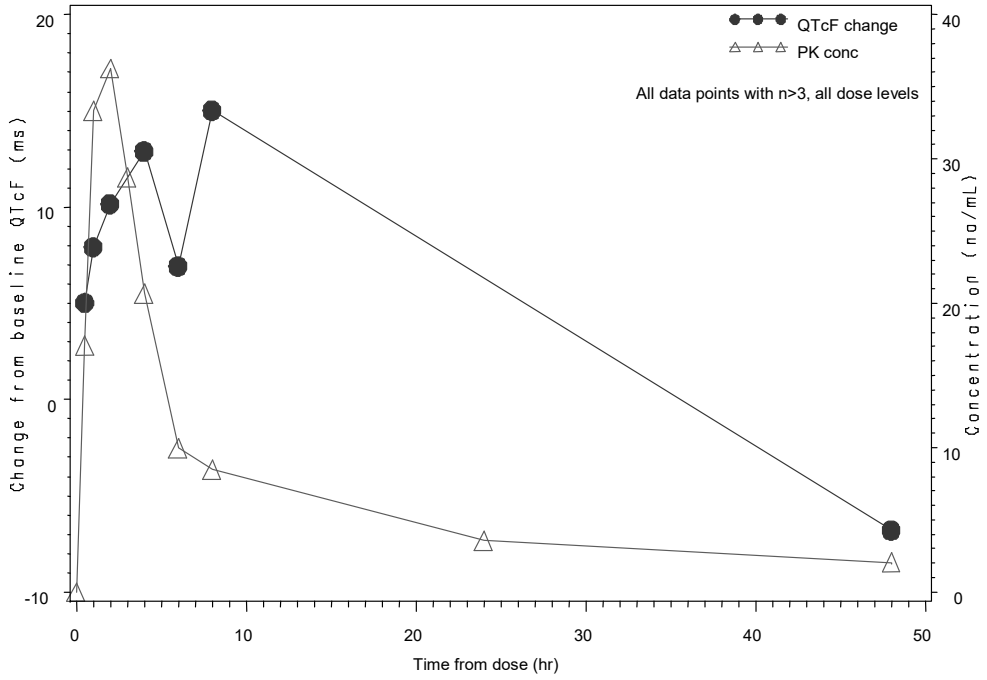


Figure 1-3 QTcF change from baseline over time vs. panobinostat conc-time course following the first oral panobinostat doses of a MWF schedule



Biomarker analysis

Chemokine production, including TARC (CCL17) and MDC1 (CCL22), are the major mechanism by which RS cells drive the intratumoral accumulation of reactive cells (Hasenclever and Diehl 1998). Crucially, TARC and MDC1 levels are elevated in the blood of HL patients and levels fall in response to therapy. Eotaxin is an eosinophil specific chemotactic agent secreted by tumour associated fibroblasts, and serum levels correlate directly with the degree of eosinophilic infiltration in HL, which has historically been correlated with a poorer survival. Pre and post-Panobinostat levels of TARC, eotaxin and MDC1 will be monitored and correlated to PET responses.

The intense inflammatory infiltrate induced by the HL cells is driven by cytokine and chemokine secretion. IL-10 is an anti-inflammatory cytokine secreted by RS cells, which down-regulates the Th1 immune response (normally associated with increased IFN-gamma and IL-2 and decreased IL-4, IL-10, and TGF-beta) in HL and is associated with an inferior overall response to chemotherapy (Barath, et al 2006). Activated TGF beta is also secreted by RS cells and eosinophils, stimulating fibroblast proliferation and collagen synthesis, and high serum levels are consistently associated with nodular sclerosing HL. Pre and post-panobinostat levels of IL-2, IL-4, IL-10, IFN-gamma and TGF-beta will be measured and correlated with PET responses.

In order to assess biomarkers such as Akt in archival tissue and to correlate with response to panobinostat, collection of the archival tumor sample is required when available.

Exploratory analysis to assess changes in adaptive immunity as a surrogate marker of the reactive cellular infiltrate may be performed by optional patient consent. Changes in the protein acetylation status of circulating T-cells may also be assessed as a surrogate marker of the reactive cellular infiltrate.

2 Study rationale/purpose

Our in vitro preclinical data indicate that LBH589 shows high activity on WM cells from patients and WM cell lines. HDAC activity in WM cells is elevated, indicating that targeting HDAC will lead to cytotoxicity of the cells. LBH589 has significant clinical activity in other lymphomas and other hematological malignancies. Based on this data, we believe that LBH589 will demonstrate a high response rate in patients with relapsed or refractory WM.

3 Study objectives

3.1 Primary

The primary objective of the phase II study is to assess the overall response rate (CR+nCR+VGPR+PR+MR) in patients with relapsed or relapsed/refractory WM.

3.2 Secondary

1. To evaluate the safety of LBH589 in patients with relapsed or relapsed/refractory WM.

2. To assess duration of response, time to progression, and progression free survival in these patients.

3. To determine the pharmacodynamic effects of LBH589 on histone acetylation, induction of apoptosis and activity on the NFkB and Akt pathways in samples obtained pre and post-treatment with LBH589.

4 Overall study design

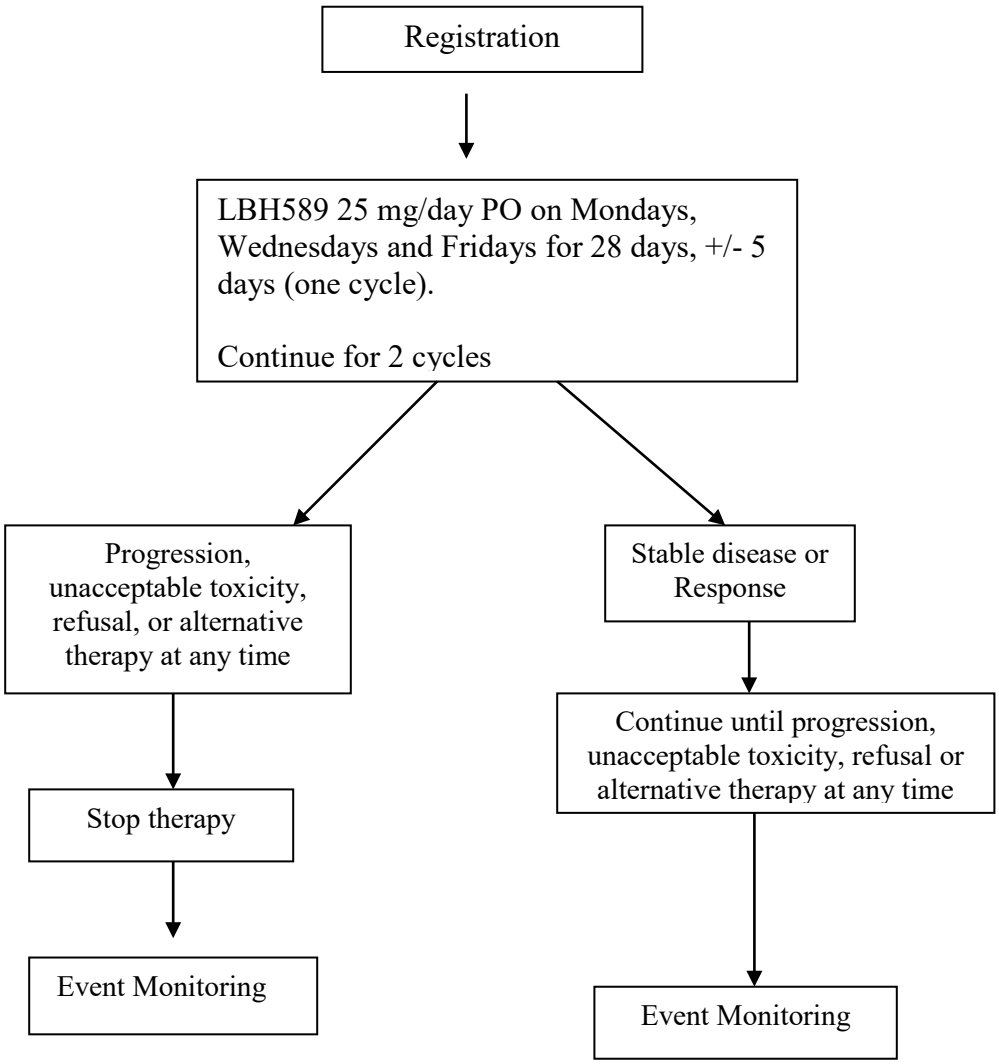
This phase II study is designed to assess the toxicity profile and the proportion of overall confirmed responses (CR+nCR+VGPR+PR+MR) in patients with relapsed or refractory WM. This will study the effect of single agent LBH589 on response in these patients.

A cycle will be 28 days (+/- 5 days). Response will be assessed after 2 cycles. If patients have stable disease or response, then they will continue on therapy until progression or unacceptable toxicity. Patients who show progression after 2 cycles will come off therapy.

Protocol Schedule: 25 mg/day PO on Mondays, Wednesdays and Fridays for every cycle.

A cycle is 28 days (+/- 5 days).

Patients will be assessed for toxicity and response after 2 cycles and then after every cycle for the first 6 cycles at the participating center. After 6 cycles, patients will be assessed every 3 months for response at the participating center.



5 Study population

5.1 Patient population

A minimum of 14 and a maximum of 37 patients will be enrolled on this phase II study.

5.2 Inclusion and exclusion criteria

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by a participating Investigator prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

Inclusion criteria

1. Male or female patients aged ≥ 18 years old.
2. Ability to provide written informed consent prior to participation in the study and any related procedures being performed.
3. Patients must have received prior therapy for their WM, any number of prior therapies is allowed.
4. Patients must have relapsed or refractory WM. Patients with relapsed WM must be symptomatic and/or have a ≥ 25% increase in their serum monoclonal IgM protein from their last treatment. Patients with refractory WM must have no response to prior therapy for at least 3 months.
5. Monoclonal IgM protein in the blood of ≥ 0.5 g/dL and ≥ 10% lymphoplasmacytic cells in the bone marrow during any previous bone marrow.
6. Patients must meet the following laboratory criteria:
   - ANC ≥ 1.0 x 10^9/L
   - Hemoglobin ≥ 8 g/dl
   - Platelets ≥ 75 x 10^9/L
   - AST and ALT ≤ 3 x ULN
   - Serum bilirubin ≤ 1.5 x ULN
   - Serum potassium ≥ LLN
   - Calculated serum creatinine clearance ≥ 50 mL/min
   - Serum magnesium ≥ LLN
   - Serum phosphorus ≥ LLN
7. Clinically euthyroid

   Note: Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.

8. ECOG Performance Status of ≤ 2

Exclusion criteria

1. Prior HDAC, DAC, HSP90 inhibitors or valproic acid for the treatment of cancer.
2. Patients who will need valproic acid for any medical condition during the study or within 5 days prior to first LBH589 treatment.
3. Peripheral neuropathy ≥ CTCAE grade 2.
4. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
   - Patients with congenital long QT syndrome
   - History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia are eligible but should be discussed with the Principal Investigator prior to enrollment)
   - Any history of ventricular fibrillation or torsade de pointes
   - Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
   - Screening ECG with a QTc > 450 msec
   - Right bundle branch block + left anterior hemiblock (bifascicular block)
   - Patients with myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
   - Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV , uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
5. Impairment of GI function or GI disease that may significantly alter the absorption of LBH589.
6. Patients with diarrhea > CTCAE grade 1.
7. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes or active or uncontrolled infection) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol.
8. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsade de pointes if treatment cannot be discontinued or switched to a different medication prior to starting study drug.
9. Patients who have received targeted agents within 2 weeks or within 5 half-lives of the agent and active metabolites (which ever is longer) and who have not recovered from side effects of those therapies.
10. Patients who have received chemotherapy or rituximab within ≤ 3 weeks; or radiation therapy to > 30% of marrow-bearing bone within ≤ 2 weeks prior to starting study treatment; or who have not yet recovered from side effects of such therapies.
11. Patients who have received corticosteroids ≤ 2 weeks prior to registration. Patients may be receiving chronic corticosteroids if they are being given for disorders other than Waldenstrom's Macroglobulinemia (e.g. hemolytic anemia).

12. Patients with an active bleeding tendency or receiving any treatment with therapeutic doses of sodium warfarin (Coumadin®) or coumadin derivatives. Low doses of Coumadin® (e.g. ≤ 2 mg/day) to maintain line patency (if applicable) is allowed.
13. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
14. Women who are pregnant or breast feeding or women of childbearing potential (WOCBP) not using an effective method of birth control. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or women ≥ 55 years of age who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months). Women of childbearing potential must have a negative serum pregnancy test within 7-days of registration.
15. Male patients whose sexual partners are WOCBP not using effective birth control.
16. Patients with a prior malignancy within the last 5 years (except for basal or squamous cell carcinoma, or *in situ* cancer of the cervix).
17. Patients with known positivity for human immunodeficiency virus (HIV) or hepatitis C; baseline testing for HIV and hepatitis C is not required.
18. Patients with any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to him/her by the study staff.

6 Treatments

6.1 Investigational therapy

LBH589 will be provided by Novartis. Oral LBH589 will be supplied as 5 mg or 20 mg pink/opaque-colored, hard gelatin capsules.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

During the study, LBH589 will be administered orally as 25 mg/day orally on Mondays, Wednesdays and Fridays.

Patients should be instructed to take their oral dose of LBH589 at the same time each morning during cycle 1. Patients may choose to take their LBH589 in the morning or evening after the completion of cycle 1. Each dose of LBH589 should be taken with an 8 oz / 240 ml glass of water, with or without food. Patients should be instructed to swallow the capsules whole and not chew them. Patients must avoid grapefruit or grapefruit juice and seville (sour) oranges during the entire study.

If the patient forgets to take his/her dose at the scheduled time on treatment day, then he/she should take LBH589 on that same day within 12 hours after the missed dose if possible. After more than 12 hours, that day's dose should be withheld, and the patient should wait to take LBH589 until the next scheduled treatment day (i.e., patients should be instructed not to try to make-up the missed dose after 12 hours). The patient should then continue treatment with the original dosing schedule.

If the patient vomits after taking LBH589, that dose should be skipped. The patient is not to take another LBH589 capsule.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study should be recorded.

6.1.1 Cardiac precautions

All patients must have an assessment of serum potassium, calcium, phosphorous and magnesium ≤ 72 hours prior to the administration of oral LBH589 on day 1 of cycle 1 and the results must all be ≥ LLN before the first dose of LBH589 is administered. Throughout the study serum biochemistry values including serum potassium, calcium, phosphorous and magnesium will be monitored closely. On any day and time in which serum potassium, calcium, phosphorous and magnesium are assessed, if the value is < LLN, then the patient's potassium, calcium, phosphorous or magnesium should be immediately supplemented following the availability of that laboratory result, in order to minimize the time patients have low values. Patients must then undergo a repeat biochemistry test to demonstrate values ≥ LLN. These values must be ≥ LLN before the patient is re-dosed with oral LBH589.

Patients must be instructed to not take LBH589 if their most recent biochemistry values demonstrates potassium, calcium, phosphorous or magnesium < LLN. At a minimum, potassium, calcium, phosphorous and magnesium will be checked according to the protocol. More frequent testing should be done if clinically indicated, e.g. patient has had prior low values, patient is taking medications (e.g., diuretics) that can result in lowering of their potassium, calcium, phosphorous or magnesium levels.

6.2 Treatment cycle and duration*:*

A treatment cycle is 28 days (+/- 5 days). Patients will be assessed every 28 days (+/- 5 days). After 6 cycles of monthly evaluations, patients will be assessed every 3 months (+/- 7 days).

Patients may continue treatment with oral LBH589 until they experience unacceptable toxicity that precludes further treatment, disease progression, and/or at the discretion of the investigator. Please see Section 6.3.4 for further details.

6.3 Dose modification, interruption or discontinuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. If administration of LBH589 must be interrupted because of unacceptable toxicity, drug dosing will be interrupted or modified according to rules described in Tables 6-1 and 6-2 and Figure 6-1. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). All interruption or changes to study drug administration must be recorded.

6.3.1 Dose modifications for non-hematologic adverse events (see section 6.3.2 for dose modifications for prolonged QTc):

Table 6.1 Criteria for dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related toxicity (excluding QTc prolongation)

Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf). Treatment modifications are based on adverse events. Each adverse event should be assessed for relationship to LBH589 so that modifications can be made accordingly. Further clarification can be obtained in consultation with the PI. If multiple toxicities are noted, the dose adjustments should be made according to the most severe toxicity guidelines. Dose modification recommendations listed below are general guidelines, and appropriate dose adjustments for patient safety should be done if needed after approval by the PI or her representative.

Dose modifications may be made at any time during a cycle of therapy. Toxicities will be collected and monitored throughout each cycle.

If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. If however the patient was clearly benefiting from LBH589 therapy, the patient may be able to continue treatment with a 10 mg dose reduction at the Investigator discretion, after resolution of the adverse event.

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)	**Dose Modification Guidelines at any time during a cycle of therapy (including intended day of dosing)**	
HEMATOLOGIC TOXICITIES		
Thrombocytopenia	Grade 4 (< 25 x 10^9/L)	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 2, or baseline, then: - restart LBH589 reduced by one dose level
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L)	Temporarily discontinue LBH589dosing until resolved to ≤ grade 3, or baseline, then: - if resolved within 7 days after suspending LBH589, then restart LBH589at an unchanged dose level - If resolved in more than 7 days after suspending LBH589, then restart LBH589reduced by one dose level
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5 ºC)	Temporarily discontinue LBH589 dosing until fever resolved and ANC ≤ grade 2, then restart LBH589 reduced by one dose level
NON-HEMATOLGOICAL TOXICITIES		
CARDIAC		
Cardiac – Prolonged QT interval **		Please refer to Section 6.3.2

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)	**Dose Modification Guidelines at any time during a cycle of therapy (including intended day of dosing)**	
GASTROINTESTINAL		
Diarrhea	Grade 2 (4-6 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 1, or baseline, then restart at unchanged dose level
	Grade 3 (≥ 7 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 1, or baseline, then restart LBH589 reduced by one dose level.
	Grade 4 (life-threatening consequences, hemodynamic collapse, etc.) despite the use of optimal antidiarrheal medications	Discontinue LBH589 dosing
Vomiting/Nausea*	Grade 1 & 2 not requiring treatment or controlled using standard anti-emetics	Maintain dose level
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 1, or baseline then restart LBH589 reduced by one dose level
FATIGUE		
Fatigue	Grade 3	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 2, or baseline, then: - if resolved within 7 days after suspending LBH589, then restart LBH589 at an unchanged dose level - If resolved in more than 7 days after suspending LBH589, then restart LBH589 reduced by one dose level
Fatigue	Grade 4	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 2, or baseline, then - restart LBH589 reduced by one dose level

Worst Toxicity CTCAE Grade* unless otherwise specified (Value)	**Dose Modification Guidelines at any time during a cycle of therapy (including intended day of dosing)**	
HEPATIC		
Total Bilirubin	Grade 3 or 4	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 2, or baseline then restart LBH589 reduced by one dose level
Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduction of one dose level and continuation of treatment is at the discretion of the Investigator)		
AST/SGOT, ALT/SGPT	> 5-10 x ULN	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 1 (or ≤ grade 2 if liver infiltration with tumor is present), or baseline, then: - If resolved within 7 days, then: -restart LBH589 at unchanged dose level - If resolved in more than 7 days, then reduce LBH589 by one dose level
	> 10 x ULN	Temporarily discontinue LBH589 dosing until resolved to ≤ grade 1, or baseline then: - restart LBH589 reduced by one dose level
Glomerular filtration rate	Calculated GFR > 30 mL.min	No change in dosing
	Calculated GFR 30 – 20 mL/min	Omit LBH589 until resolved < grade 1. Restart LBH589 with one dose-reduction
	Calculated GFR < 20 mL/min OR Chronic dialysis OR Renal transplantation	Omit LBH589 and discontinue participant from study.
All dose modifications should be based on the worst preceding toxicity.		
* Common Terminology Criteria for Adverse Events (CTCAE Version 3.0)		
** It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing		
***See also concomitant medication Section 6.4		

6.3.2 Dose modifications for prolonged QTc

QTc monitoring schedule

Patients on this study will have extensive QTc monitoring on specified days. If a prolonged QTc interval is noted, additional days of extensive QTc monitoring may be required (see details below). Treatment decisions will be based on QTc as determined by the automated machine reading at Dana-Farber Cancer Institute (DFCI) or participating centers (or as measured and calculated by trained personnel at DFCI or participating centers).

All ECG tracings will be submitted to eRT for central review and results will be faxed back to DFCI or participating center within 3 working days (72hr turn-around time). The ECG interpretations from eRT will be the formal data entered into the clinical trial database.

ECG requirements:

Screening:

- Single ECG to assess eligibility.

Baseline/Cycle 1:

- Pre dose ECGs on cycle 1 day 1: 3 ECGs will be performed 5-10 minutes apart before the first dose. On day 1 post the first dose, 3 ECGs will be performed 5-10 minutes apart 3 hrs post dose. On day 5 (+ 2 days), 3 ECGs pre-dose, and 3 ECGs 3-hours post dose will be performed (these ECGs may be completed at the participant's local doctor's office and faxed to the participating center, see note below). These ECGs will be performed only for the first cycle.

Cycle 2 through Cycle 8:

- Three pre-dose ECGs will be performed 5-10 minutes apart on Day 1.

Note: If participants choose to have Cycle 1 Day 5 ECGs performed at their local physician's office, they will be given the information sheet provided in Appendix 6. This information sheet must accompany them to their doctor's office at the time of the ECGs. Participants are only to proceed with LBH589 dosing after the ECGs have been sent, and reviewed by a study doctor at DFCI or participating center.

Note: If participants experience QTc > 480 msec in Cycle 1 or in any subsequent cycle, then repeat Cycle 1 monitoring schedule until they have a Cycle with no QTc prolongation.

Note: If no significant QTc prolongation is noted during first 8 Cycles, the QTc monitoring is no longer required and may be performed at the Investigator's discretion, if medically indicated.

At end of treatment

- A single ECG will be performed at the end of study treatment

Table 6.2 outlines the criteria for interruption and re-initiation of LBH589 treatment due to QTc changes. Table 7-2 outlines the schedule for ECG monitoring.

General monitoring principles

1. On treatment days when ECGs are to be obtained, the patients will take their medication in the clinic. For the multiple pre-dose ECGs, the <u>average</u> of the QTc intervals must be ≤ 450 msec before the patient is dosed.

2. If the patient does not meet the QTc criteria for dosing at any time, the Principal Investigator must be notified immediately. In addition, the patient's serum potassium, magnesium, calcium and phosphorus must be measured immediately, and the patient must receive supplements to correct any low values.
3. At any time, if any ECGs (pre- or post-dose) demonstrate a QTc value ≥ 480 msec the Principal Investigator must be notified and transmit ECGs to DFCI immediately. In addition, the patient's serum potassium, magnesium, calcium and phosphorus must be measured immediately, and the patient must receive supplements to correct any low values.

   Any final decisions concerning any dose modification or patients discontinuing study drug permanently will be based on assessments of the ECG by the Principal Investigator at the Dana-Farber Cancer Institute and evaluated via a discussion with the Principal Investigator.
4. In general, dose reductions will occur in the following circumstances:
   - Repeat dosing delays due to prolonged QTc intervals
   - Multiple QTc ≥ 480 msec but < 500 msec
   - Any QTc ≥ 500 msec but < 515 msec

   For patient's requiring a dose reduction, extensive ECG monitoring will be done on the first day of the new reduced-dose as well as 5 and 26 days following the first day of the lowered dose.
5. Any QTc ≥ 515 msec will lead to the patient being permanently discontinued from study treatment.

All other cardiac events should be treated as per the local standard of care or referred to a Cardiologist by the investigator (if clinically indicated)

Table 6.2 Criteria for dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related QTcF abnormalities

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
Cycle 1 dose modification criteria:		
Pre-dose on cycle 1, days 1 and 5: 3 ECGs separated by 5-10 minutes, obtained prior to panobinostat dosing		**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Notify Sponsor and transmit to eRT immediately for prompt review.
	Day 1: Average QTcF > 450 msec	If abnormality noted on Day 1 of Cycle 1: Repeat 3 pre-dose ECGs. If the 3 pre-dose ECGs: **Do not meet** criteria again, discontinue patient from study. **Do meet** criteria for dosing; administer study drug treatment.
	Day 5: Average QTcF: ≥ 480 msec to < 500 msec OR > 60 msec increase from baseline average	If abnormality noted on Day 5 of Cycle 1: Delay dose at least 3 days and repeat 3 pre-dose ECGs. If the repeat 3 pre-dose ECGs: **Do not meet** pre-dose ECG criteria again, discontinue patient from study. **Do meet** pre-dose ECG criteria for dosing and QT prolongation determined to be related to study drug, resume study drug treatment with a dose reduction of 5 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Sponsor and transmit to eRT immediately for prompt review. **Discontinue** patient from study therapy. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: Omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.
Post-dose on cycle 1, days 1 and 5: 3 ECGs separated by 5-10 minutes, obtained 3 hours +/- 0.5 hours after panobinostat dosing:	Average QTcF ≥ 480 msec to < 500 msec OR > 60 msec increase from baseline	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. **Monitor ECG hourly** or by telemetry until at least 2 consecutive hourly ECGs performed at least 6 hours post dose are <480. Notify Sponsor and transmit to eRT immediately for prompt review. Next scheduled dosing day: repeat 3 pre-dose ECGs. If these 3 pre-dose ECGs: Do not meet pre-dose ECG criteria for dosing (average QTcF ≤ 480 msec), discontinue patient from study. Do meet pre-dose ECG criteria for dosing (average QTcF ≤ 480 msec) and QT prolongation determined to be related to study drug, resume study drug treatment with a dose reduction of 5 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3) on the next scheduled dosing day.

ECGs to be performed at specified time point	Abnormality Noted	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Dose modifications are based on local readings of the average QTcF of triplicate ECGs.		
	Average QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Sponsor and transmit to eRT immediately for prompt review. **Discontinue** patient from study therapy If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds: omit dose. On the next scheduled dosing day continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), on the next scheduled dosing day.

6.3.3 Dose Reduction levels for LBH589

Dose reduction levels for LBH589

Dose Level	LBH589 Dose
Starting Dose	25 mg (M, W, F)
-1	20 mg (M, W, F)
-2	20 mg (M, W, F every other week)*
-3	15 mg (M, W, F every other week)*

Once a dose has been reduced, it cannot be re-escalated.

***Note**: If a patient is dose reduced to dose level -2, patients will be instructed to take 20 mg of LBH589 on M, W, F every other week. Cycles will remain 28 (+/- 5 days) long.

6.3.4 Study drug discontinuation

It will be documented whether or not each patient completed the clinical study. If, for any patient, either study treatment or observations were discontinued, the reason will be recorded.

Reasons that a patient may discontinue treatment are considered to constitute one of the following:

1. Subject's condition no longer requires study treatment (e.g. satisfactory therapeutic response)
2. Disease progression

   Note: If biochemical progression is confirmed by m-spike, but the participant is clinically benefitting from therapy, or had been holding therapy, participants may remain on study at the discretion of the overall Principal Investigator. If the treating physician and overall Principal Investigator are in agreement that the participant may benefit from continued LBH589, the participant may continue on treatment for one additional cycle to assess response again and re-discuss benefit of therapy.
3. Adverse event(s)
4. Abnormal laboratory value(s)
5. Abnormal test procedure result(s)
6. Protocol violation
7. Subject withdrew consent
8. Lost to follow-up
9. Administrative problems
10. New cancer therapy
11. Death

6.3.5 Follow-up

After progression, or removal from the study for other reasons (as outlined in 6.3.4), patients will be observed for Event Monitoring every 3 months (as outlined in the Test Schedule, Section 7.1, page 50). This will include the notation of death, any second malignancies, and other therapy for Waldenstrom's Macroglobulinemia. This information may be obtained by mail or phone contact.

If a patient refuses treatment after they have been registered (and is classified as a cancel), it is not necessary to provide follow-up information. On-study material is to be submitted.

If a participant experiences one of the following, the participant will be removed from event monitoring:

- Decision of the patient to withdraw from the study
- Patient death
- Administration of alternative therapy for Waldenstrom's Macroglobulinemia
- Lost to follow-up

6.3.5.1 Toxicity Follow-up

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first.

If a patient requires a dose delay of > 28 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. If however the patient was clearly benefiting from LBH589 therapy, the patient may be able to continue treatment with a 10 mg dose reduction at the Investigator

discretion, after resolution of the adverse event. All patients will be followed for adverse events and serious adverse events for at least 4 weeks following the last dose of oral LBH589.

6.4 Other concomitant medications

Patients should receive full supportive care while on this study. This includes blood product support (platelets and G-CSF), antibiotic treatment and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, anti-emetics received from the first administration of study drugs until 28 days after the final dose are to be recorded in the medical record.

Each patient should be instructed to have loperamide readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Loperamide 4 mg should be taken at the first loose stool or more frequent than usual bowel movements, followed by 2 mg as needed, no more frequently than every 4 hours not to exceed a total of 16 mg in 24 hours. Patients with diarrhea ≥ grade 2 despite this loperamide regimen should interrupt treatment with LBH589 as described in Table 6.1. If the above regimen is inadequate then additional evaluation and treatment should be pursued as medically indicated.

Some concomitant medications are discouraged, or prohibited, as described:

- Any medications listed in Appendix 1.1 which may cause QTc prolongation or inducing torsades de pointes should not be used.
- Any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias.
- No other investigational therapy should be given to patients
- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Leukocyte growth factors (e.g. G-CSF and GM-CSF) are not to be administered systematically but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate.
- Medications known to be substrates of the isoenzyme CYP2D6 should be used with caution with LBH589 as LBH589 can inhibit isoenzyme CYP2D6 at low micromolar ranges. Please refer to Appendix 1.3 for the list of CYP2D6 substrates.

6.4.1 Drugs that can inhibit/induce CYP3A4/5

- Oral contraceptives are generally metabolized by CYP3A4. Since the induction potential of LBH589 to induce CYP3A4 is unknown, patients who are using oral contraceptives as a method of contraception, and are sexually active, should use another effective contraceptive method in addition to the oral contraceptive.

6.4.1.1 Drugs that can inhibit CYP3A4/5

- Panobinostat is metabolized *in vitro* by CYP3A4/5. A clinical drug-drug interaction study with ketoconazole and panobinostat has recently been completed The less than 2-fold increase in panobinostat AUC upon co-administration with ketoconazole suggests that CYP3A contribution to the total clearance of panobinostat is low. The observed interaction is not considered clinically relevant, as panobinostat doses at least 2-fold greater than 20 mg (40 and 60 mg) have been safely administered in patients. CYP3A4 inhibitors should have no major impact on the exposure of panobinostat and may be co-administered when medically necessary. Drugs which are listed in Appendix 1.2 may be co-administered when medically necessary." Drugs which are listed in Appendix 1.2 may be co-administered when medically necessary.

6.4.1.2 Drugs that are potent CYP3A4/5 inducers

- As it is with other medications that are metabolized by CYP3A4, clinical judgment is to be exercised when potent CYP3A4 inducers are concomitantly taken with LBH589.

6.5 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted and patients will be asked to return all unused study medication.

7 Investigational Plan

7.1 Visit Schedule

Table 7.1 Test and Visit Schedule

	Pre-Registration		Treatment Phase					Follow-Up
Tests and Procedures	≤ 28 Days Prior to Registration	≤ 14 Days Prior to Registration	Weekly During Cycle 1	Day 1 of Cycles 1-6 (q 28 days)[1]	Day 1 of Cycle 4	At the End of Cycle 6, and/or End of Therapy	Maintenance Therapy, Every 3 Cycles	Every 3 months
History, Exam[2], Vital Signs [2A]	X			X	X	X	X	
ECOG	X			X	X	X	X	
Toxicity Assessment	X			X	X	X	X	
Hematology Labs[3]		X	X	X	X	X	X	X
Biochemistry[4]		X		X	X	X	X	X
Serum Protein Electrophoresis[5]	X			X	X	X	X	X
Viscosity	X			X	X	X	X	
beta-2 Microglobulin	X				X	X	X	
Serum Pregnancy Test[6]		X						
ECG[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X[7]	
CT (chest, abdomen, pelvis)	X					X		
Unilateral Bone Marrow Aspirate & Biopsy; Cytogenetics	X				X[8]	X		
Research Bone Marrow & Aspirate[R]	X				X	X		

1 A cycle is 28 days, +/- 5 days to accommodate scheduling conflicts. Day 1 procedures may be completed +/- 5 days before the start of LBH589 (Day 1 of the Cycle)
2 - Physical exams include: a total body examination (general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system)

2A - Vital Signs include: height (first visit only), pulse, blood pressure, respiration rate, temperature and weight

3 - Hematology Includes: CBC with differential, platelet count, hemoglobin, absolute neutrophil count
4 - Biochemistry Includes: Blood urea nitrogen (BUN), creatinine (for calculated creatinine clearance), sodium, potassium, chloride, CO_2, glucose, calcium, albumin, total protein, total bilirubin (if elevated, draw direct and indirect bilirubin), alkaline phosphatase, LDH, AST, ALT, phosphorous, magnesium

5 - Serum Protein Electrophoresis Includes: quantitative M-spike, quantitative IgM level and serum free light chain

6 - For women of childbearing potential; must be done ≤ 7 days prior to registration

7 - Please see Table 7.2 for detailed ECG schedule

8 - Bone marrow and aspirate will be required at this time point only to confirm a CR.

R – These are OPTIONAL procedures (research funded)

Table 7.2 Cardiac assessment monitoring schedule

Cycle	Day of cycle	ECG monitoring [a]
Cycle 1	Screening[b]	Single ECG to assess eligibility
	1	Pre-dose: 3 sequential ECGs separated by 5-10 minutes Post-dose: 3 sequential ECGs separated by 5-10 minutes, 3 hours (± ½ hour) after dosing
	5 (+ 2 days)	Pre-dose: 3 sequential ECGs separated by 5-10 minutes Post-dose: 3 sequential ECGs separated by 5-10 minutes, 3 hours (± ½ hour) after dosing
Cycle 2 -8[c]	1	Pre-dose: 3 sequential ECGs separated by 5-10 minutes
End of treatment	Last	Single ECG

[a] Refer to Table 6.2 for the recommended dose modifications due to QTc interval prolongation

[b] The mean QTc interval at baseline must be ≤ 450msec for the patient to be eligible for participation in the trial.

[c] Note: If participants experience QTc > 480 msec in Cycle 1 or in any subsequent cycle, then repeat Cycle 1 monitoring schedule until they have a Cycle with no QTc prolongation.

If no significant QTc prolongation is noted during first 8 Cycles, the QTc monitoring is no longer required and may be performed at the Investigator's discretion, if medically indicated.

7.2 Registration Procedures

The below procedures outline the process of registering DFCI patients. To register a patient from a participating center, please follow registration procedures as outlined in DF/HCC multi-center DSMP (Appendix 9, Section 5.7).

The QACT registration staff is accessible on Monday through Friday, from 8:00 AM to 5:00 PM Eastern Standard Time. In emergency situations when a participant must begin treatment during off-hours or holidays, call the QACT registration line at 617-632-3761 and follow the instructions for registering participants after hours.

The registration procedures are as follows:

1. Obtain written informed consent from the participant prior to the performance of any study related procedures or assessments.

2. Complete the protocol-specific eligibility checklist using the eligibility assessment documented in the participant's medical/research record. **To be eligible for registration to the study, the participant must meet each inclusion and exclusion criteria listed on the eligibility checklist.**

   Reminder: Confirm eligibility for ancillary studies at the same time as eligibility for the treatment study. Registration to both treatment and ancillary studies will not be completed if eligibility requirements are not met for all studies.

3. Fax the eligibility checklist(s) and all pages of the consent form(s) to the QACT at 617-632-2295.

4. The QACT Registrar will (a) validate eligibility, (b) register the participant on the study, and (c) randomize the participant when applicable.

5. The QACT Registrar will send an email confirmation of the registration and/or randomization to the person initiating the registration immediately following the registration and/or randomization.

7.3 Efficacy assessments

Efficacy measures will include both objective clinical measurements and investigator-reported outcomes. Response and time to event analyses will follow the criteria set forth in the International Waldenstrom consortium recommendations. Prior to the start of the study, investigators will assess disease and perform a CT scan of the chest, abdomen and pelvis. Response to treatment will be determined after cycle 2 is complete and then after every cycle until the end of the sixth cycle. After 6 cycles, response will be assessed every 3 months. All responses will be assessed by M-protein quantification and immunofixation from serum and IgM monoclonal protein level. In addition, BM biopsies will be done at baseline, at the end of cycle 6 and at the end of all therapy. An optional BM assessment will occur at the beginning of cycle 4. Assessment of BM malignant cells, lymphadenopathy or hepatosplenomegaly will be conducted to confirm responses on all patients who complete therapy.

Definition of Efficacy Measures

Time to progression is defined as the elapsed time from the date of study enrollment to the date of objectively determined PD. Analysis of TTP will be as follows:

- For patients who die without documented objective PD (including death from study disease), TTP will be censored at the date of the last objective progression-free disease assessment.
- For patients not known to have died as of the data cut-off date and who do not have objective PD, TTP will be censored at the date of the last objective progression-free disease assessment.
- For patients who receive subsequent systemic anticancer therapy (after discontinuation from study treatment) prior to objectively determined disease progression, TTP will be censored at the date of the last objective progression-free disease assessment prior to post discontinuation therapy.
- The duration of response is defined as the elapsed time from the date when the measurement criteria are first met for a complete or partial response (whichever status is recorded first) until the date of first observation of objective disease progression. Analysis of duration of response will be as follows:
- For responding patients who die without objective PD (including death from study disease), duration of response will be censored at the date of the last objective progression-free disease assessment.
- For responding patients not known to have died as of the data cut-off date and who do not have objective PD, duration of response will be censored at the date of the last objective progression-free disease assessment.
- For responding patients who receive subsequent systemic anticancer therapy (after discontinuation from the study chemotherapy) prior to objectively determined disease progression, duration of response will be censored at the date of the last objective progression-free disease assessment prior to postdiscontinuation therapy.

Hematologic Response Considerations

Terms and definitions

M-protein: synonyms include M-spike, serum monoclonal IgM concentration, monoclonal protein, monoclonal paraprotein, M-component.

Response terms: The following response terms will be used: complete response (CR), near complete response (nCR), very good partial response (VGPR), partial response (PR), minimal response (MR), stable disease or no response (NR), and progression or relapse (PD).

Measurable disease: Patients who have a measurable serum M-protein and IgM protein level are eligible for this protocol. Other measurable disease includes the lymph nodes and organomegaly as assessed by CT scan.

The serum free light chain (FLC) assay will also be used in monitoring response to therapy, but is not considered part of the official response measurements. When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and do not solely represent monoclonal elevations. Thus both the level of the involved and the uninvolved FLC isotype (i.e., the kappa/lambda ratio) should be considered in assessing response.

Patients will be formally evaluated for response using the following criteria (taken from the Second International Workshop on Waldenstrom's Macroglobulinemia):

NOTE: If a participant's serum m-protein is not quantifiable for any reason (e.g., atypical m-spike, migration to beta region, etc), the immunoglobulin M (serum IgM) may be used to assess response.

Table 7.3: response criteria for WM:

Complete Response (CR)	Disappearance of monoclonal protein by immunofixation; no histologic evidence of bone marrow involvement, resolution of any adenopathy/organomegaly (confirmed by CT scan), or signs or symptoms attributable to WM. Reconfirmation of the CR status is required with a second immunofixation.
Near complete response (nCR)	As above except that immunofixation is still positive.
Very good partial response (VGPR)	At least 90% reduction of serum monoclonal IgM concentration on protein electrophoresis.
Partial Response (PR)	At least 50% reduction of serum monoclonal IgM concentration on protein electrophoresis and at least 50% decrease in adenopathy/organomegaly on physical examination or on CT scan. No new symptoms or signs of active disease.
Minor Response (MR)	At least 25% but less than 50% reduction of serum monoclonal IgM by protein electrophoresis. No new symptoms or signs of active disease.
Stable Disease (SD)	Less than 25% reduction and less than 25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease (PD)	At least 25% increase in serum monoclonal IgM protein electrophoresis confirmed by a second measurement , or progression of clinically significant findings due to disease (i.e., anemia, thrombocytopenia, leucopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever of at least 38.4^{o}C, drenching night sweats, at least 10% body weight less, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia, or amyloidosis) attributable to WM.

8 Safety Assessments and Monitoring

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, vital signs, ECOG performance status, and the regular physical examinations and ECG assessments.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. CTCAE v3.0 can be accessed on the NIH/NCI website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf.

8.1 Adverse events

Adverse Event Definition

An **adverse event** (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

Serious Adverse Event Definition

A **serious adverse event** (SAE) is any adverse event, occurring at any dose and regardless of causality that:

- Results in **death**.
- Is **life-threatening**. Life-threatening means that the patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires inpatient **hospitalization or prolongation of existing hospitalization**. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the patient was enrolled in the trial, provided that it did not deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned).
- Results in **persistent or significant disability/incapacity**. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an **important medical event**. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Clarification should be made between the terms "serious" and "severe" since they ARE NOT synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as a severe headache). This is NOT the same as "serious," which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. For example, persistent nausea of several hours duration may be considered severe nausea but not an SAE. On the other hand, a stroke resulting in only a minor degree of disability may be considered mild, but would be defined as an SAE based on the above noted criteria. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

Additionally, the following events must be reported:

- Grade 2 (moderate) or Grade 3 (serious) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening) events that are unexpected and not specifically listed in the protocol as not requiring reporting.
    - Note: Grade 4 expected hematological toxicities (thrombocytopenia, anemia, and low white blood cell counts) do not require reporting.
- All Grade 5 (fatal) events while the subject is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Procedures for AE and SAE Reporting

The investigator must report all serious adverse events (SAE) regardless of relationship with any study drug or expectedness to the principal investigator at Dana Farber as soon as possible, but no later than 5 calendar days of the investigator-sponsor's observation or awareness of the event. Any serious adverse event occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported. Any deaths occurring on treatment or within 30 days of ending treatment must be reported within 5 days of awareness. Dana Farber's principal investigator will submit all SAEs to Novartis (please refer to Section 8.4). All sub-investigators must report all SAEs to the investigator so that the investigator can meet his/her foregoing reporting obligations to Dana-Farber Safety Monitoring Board, FDA and supporting organizations (Novartis). The FDA MedWatch 3500A form should be used to report this event to the investigator-sponsor.

These reports should be sent by FAX or E-MAIL to:

Irene M Ghobrial, MD
Dana Farber Cancer Institute
44 Binney Street
Boston, MA 02115
Phone: 617-632-4198
Fax: 617-582-7153
Email: irene_ghobrial@dfci.harvard.edu

For both serious and non-serious adverse events, the investigator or sub-investigator must determine both the intensity of the event and the relationship of the event to drug administration.

Relationship to drug administration will be determined by the investigator or sub-investigator responding yes or no to the question: Is there a reasonable possibility that the adverse event is associated with the drug?

Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 3.0, as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient

during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

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

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

Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es). All SAEs will be submitted to the Safety and monitoring Board of each institution and to Novartis.

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue drug therapy. must also be contacted immediately by faxing a completed Pregnancy Form. The pregnancy must be followed through outcome (i.e. delivery, still birth, miscarriage).

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

8.2 Safety Meetings

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this trial. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Principal Investigator and study team.

The DSMC will meet quarterly and/or more often if required to review toxicity and accrual data. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days for Phase I or II protocols; for gene transfer

protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

8.3 Monitoring

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the Principal Investigator (or Protocol Chair) or DF/HCC. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

All data will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion.

8.4 Novartis instructions for rapid notification of serious adverse events

The principal investigator has the obligation to report all serious adverse events to the FDA, IRB, and Novartis Pharmaceuticals Clinical Safety and Epidemiology Department (CS&E).

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

All events must be reported, by FAX (888-299-4565), to Novartis Pharmaceuticals CS&E Department within 24 hours of learning of its occurrence. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 5 working days.

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

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

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

8.5 Pregnancies

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

8.6 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight. Blood pressure, pulse and respiration rate should be measured on patients after at least 3 minutes in the sitting position

8.7 Physical examination

Physical examinations will be performed which must comprise a total body examination (general appearance, skin, neck, including thyroid, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities and basic nervous system).

Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

8.8 Laboratory evaluations

Laboratory evaluation should be done at baseline (within ≤ 72 hours prior to dosing prior to the first administration of oral LBH589), during the course of the study and at the time of the study treatment completion visit. Results must be reviewed prior to administering LBH589. More frequent examinations may be performed if medically indicated; results should be recorded.

8.8.1 Hematology

Hematology must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential.

8.8.2 Blood chemistry

Biochemistry includes the following parameters: BUN, creatinine, sodium, potassium, chloride, CO_2 (HCO_3), glucose, calcium, albumin, total protein, total bilirubin, alkaline phosphatase, LDH, AST/SGOT, ALT/SGPT, phosphorous, magnesium, and uric acid. If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed.

8.8.3 Serum Pregnancy Test

All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of LBH589 on day 1 of cycle 1. Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered “of non-childbearing potential”.

8.9 ECG

See Section 6.1.1 (Cardiac precaution) Section 6.3.2 (Dose modification for prolonged QTc) for guidelines on the required close monitoring of patients’ serum biochemistry values (in particular,

potassium, magnesium, calcium and phosphorous) and the requirement for rapid correction of low values).

A screening 12-lead ECG will be performed to assess study eligibility. Additional 12-lead ECGs will be performed at a minimum at scheduled time points as indicated in Table 7.2. For all patients, a minimum of 3 sequential 12-lead ECGs, separated by 15-30 minutes, must be performed on cycle 1 day 1 prior to the first administration of oral LBH589 or within 24 hours prior to that day. This is necessary to get an accurate baseline QTc calculation.

All ECGs will be sent to eRT for central review. The ECG interpretations from eRT will be the formal data entered into the database. Please contact Karen Kubacke at eRT (215-282-5573, or KKubacke@ert.com) to request information and supplies regarding this process.

8.10 Performance status

ECOG Performance status will be assessed. Please see Appendix 2.

8.11 Special tests

A CT of the chest, abdomen and pelvis will be completed at screening (within 28 days of registration), at the end of cycle 6 and at end of therapy.

9 Pharmacodynamic assessments and correlative studies

No pharmacokinetics or drug levels will be performed; however pharmacodynamic (PD) assessments will be done on research bone marrow and aspirates.

The purpose of these studies is to identify the role of epigenetic alterations in WM and their role in resistance to therapy.

1. We will first determine the level of HDAC and HAT in samples obtained pre-therapy
2. We will then determine mechanisms of activation or overexpression of HDACs in WM, through mutation, SNP and epigenetic regulation such as miRNA and methylation studies
3. We will also determine the effect of LBH589 on signaling pathways and miRNA expression in post-treatment samples.

Sample collection and prioritization of studies: At the time of collection**,** 10-15 ml BM aspirate will be collected in heparinized tubes and submitted to the Ghobrial lab (please see Appendix 5). Samples may be shipped Monday – Friday (we can accept Saturday deliveries if given 1 week notice). Prior to shipment, please notify the Ghobrial lab that a sample is being shipped by calling 617-582-8665.

Mononuclear cells (MNC) will be separated from the samples by density gradient centrifugation as described in the preliminary data. Malignant cells will then be separated using magnetic bead technology with negative selection. We typically isolate 10-30x10^6 CD19+ cells from the bone marrow using this technique.

Timing of BM samples: Pre-therapy, day 1 of cycle 4, and at the end of therapy.

Table 9.1: Studies proposed using samples of patients' pre and post-therapy

	LBH589	
	Response	**No-response**
Pre-therapy samples	1. Is there constitutive activation of HDACs? a. If Yes to #1, then identify mechanism of activation of this pathway: mutation, SNP of key regulators b. If Yes to #1, identify if miRNAs or methylations status are key regulators of activation of HDACs	
Post-therapy samples	1. Did we hit the target? a. Determine the level of downstream proteins of LBH589 and correlate with clinical activity and pre-sample results b. miRNA profile of miRs inhibited by these agents.	

Table 9.2 : Experimental approach, timing, source, and priority of studies proposed

Studies proposed	Experimental approach	Timing
Identify whether HDACs are constitutively activated	HDAC/HAT activity using Colorimetric HDAC Activity Assay Kit, and immunofluorescence on BM clots	Pre-therapy
Identify mechanism of activation of HDACs	mutation, SNP of regulators of he pathway.	Pre-therapy
Identify if miRNA are key regulators of resistance	miRNA by Luminex Methylation status of key regulators by ChIP on chip	Pre-and post-therapy
Identify the level of main signaling proteins downstream of LBH589: did we hit the target?	Luminex phosphoprotein detection and immunofluorescence on BM clots	Pre and post-therapy

10 Regulatory Considerations

10.1 Protocol Review and Amendments

A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to Novartis before study initiation.

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before being submitted to the IRB. Any changes to the protocol, informed consent and all forms of participant information related to the study (e.g., advertisement used to recruit patients) and any other necessary documents must be submitted, reviewed and approved by the IRB prior to implementation.

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

11 Data management

11.1 Data collection

The QACT will collect, manage, and monitor data for this study.

11.2 Data Submission

The schedule for completion and submission of case report forms to the QACT is as follows:

Form	**Submission Timeline**
Eligibility Checklist	Complete prior to registration with QACT
On Study Form	Within 14 days of registration
Baseline Assessment Form	Within 14 days of registration
Treatment Form	Within 10 days of the last day of the cycle
Adverse Event Report Form	Within 10 days of the last day of the cycle
Response Assessment Form	Within 10 days of the completion of the cycle required for response evaluation
Off Treatment/Off Study Form	Within 14 days of completing treatment or being taken off study for any reason
Follow up/Survival Form	Within 14 days of the protocol defined follow up visit date or call

12 Statistical methods

12.1 Statistical methods

Overview:

The primary endpoint of the phase II study is the overall response rate (defined as MR or better) of single agent LBH589 in patients with relapsed or relapsed/refractory WM.

Design:
An overall response rate (defined as CR + nCR+ VGPR +PR+MR) of 40% is considering promising in this population, whereas a overall response rate of 20% is considering non promising . This study will use a two-stage design to allow for early termination of the study if the drug is unlikely to be promising. The following two-stage Simon design will be used: a minimum of 14 eligible patients and a maximum of 37 eligible patients will be entered in the study. The study is designed to have at least 93% probability of concluding the treatment is effective if the response rate is at least 40% and a 10% or less chance of concluding that the treatment is not effective with true response rate of 20% or less.

Decision rule:
In this design 14 eligible patients will enter the first stage. If 2 or fewer response (MR or better) is observed, the treatment consideration will be given to early termination of the study. If 3 or more responses are observed, accrual will continue to the second stage with an additional 23 eligible patients entered onto the study. If 10 or fewer responses are observed after 37 eligible patients, this treatment will be considered non-promising. If 11 or more responses are observed among the 37 eligible patients, the single agent LBH589 will be considered promising for further study.

Design properties:
Assuming that the number of response is binomially distributed, the probability that the single agent LBH589 will considered promising for future study is at least 0.90 if the true response rate is ≥40% and <0.1 if the response rate is ≤20%. The probability of declaring that the drug is promising and the probability of stopping accrual after the first stage is provided in the table below under various true response rates .

True response rate	0.20	0.25	0.30	0.35	0.40
probability of observing 11 or more responses among 37 evaluable patients	0.1	0.30	0.57	0.77	0.93
probability of early stopping at stage 1 (0, 1 or 2 responses among 14 evaluable patients in first stage)	0.44	0.28	0.16	0.08	0.04

With 37 eligible patients entered on study, the 90% confidence interval of the estimated response rate will be no wider than 29% (CI 90%:34-63). The 90% confidence interval width is 25% (CI 90%: 44-18), if 11 responses are observed among 37.

Stopping rule for toxicity:
The study will be monitored continuously for all toxicities. If grade 3 or 4 unexpected non-hematologic toxicities are observed in 1 or more patients the study will be suspended for toxicity evaluation. The probability of suspending the trial (observing 1 or more toxicity) with 10, 20, or 30 patients treated under various true underlying true toxicity percentages are given below. The probability of observing at least 1 patient among the 37 patients with unexpected grade 3 or 4 non-hematologic toxicity is 0.04, 0.17, 0.31, 0.53 and 0.85 for true toxicity percentages of 0.1, 0.5, 1,2 and 5%, respectively.

True toxicity percentage	0.1	0.5	1	2	5
Pr (observing at least one toxicity with 10 patients)	0.01	0.05	0.10	0.18	0.40
Pr (observing at least one toxicity with 20 patients)	0.02	0.10	0.18	0.33	0.64
Pr (observing at least one toxicity with 30 patients)	0.03	0.14	0.26	0.46	0.79

In addition, if ECG QTC prolongation is observed in 2 or more patients, the study will be suspended for toxicity evaluation. The probability of suspending the trial with 10, 20, or 30 patients treated for various true underlying true toxicity percentages are given below. The probability of observing at least 2 patients among the 37 patients with ECG QTC prolongation is 0.015, 0.05, 0.17, 0.44 and 0.81 for true toxicity percentages of 0.1, 1, 2, 4 and 8%, respectively.

True toxicity percentage	0.1	1	2	4	8
Pr (observing at least one toxicity with 10 patients)	0.001	0.004	0.016	0.058	0.19
Pr (observing at least one toxicity with 20 patients)	0.004	0.017	0.06	0.19	0.48
Pr (observing at least one toxicity with 30 patients)	0.010	0.036	0.12	0.34	0.70

Accrual time and study duration:
The anticipated accrual rate based on 06077 (perifosine relapsed/refractory WM protocol) for this group of patients is approximately 2-3 patients per month. It will take approximately 6 months to complete the first stage of accrual and approximately 10 months to complete the second stage of accrual.

Secondary objectives:
Secondary objectives include further assessing toxicity, and to assess duration of response (DR), time to progression (TTP) and progression-free survival (PFS).

Duration of remission (DR), Time to progression (TTP) and progression free survival (PFS) will be estimated using the method of Kaplan and Meier. DR is defined as the time from the date of first response after treatment to the date of disease progression or death for any cause. Patients who have died or progressed are censored at the date the patient is last know to be progression-free. TTP is defined as the time from start of treatment to progression., Patients who have not progressed are censored at the date the patient is last known to be progression free.. PFS is defined as the time from start of treatment to disease progression or death from any cause. Patients who have not progressed and are alive are censored at the date the patient is known to be progression-free.

The proportion of patients who have reported any toxicity and specific toxicities will be provided along with the 90% confidence interval. The 90% confidence interval width will be no wider than 29%. The table below gives the probability of detecting rare events based assuming true toxicity incidence between 0.1%-5%.

True Incidence rate	0.1%	0.5%	1%	5%
Pr (observe at least one toxicity)	0.04	0.17	0.31	0.85

13 Procedures and instructions

13.1 Publication of results

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

13.2 Disclosure and confidentiality

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

13.3 Discontinuation of study

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

14 Ethics and Good Clinical Practice

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

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996. Directive 91/507/EEC, The Rules Governing Medicinal Products in the European Community.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).

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

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

14.1 Informed consent

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

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

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

14.2 Declaration of Helsinki

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

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Appendix 1. LBH589 study prohibited medication list.

1. Drugs that prolong the QT interval and/or induce Torsades de Pointes ventricular arrhythmia

Patients who are currently receiving treatment with any of the medications in Table 1-1, and cannot either discontinue this treatment or switch to a different medication prior to study enrollment, will be excluded from the study. Patients may not begin treatment with any of the medications listed in Table 1-1 while on treatment with LBH589. If a patient must receive these drugs, this patient should be discontinued from the study. The patient should be off-treatment with LBH589 for at least 72 hours prior to taking the first dose of a medication listed in Table 1-1.

Table 1-1 Medications which may prolong the QT interval ALL Class IA

ALL Class IA antiarrhythmics • **quinidine** • **procainamide** • **disopyramide** • **any other class IA antiarrhythmic drug**
ALL Class III antiarrhythmics • **amiodarone** • **sotalol** • **bretylium** • **dofetilide** • **ibutilide** • **any other class III antiarrhythmic drug**
Antibiotics • **Macrolide antibiotics*** • **erythromycin** • **clarithromycin** • **telithromycin** **Quinolone antibiotics*** • **gatifloxacin** • **moxifloxacin** • **sparfloxacin**
Antipsychotics • **thioridazine** • **mesoridazine** • **chlorpromazine** • **pimozide**

• **risperidone** • **ziprasidone**
Antidepressants • **amitriptyline** • **imipramine** • **desipramine** • **doxepin** • **maprotiline** • **venlafaxine**
Antifungals (azoles)* • **ketoconazole** • **itraconazole**
Antimalarials • **halofantrine** • **chloroquine**
Anti-emetics* • **dolasetron** • **ondansetron** • **tropisetron**
Miscellaneous drugs • **arsenic trioxide** • **bepridil** • **domperidone** • **methadone** • **pentamidine** • **droperidol** • **cisapride** • **tacrolimus**

* Note: azithromycin, ciprofloxacin, levofloxacin, granisetron are allowed.

This is not a comprehensive list of medications which may prolong the QT interval. This list of medications was developed in collaboration with an external cardiology consultant, and represents those medications which are deemed to have an unacceptable risk of co-administration with LBH589.

The following website may be referenced as a supplemental guide for drugs which may prolong the QT interval: http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm#. Medications listed on the website which do not appear in Table 1-1 above may be used at the discretion of the investigator.

2. Drugs that can inhibit CYP3A4/5

Since LBH589 is metabolized in vitro by CYP3A4 clinical judgment is to be exercised when potent CYP3A4 inducers are concomitantly taken with LBH589. Below is a list of CYP3A4/5 drugs.

Table 2-1 List of drugs known to inhibit CYP3A4/5

Macrolide antibiotics*
• **erythromycin**
• **clarithromycin**
• **telithromycin**
• **troleandomycin**
Antifungals (azoles)
• **fluconazole (5 days)**
• **ketoconazole**
• **itraconazole (12 days)**
• **voriconazole**
Antidepressants
• **fluvoxamine**
• **nefazodone**
Calcium channel blockers*
• **diltiazem**
• **verapamil**
HIV protease inhibitors:
• **indinavir**
• **nelfinavir**
• **ritonavir**
• **any other HIV protease inhibitors**
Miscellaneous drugs or products
• **cimetidine**
• **aprepitant**
• **grapefruit product or juice**
• **Seville (sour) orange or juice***

* azithromycin, regular orange juice and dihydropyridine calcium channel blockers (e.g. amlodipine, felodipine, nicardipine, nifedipine) are allowed.

This is not a comprehensive list of medications which may inhibit CYP3A4/5. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/flockhart/clinlist.htm

3. Drugs that are CYP2D6 substrates

If CYP2D6 substrates listed in Table 3-1 are used concomitantly with LBH589, patients must be carefully monitored for potentiation of toxicity due to any individual concomitant medications and may require dose titration or reduction of the CYP2D6 substrate.

Table 3-1 CYP2D6 substrates

CYP2D6 substrates
Beta blockers (listed below):
carvedilol
metoprolol
bufuralol
alprenolol
nebivolol
propranolol
timolol
Antidepressants (listed below):
amitriptyline
clomipramine
desipramine
imipramine
nortriptyline
paroxetine
venlafaxine
Antipsychotics (listed below):
aripiprazole
haloperidol
perphenazine
risperidone
thioridazine
chlorpromazine
duloxetine
fluoxetine
fluvoxamine
venlafaxine
Antiarrhythmics (listed below):
encainide
flecainide

lidocaine
mexiletine
propafenone
Antiemetics (listed below):
dolasetron
ondansetron
metoclopramide
Others:
amphetamine
atomoxetine
dextromethorphan
promethazine
tamoxifen
tramadol

This is not a comprehensive list of medications that are CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/

Appendix 2: Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	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
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.

Appendix 3: New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Appendix 4: Study Medication Diary

Medication Diary for LBH589

Protocol No	Participant ID	Participant Initials	Cycle	Dose
LBH589 DFCI 09-071				_____ mg

Please complete this diary on the days that you take your study medication. Please enter the **date and time** you take the study medication in the appropriate box.

You will receive 5 weeks worth of study medication at the beginning of each cycle (each cycle is 28 days, +/- 5 days). Please remember to bring the medication bottle and any remaining pills with you every time you have a doctor's appointment.

You are to take LBH589 by mouth on Mondays, Wednesdays and Fridays, with a glass of water (8 oz), with or without food. During the first cycle, please take LBH589 in the morning. After cycle 1 you may choose to take LBH589 in the evening. However, please discuss this with your study doctor before making any changes to your dosing schedule.

If you vomit while taking LBH589, then you should not take another dose until your next scheduled dose of LBH589. If you forget to take your medication in the morning, you can take it up to 12 hours after the usual time you take it. After 12 hours, do not take LBH589 that day; instead, wait until your next scheduled dose. **Do not make up missed doses**.

Week 1

	Monday	Wednesday	Friday
Date:			
Time:			

Week 2

	Monday	Wednesday	Friday
Date:			
Time:			

Week 3

	Monday	Wednesday	Friday
Date:			
Time:			

Week 4

	Monday	Wednesday	Friday
Date:			
Time:			

Week 5

	Monday	Wednesday	Friday
Date:			
Time:			

Participant Signature: _____

Date: _____

For Site Use Only RN Initials: _____ Date: _____	Pill Count Comments: # Pills remaining: _____ # Pills returned to pharmacy: _____ # Pills given to participant: _____

Appendix 5: Address and Instructions for Shipping Pharmacodynamic Sample

Please ship the research bone marrow aspirate to:

Dr. Irene Ghobrial
Dana-Farber Cancer Institute
44 Binney St, Dana 802
Boston, MA 02115

Instructions for shipping the research bone marrow aspirate (taken at ≤28 days prior to registration, at the end of cycle 3, and at the end of cycle 6 or at the end of therapy):

Package aspirate green top tube at room temperature and wrap in a liberal amount of paper towel around the tube to ensure adequate insulation of the specimen(s) and absorption in the event of a breakage. Place wrapped specimen in a biohazard labeled Ziploc bag and zip close. Wrap bubble wrap around the bag and place in a plastic container. Place the plastic container in a cardboard box. If space remains in the box, stuff with extra paper towel to reduce shifting of samples. Complete the shipping label using the above address. Prepare the package for shipping, applying packing tape as needed. Ship the package using FedEx and UPS next day or overnight delivery the same day the sample was collected. Please only ship Monday – Friday, the lab is only able to accept Saturday shipments with 1 week advance notice. Notify Dr. Ghobrial or study staff at 617-632-4198 or 617-582-8664 that the package has been shipped. Please provide the sample type(s), number of tubes, and the tracking number.

Appendix 6A: Information Sheet for ECGs and Labs Completed at Local Physician's Offices

Dana-Farber Cancer Institute Letter:

Participant name: _____ Date: _____

Cycle: _____ Day: _____ Dose: _____

Please take this information sheet with you to your local doctor's office on the day(s) that you will have ECGs and/or labs done.

Triplicate ECGs are to be done on Cycle 1 Day 5:
3 ECGs before your LBH589 dose
3 ECGs three hours following your LBH589 dose

Hematology labs are to be completed weekly during the first cycle:
CBC with differential
Platelets
Hemoglobin
Absolute Neutrophil Count

All ECGs and labs are to be faxed to:
Dr Irene Ghobrial
617-582-7153

If you, or your local doctor, have any questions about the ECG or lab schedule, please call:
Tiffany Poon
617-632-3742

You should not take your LBH589 dose until the ECG and laboratory results have been received and reviewed by a clinician at Dana-Farber. A member of the research team will call you or your local doctor to review and discuss the ECG and lab results. If your ECG is normal and your lab results meet dosing requirements, you will be instructed to take your LBH589 dose as planned. If your ECG or lab results are abnormal, your local doctor and your study doctor will discuss the findings and determine the next step. It is possible that you will need blood tests and/or additional ECGs completed.

It is important to remember not to take your LBH589 dose until after your ECG and lab results are reviewed, and a member of the research team has instructed you to take your LBH589 dose.

Any invoices or bills you receive for the ECGs should be given to the research team at Dana-Farber. ECGs completed for the above timepoints will be paid for by the research study. Any additional ECGs

completed for clinical purposes will not be reimbursed by the research study. All labs completed while on study will be charged to your insurance.

Appendix 6B: Information Sheet for ECGs and Labs Completed at Local Physician's Offices

Participating Centers Letter:

Participant name: _____ Date: _____

Cycle: _____ Day: _____ Dose: _____

Please take this information sheet with you to your local doctor's office on the day(s) that you will have ECGs and/or labs done.

Triplicate ECGs are to be done on Cycle 1 Day 5:
3 ECGs before your LBH589 dose
3 ECGs three hours following your LBH589 dose

Hematology labs are to be completed weekly during the first cycle:
CBC with differential
Platelets
Hemoglobin
Absolute Neutrophil Count

All ECGs and labs are to be faxed to:

_____

At: _____

If you, or your local doctor, have any questions about the ECG or lab schedule, please call:

_____

At: _____

You should not take your LBH589 dose until the ECG and laboratory results have been received and reviewed by a clinician. A member of the research team will call you or your local doctor to review and discuss the ECG and lab results. If your ECG is normal and your lab results meet dosing requirements, you will be instructed to take your LBH589 dose as planned. If your ECG or lab results are abnormal, your local doctor and your study doctor will discuss the findings and determine the next step. It is possible that you will need blood tests and/or additional ECGs completed.

It is important to remember not to take your LBH589 dose until after your ECG is reviewed, and a member of the research team has instructed you to take your LBH589 dose.

Any invoices or bills you receive for the ECGs should be mailed to the address listed below. ECGs completed for the above timepoints will be paid for by the research study. Any additional ECGs completed for clinical purposes will not be reimbursed by the research study. All labs completed while on study will be charged to your insurance.

Please send any invoices to:
Irene M Ghobrial
44 Binney St
LG-LC
Boston, MA 02115

Appendix 7: Study Summary for Participant Reference

Phase II
LBH589 (Panobinostat) in relapsed/relapsed refractory
Waldenstrom's Macroglobulinemia
Novartis

Primary objective is to assess the overall response rate in patients with relapsed or relapsed/refractory WM.

Cycle=28 days (+/- 5 days)
Response assessed after 2 cycles

Schedule:
25 mg/day, orally on Mondays, Wednesdays and Fridays

LBH589 will be provided by Novartis and will be supplied as 5 mg or 20 mg pink/opaque-colored, hard gelatin capsules.

Patients should take LBH589 by mouth on Mondays, Wednesdays and Fridays, with a glass of water (8 oz), with or without food. During the first cycle, please take LBH589 in the morning. After cycle 1 patients may choose to take LBH589 in the evening. However, please discuss this with the study doctor before making any changes to the dosing schedule. The capsules should be swallowed whole and not chewed. Avoid grapefruit or grapefruit juice and Seville (sour) oranges while on study.

If patient forgets to take his/her dose during the morning on the scheduled treatment day then they should take it the same day within 12 hours of the missed dose. After more than 12 hours, that day's dose should be held and patient should wait to take LBH589 until the next scheduled treatment day.

Patients will be assessed every 28 days (+/- 5 days). After 6 cycles of monthly evaluations, patients will be assessed every 3 months.

Patients may continue to receive treatment with LBH589 until they experience an unacceptable toxicity, disease progression and/or discretion of investigator.

ECG Schedule:

Cycle 1

Day 1 **At Study Doctor's Office**
Pre-dose: 3 sequential ECGs separated by 5-10 minutes
Post-dose: 3 sequential ECGs separated by 5-10 minutes, 3 hours (+/- 30 minutes) after dosing

Day 5 **At Study Doctor's Office or Locally**
Pre-dose: 3 sequential ECGs separated by 5-10 minutes
Post-dose: 3 sequential ECGs separated by 5-10 minutes, 3 hours (+/- 30 minutes) after dosing

Cycle 2 – 8

Day 1 **At Study Doctor's Office**
Pre-dose: 3 sequential ECGs separated by 5-10 minutes

**If participants choose to have ECGs performed at their local physician's office, they will be given an information sheet. The information sheet will accompany them to their doctor's office at the time of the ECGs. Participants are only to proceed with LBH589 dosing after the ECGs and some lab results have been sent and reviewed by a clinician at DFCI.

The research ECGs are not to be charged to patient's insurance. Instead, the local office should provide patient with an invoice to be hand delivered to the patient's study team at DFCI or participating center. Once we have the invoice, the local office will be reimbursed directly from the DFCI research department. However, please note, any additional ECGs completed for clinical purposes will not be reimbursed by the research study.

****If an abnormality occurs on an ECG then additional days of extensive ECG monitoring may be required.**

Appendix 8: LBH589 Order Form

Please Fax Request to: 973-781-3478 (Attn: Dorothy Muriuki)

Date: _____
Study Title: _____

Investigator's Name: _____
Novartis Protocol Number: _____

Requestor's Name: _____
Requestor's Phone#: _____

Institution: _____
Shipping Address: _____
_____
_____

Shipping Phone#: _____

Is this Initial Shipment:
Yes ☐ **No** ☐

Date by when this shipment is required: _____

*******Please note that oral LBH589 will be provided by Novartis and will be supplied as 5-mg or 20-mg hard gelatin capsules. Please note that LBH589 5mg are 45-fill label bottle and 20mg Caps in 15-fill label bottle.**

15 Drug	Label Strength	Number of Bottles Requested
LBH589	**5 mg (45 caps/bottle)**	
LBH589	**20 mg (15 caps/bottle)**	

Note: Please allow 10 days for processing of this request and delivery of the shipment.

Appendix 9: Novartis Pregnancy Reporting Form

Trial Drug **Protocol** **Tip No.**	ID ⌊_____⌋ ⌊_____⌋ Centre No. Subject No. Subject's Initials 1. ⌊2⌋ fam. Randomisation Number	REPORT TYPE ☐ Initial ☐ Follow-Up

CLINICAL TRIAL PREGNANCY FORM

1. Country:	2. LOCAL CASE ID:

I. MATERNAL INFORMATION

3. DATE OF BIRTH day month year	4. AGE yrs./mo.	5. RACE ☐ Caucasian ☐ Oriental ☐ Black ☐ Other	6. HEIGHT cm	7. WEIGHT kg

8. Date of Last Menstrual Period day month year	9. Expected Date of Delivery day month year

10. Method of Contraception	11. Contraception used as instructed ☐ yes ☐ no ☐ uncertain

II. HISTORY

12. PATIENT'S PAST MEDICAL HISTORY (include information on familial disorders, known risk factors or conditions that may affect the outcome of the pregnancy e.g. alcohol, smoking, other substance consumption, infections, hypertension, diabetes including gestational, environmental or occupational exposure that may pose a risk factor).

13. PREVIOUS OBSTETRIC HISTORY – provide details on all previous pregnancies below, including abortion or stillbirth (use page 3 if needed)

	Gestation week	Outcome including any abnormalities
1		
2		
3		
4		

14. DRUG INFORMATION – please list the Novartis drug(s) first and all other therapies taken prior to or during pregnancy

Drug Names	Daily Dose	Route	Treatment Dates Start	Treatment Dates Stop	Indication	(specify week of pregnancy) Start	(specify week of pregnancy) Stop

MANUFACTURER INFORMATION (FOR INTERNAL USE ONLY)

15. DATE MANUFACTURER NOTIFIED day month year	16. DATE OF THIS REPORT day month year

17. NAME AND ADDRESS OF REPORTING MANUFACTURER	*PLEASE FILL IN THE CORRECT LOCAL IMS PVO ADDRESS*

PLEASE SEND FORM TO LOCAL INTEGRATED MEDICAL SAFETY/PVO.

Trial Drug **Protocol** **Tip No.**	ID ⌊_____⌋ ⌊_____⌋ Centre No. Subject No. Subject's Initials 1. ⌊__2__⌋ fam. Randomisation Number	REPORT TYPE ☐ Initial ☐ Follow-Up

CLINICAL TRIAL PREGNANCY FORM

2. LOCAL CASE ID:

III. PREGNANCY INFORMATION

18. PRENATAL
Have any specific tests, e.g. amniocentesis, ultrasound, maternal serum AFP, been performed during the pregnancy so far?
☐ No ☐ Yes ☐ Not known
If yes, please specify test date and results:

19. PREGNANCY OUTCOME
Delivery
☐ Normal ☐ Forceps/Ventouse ☐ Caesarean section
Maternal complications or problems related to birth: _____
Abortion
☐ Therapeutic ☐ Planned ☐ Spontaneous Please, specify reason and any abnormalities (if known) _____
_____
Date of abortion/delivery day month year
at week _____ ⌊_____⌋⌊_____⌋⌊_____⌋

20. MATERNAL PREGNANCY ASSOCIATED EVENTS:
If the mother experiences a serious adverse event (SAE) during a pregnancy, please complete an SAE form and submit as requested

IV. CHILD INFORMATION

21. Neonate
☐ Normal ☐ Abnormal ☐ Stillbirth please specify any abnormalities with dates: _____

Sex	Height	Weight	Apgar Scores	Head circumference
☐ Male ☐ Female	cm	kg	1 min. 5 mins. 10 mins.	cm

For additional information, please use page 3 (please provide copies of relevant documentation)

V. ASSESSMENT OF PREGNANCY OUTCOME

22. SERIOUSNESS CRITERIA
☐ Non Serious
☐ Mother died day month year ⌊_____⌋⌊_____⌋⌊_____⌋
☐ Stillbirth / Neonate died day month year ⌊_____⌋⌊_____⌋⌊_____⌋
☐ Involved or prolonged inpatient hospitalisation
☐ Life-threatening
☐ Results in persistent or significant disability/incapacity
Other Seriousness Criteria: ☐ Congenital anomaly/birth defect ☐ Other significant medical events

23. ASSESSMENT OF CAUSALITY
Please indicate the relationship between pregnancy outcome and Novartis investigational drug

☐ Not suspected ☐ Suspected	
INFORMATION SOURCE	
24. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR Signature:	25. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT day month year
PLEASE SEND FORM TO LOCAL INTEGRATED MEDICAL SAFETY/PVO.	

Trial Drug **Protocol** **Tip No.**	ID ⌊_____⌋ ⌊_____⌋ Centre No. Subject No. Subject's Initials 1. ⌊__2.__fam. Randomisation Number	REPORT TYPE ☐ Initial ☐ Follow-Up

CLINICAL TRIAL PREGNANCY FORM

2. LOCAL CASE ID:

FOR ADDITIONAL INFORMATION:

INFORMATION SOURCE

32. NAME, ADDRESS AND TELEPHONE NUMBER OF INVESTIGATOR Signature:	32. REPORTING DATE BY INVESTIGATOR/PERSON REPORTING EVENT day month year

PLEASE SEND FORM TO LOCAL INTEGRATED MEDICAL SAFETY/PVO.

APPENDIX 10

DFCI IRB Protocol #: 09-071

Dana-Farber/Harvard Cancer Center
Multi-Center Data and Safety Monitoring Plan

Table of Contents

1.0 INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for a DF/HCC Multi-Center research protocol.

1.1 Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center (DF/HCC) Multi-center protocol will comply with Federal regulations (21 CFR Part 11); Good Clinical Practice (GCP) Guidelines; and Health Insurance Portability and Accountability Act (HIPAA) requirements in accordance with the CTEP Multi-center Guidelines.

1.2 Multi-Center Data and Safety Monitoring Plan Components

The Multi-Center Data and Safety Monitoring Plan includes the following components:

DF/HCC Multi-center Protocol: One or more outside institutions collaborating with Dana-Farber/Harvard Cancer Center on a research protocol where DF/HCC is the Lead Institution. Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates are not viewed as outside sites in this definition.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center sites (DFCI, MGH, BIDMC, CH, BWH) will be the Lead Institution and will be responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, FDA, OBA etc.).

DF/HCC Contract Principal Investigator: Investigator located at the Lead Institution who will be charged with the responsibility of the administration of the DF/HCC Project. This most often will be the Protocol Chair, but occasionally this may be the overall grant or contract holder, as applicable.

Protocol Chair: The Protocol Chair is the Principal Investigator for the DF/HCC protocol submitted as the Lead Institution. For applicable protocols, the Protocol Chair will be the single liaison with any regulatory agencies (i.e. CTEP Protocol and Information Office (PIO), FDA, OBA etc.).

Participating Institution: A participating institution is an institution that desires to collaborate with DF/HCC and commits to accruing participants to a DF/HCC protocol. The participating institution acknowledges the Protocol Chair as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The Lead Institution is the Coordinating Center for the DF/HCC Multi-center Protocol. The Coordinating Center will provide the administrative support to the Protocol Chair in order that he/she may fulfill the responsibilities outlined in the DSMP and as specified in applicable regulatory guidelines (i.e. CTEP Multi-Center Guidelines). In addition to the Lead Institution, the Quality Assurance Office for Clinical Trials (QACT) provides support services to assist the Protocol Chair.

2.0 GENERAL ROLES AND RESPONSIBILITIES

In accordance with the CTEP Multi-center Guidelines, the Protocol Chair (DF/HCC Principal Investigator), Coordinating Center (Lead Institution or designee), and the Participating Institutions will all agree to the general responsibilities as follows (specific procedures for these general responsibilities are detailed in the DSMP):

2.1 Protocol Chair (DF/HCC Principal Investigator)

The Protocol Chair, Irene Ghobrial, MD will accept responsibility for all aspects of the Multi-Center Data and Safety Monitoring Plan to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Submit the Multi-Center Data and Safety Monitoring Plan as an inclusion to the protocol.
- Assure all participating institutions are using the correct version of the protocol.
- Monitor progress and overall conduct of the study at all participating institutions.
- Ensure all DFCI IRB, DF/HCC and other applicable (i.e. FDA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA.

2.2 Coordinating Center (Lead Institution)

The Coordinating Center is the DF/HCC Lead Institution's study team or designee (i.e Medical Monitor, Clinical Research Organization). The DF/HCC Lead Institution, Dana-Farber Cancer Institute, will ensure that all participating sites within the Multi-Center Protocol demonstrate their intent and capability of complying with Federal Regulations, GCPs and Health Insurance Portability and Accountability Act (HIPAA) requirements. To assist the Protocol Chair in meeting his/her responsibilities as required by the DSMP, the DF/HCC Lead Institution's study team or designee will assume the following general responsibilities:

- Assist in protocol review.
- Maintain copies of Institutional Review Board (IRB) approvals from all participating institutions.
- Maintain FDA correspondence.
- Maintain updated roster of participants.
- Verify eligibility.
- Verify response.
- Collect data on protocol specific CRFs.
- Prepare all submitted data for review by the Protocol Chair.
- Maintain documentation of Serious Adverse Event (SAE) reports submitted by Participating Institutions and submit to Protocol Chair for timely review.
- Distribute external Serious Adverse Event safety reports.
- Monitor and audit Participating Institutions either by on-site inspection of selected participant records and/or with source documents and research records submitted to the Lead Institution.

In addition to the Lead Institution, the DF/HCC Quality Assurance Office for Clinical Trials provides the following support services to assist the Protocol Chair:

- Develop protocol specific case report forms (CRF/eCRFS).
- QA/QC data of protocol specific CRFs.
- Provide Central Participant Registration.
- Confirm eligibility and consent.
- Provide auditing services (funding and QACT approval required).

2.3 Participating Institution

The Participating Institution(s) will be identified on the title page for each protocol. In addition, each participating institution will provide to the Lead Institution or designee a list of the key personnel assigned to the role for oversight of data management at their site. All sites must have office space, office equipment, and internet access that meet HIPAA standards.
The general responsibilities for each participating institution are as follows:

- Commit to accrual to the Lead Institution's (DF/HCC) protocol.
- Submit protocol and/or amendments to their local IRB.
- Update Coordinating Center (Lead Institution or designee) with research staff changes on a timely basis.
- Register participants through the QACT.
- Submit source documents, research records, and CRFs per protocol specific submission guidelines to the Coordinating Center (Lead Institution or designee).
- Submit Serious Adverse Event reports to local IRB and directly to the Coordinating Center (Lead Institution or designee).
- Submit deviations and violations to local IRB and the Coordinating Center (Lead Institution or designee).
- For protocols using investigational agents, the participating institution will order their own investigational agents regardless of the supplier (i.e. NCI, pharmaceutical company).

3.0 DF/HCC QUALITY ASSURANCE OFFICE FOR CLINICAL TRIALS

The DF/HCC QACT is a unit that has been developed to computerize, manage, and monitor data for DF/HCC trials. The DF/HCC QACT is located administratively in the office of the Senior Vice President for Clinical Research, at Dana-Farber Cancer Institute. The QACT uses DF/HCC computerized institutional databases for participant registrations and for the management of trial data as well as a set of quality assurance programs designed to monitor DF/HCC trials.

3.1 Organizational Structure

The DF/HCC Quality Assurance Office for Clinical Trials administrative structure consists of:

DF/HCC Quality Assurance Officer for Clinical Trials: Oversees the functions of the DF/HCC QACT.

QACT Assistant Director for Data: Provides direct oversight to the QACT Data Analysts assigned to CRF design, data collection and computerization for DF/HCC trials.

The DF/HCC QACT Data Analysts will be assigned on a protocol by protocol basis. Each protocol's data analyst is responsible for database management, data entry, data quality assurance, and protocol specific correspondence related to the collection and quality assurance of data.

QACT Assistant Director for Monitoring: Provides direct oversight to the QACT Protocol Registrars and Clinical Research Auditors.

The DF/HCC Protocol Registrars are responsible for the confirmation of each participant's eligibility and consent prior to protocol registration.

If funded and QACT approved, the DF/HCC Clinical Research Auditors may assist the Lead Institution in their auditing responsibilities for multi-center trials. The QACT auditor is responsible for systematically evaluating participant safety, protocol compliance, institutional SOPs, ICH GCP and Federal regulation compliance, data accuracy and investigational drug handling to assure a high standard of quality for DF/HCC trials.

4.0 PROTOCOL DEVELOPMENT

4.1 Activation of a Protocol

The Protocol Chair is responsible for the coordination, development, and approval of the protocol as well as its subsequent amendments, and reporting SAEs, violations and deviations per DFCI IRB guidelines and FDA Guidelines. Further, the Protocol Chair will be the single liaison with the FDA.

To meet these requirements, the Protocol Chair will be responsible for the following minimum standards:

- Inclusion of the DF/HCC Multi-Center Data and Safety Monitoring Plan in the protocol as an appendix.
- Identify participating institutions and obtain accrual commitments. The title page must include the names and contact information for all participating institutions that perform the function of recruiting, enrolling, and treating participants for the protocol. The Coordinating Center (Lead Institution or designee) must be designated on the title page.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the Protocol Chair.
- Ensure that there is only one version of the Protocol and that all Participating Institutions use the correct version.
- Oversee the development of data collection forms (case report forms) that are of common format for use at all the Participating Institutions.

4.2 Coordinating Center Support Function

The DF/HCC Lead Institution's study staff or designee will provide administrative and clerical support to the Protocol Chair for the development and distribution of the protocol.

The tasks to be performed by the DF/HCC Lead Institution's study staff or designee include:

- Review of the protocol and consent to check for logistics, spelling, and consistency. Provide the Protocol Chair a list of queries related to any inconsistencies.
- Provide necessary administrative sections, including paragraphs related to registration logistics, data management schedules, and multi-center guidelines.
- Maintenance of contact list of all participating institutions in the DF/HCC Multi-Center Protocol and the distribution of updates to the sites as needed.
- Derivation of the study calendar, if applicable.
- Assistance in preparation and maintenance of case report forms. Conduct regular communications with all participating sites (conference call, emails, etc). Maintain documentation of all communications.

5.0 PROTOCOL MANAGEMENT

The Coordinating Center (Lead Institution of designee) is responsible for assuring that each Participating Institution in the DF/HCC Multi-center Protocol has the appropriate assurance on file with the Office of Human Research Protection (OHRP). Additionally, the Lead Institution or designee must maintain copies of all IRB approvals, for each participating institution.

5.1 Protocol Distribution

The Coordinating Center (Lead Institution or designee) will distribute the final approved protocol and any subsequent amended protocols to all Participating Institutions.

5.2 Protocol Revisions and Closures

The participating institutions will receive phone, fax, mail or e-mail notification of protocol revisions from the Lead Institution or designee. It is the individual participating institution's responsibility to notify its IRB of these revisions.

Non life-threatening revisions: Participating institutions will receive written notification of protocol revisions regarding non life-threatening events from the Lead Institution or designee. Non-life-threatening protocol revisions should be IRB approved and implemented within 90 days from receipt of the notification.

Revisions for life-threatening Causes: Participating institutions will receive telephone notification from the Lead Institution or designee concerning protocol revisions required to protect lives with follow-up by fax, mail or e-mail. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

Protocol Closures and Temporary Holds: Participating institutions will receive fax, e-mail, or phone notification of protocol closures and temporary holds, with follow-up by mail from the Lead Institution or designee. Closures and holds will be effective immediately. In addition, the Lead Institution or designee will update the Participating institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

5.3 Informed Consent Requirements

The Principal Investigator (PI) at each participating site will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. It is DF/HCC policy that Nurses and Fellows cannot obtain consent to greater than minimal risk trials.

5.4 IRB Documentation

The following must be on file with the DF/HCC Lead Institution or designee prior to participant registration:

- Approval Letter of the institution's IRB (An Expedited IRB first approval is NOT acceptable)
- IRB approval for all amendments

It is the individual institution's responsibility to notify its IRB of protocol revisions. Participating institutions will have 90 days from receipt to provide the DF/HCC Lead Institution or designee their IRB approval for Major Amendments to a protocol.

DF/HCC defines a Major Amendment as: A substantive change in the study which may increase or decrease the risk to study participants. Major revisions require full IRB approval. The following criteria are examples of revisions to a protocol that are considered to be major amendments:

- Change of eligibility (inclusion/exclusion) criteria
- Change in design of protocol
- Change in statistical section
- Change in sample size/accrual (e.g., doubling the sample size)
- Change in informed consent
- Change of estimated dropout rate
- Change of treatment or intervention
- Change of device
- Change in primary objective evaluation process

5.5 IRB Re-Approval

Annual IRB re-approval from the Participating institution is required in order to register participants onto a protocol. There is no grace period for annual re-approvals.

Protocol registrations will not be completed if a re-approval letter is not received by the DF/HCC Lead Institution or designee from the Participating Institutions on or before the anniversary of the previous approval date.

5.6 Participant Confidentiality and Authorization Statement

The Health Insurance Portability and Accountability Act of 1996 contains, as one of its six major components, the requirement to create privacy standards for health care information that is used or disclosed in the course of treatment, payment or health care operations. The original Privacy Rule, as it has come to be known, was published in December 2000. The Final Rule was published on August 14, 2002, which has modified the privacy rule in significant ways vis-à-vis research.

In order for covered entities to use or disclose protected health information during the course of a DF/HCC Multi-Center Protocol the study participant must sign an Authorization. This Authorization may or may not be separate from the Informed Consent. The DF/HCC Multi-Center Protocol, with the approval from the DFCI IRB and if applicable NCI/CTEP, will provide an Informed Consent template, which covered entities (DF/HCC Multi-Center Protocol participating institutions) must use.

The DF/HCC Multi-Center Protocol will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected per National Cancer Institute requirements. These are the primary reasons why DF/HCC has chosen to use Authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

5.7 Participant Registration and Randomization

To register a participant, the following documents should be completed by the DF/HCC Multi-Center Protocol participating site and faxed to or e-mailed to Meghan Rourke at DFCI (Meghan_Rourke@dfci.harvard.edu, fax: 617-632-6752):

- Copy of all required screening labs and assessments (please refer to Section 7.1 of protocol)
- Signed informed consent form by a physician listed on the 1572
- HIPAA authorization form (if separate from the informed consent document)
- Eligibility Checklist signed by the treating physician, physician assistant, nurse practitioner and/or registered nurse.

The research DF/HCC Multi-center Protocol participating site will then call or e-mail Meghan Rourke to verify eligibility. To complete the registration process, Meghan Rourke will:

- Register the participant on the study with the DF/HCC Quality Assurance Office for Clinical Trials (QACT)
- Fax or e-mail the participant case number, and if applicable the dose treatment level, to the participating site
- Call the research nurse or data manager at the participating site and verbally confirm registration

Randomization can only be done between normal QACT business hours, 8:30am-5:00pm EST.

5.8 DF/HCC Multi-center Protocol Case Number

Once eligibility has been established and the participant successfully registered, the participant is assigned a five digit protocol case number. This number is unique to the participant on this trial and must be used for QACT eCRF completion and written on all data and QACT correspondence for the participant.

5.9 DF/HCC Multi-center Protocol Registration Policy

5.9.1 Initiation of Therapy: Participants must be registered with the DF/HCC QACT before receiving treatment. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the participant's Registration Confirmation memo from the DF/HCC QACT. Therapy must be initiated per protocol guidelines. The Protocol Chair and DFCI IRB must be notified of any exceptions to this policy**.**

5.9.2 Eligibility Exceptions: The DF/HCC QACT will make no exceptions to the eligibility requirements for a protocol without DFCI IRB approval.

5.9.3 Verification of Registration, Dose Levels, and Arm Designation: A registration confirmation memo for participants registered to DF/HCC Multi-Center Protocol will be faxed or emailed to the registering institution within one working day of the registration. Treatment may not be initiated until the site receives a faxed or e-mailed copy of the registration confirmation memo.

5.9.4 Confidentiality: All documents, investigative reports, or information relating to the participant are strictly confidential. Any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Lead Institution or designee must have the participant's full name & social security number "blacked out" and the assigned DF/HCC QACT case number and protocol number written in (with the exception of the signed informed consent document). Participant initials may only be included or retained for cross verification of identification.

5.10 Schedule of Data Submission

The DF/HCC QACT develops a set of either paper or electronic case report forms, (CRF/eCRFs) for use with the DF/HCC Multi-Center Protocol. QACT provides a web based training for eCRF users. These forms are designed to collect data for each study. The schedule for submission of case report forms to the DF/HCC QACT is specified in Section 11.2.

5.11 Data Form Review

When data forms arrive at the DF/HCC QACT, they are reviewed for:

Timeliness:
Did the form arrive on time as specified in the protocol?

Completeness:
Is all the information provided as required per protocol?

Participant Eligibility:
Does the participant meet the eligibility requirements for the study based on the demographic data, lab values and measurements provided?

Stratification:
Are the stratification parameters consistent with what was given at the time of registration?

Protocol Treatment Compliance:
Are the body surface area (BSA) and drug dosage calculations correct? The dose must be within 10% of the calculated protocol dose.

Adverse Events (Toxicities):
Did the participant experience adverse events (toxicities or side effects) associated with the treatment? Was the treatment delayed due to the adverse event? What was the most severe degree of toxicity experienced by the participant?

Notations concerning adverse events will address relationship to protocol treatment for each adverse event grade. All adverse events encountered during the study will be evaluated according to the NCI Common Toxicity Criteria assigned to the protocol and all adverse events must be noted on the participant's Adverse Event (Toxicity) Forms.

Response:
Did the participant achieve a response? What level of response did they achieve? On what date did the participant achieve the response and how was the response determined?

Response criteria are defined in the protocol. A tumor assessment must be performed prior to the start of treatment and while the participant is on treatment as specified by the protocol.

Objective responses must have documentation such as physical measurements, x-rays, scans, or laboratory tests.

A subjective response is one that is perceived by the participant, such as reduction in pain, or improved appetite.

5.12 Missing and Deficient Memorandum

Data submissions are monitored for timeliness and completeness of submission. Participating institutions are notified of their data submission delinquencies in accordance with the following policies and procedures:

Incomplete or Questionable Data

If study forms are received with missing or questionable data, the submitting institution will receive a written query from the DF/HCC QACT Data Analyst. Responses to the query should be completed and returned within 14 days. Responses may be returned on the written query or

on an amended case report form. In both instances the query must be attached to the specific data being re-submitted in response.

Missing Forms

If study forms are not submitted on schedule, the participating institution will receive a Missing Form Report from the DF/HCC QACT noting the missing forms. These reports are compiled by the DF/HCC QACT and distributed a minimum of three times a year.

6.0 REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in Appendix 8 (LBH589 Order Form).

Participating sites should order their own agent regardless of the supplier (i.e., NCI or a pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB. If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

7.0 SAFETY ASSESSMENTS AND TOXICITY MONITORING

All participants receiving investigational agents will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported to the investigator by participants. All toxicities encountered during the study will be evaluated according to the NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) and recorded prior to each course of therapy. Life-threatening toxicities should be reported immediately to the Protocol Chair and Institutional Review Board (IRB).

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

7.1 Serious Adverse Events

A serious adverse event (SAE) is any adverse drug experience at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions in a participant who has never had seizure activity in the past that do not result in inpatient hospitalization, or the development of drug dependency or abuse.

The NIH-NCI Common Terminology Criteria for Adverse Events, version 3.0 (CTCAEv3.0, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf) will be utilized for AE reporting.

7.2 Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Serious Adverse Events (SAEs) will be followed as is delineated in the protocol Section 8.

In addition, the Participating Institutions must report the serious adverse events to the Protocol Chair and the Coordinating Center (Lead Institution) following the DFCI IRB SAE Reporting Requirements.

The Lead Institution will maintain documentation of all Adverse Event Reporting and be responsible for communicating all SAEs to all Participating sites.

7.3 Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. In compliance with these FDA regulations, the Protocol Chair is responsible for reviewing all IND Safety Reports and forwarding the IND Safety Reports to the Participating Institutions. The investigators are to file a copy with their protocol file and send a copy to their IRB according to their local IRB's policies and procedures.

8.0 PROTOCOL VIOLATIONS AND DEVIATIONS

Neither the FDA nor the ICH GCP guidelines define the terms "protocol violation" or "protocol deviation." All DF/HCC Protocol Chairs must adhere to those policies set by the DFCI IRB, the definitions for protocol violation and deviation as described by the DFCI IRB will be applied for reporting purposes for all institutions participating in the DF/HCC Multi-center Protocol.

8.1 Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a subject who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol deviation that was not prospectively approved by the IRB prior to its initiation or implementation.

8.2 Reporting Procedures

The Protocol Chair: is responsible for ensuring that clear documentation is available in the medical record to describe all protocol exceptions, deviations and violations. The Protocol Chair will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from DFCI IRB. The Participating institution must submit the deviation request to the Protocol Chair or designee, who will submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation should be submitted to the participating site's own IRB, per its institutional policy.
A copy of the participating institution's IRB report and determination will be forwarded to the DF/HCC Lead Institution or designee by mail, facsimile, or via e-mail within 10 business days after the original submission.

All protocol violations must be sent to the DF/HCC Lead Institution Protocol Chair or designee in a timely manner.

Coordinating Center: Upon receipt of the violation/deviation report from the participating institution, the DF/HCC Lead Institution or designee will submit the report to the Protocol Chair for review. Subsequently, the participating institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

9.0 QUALITY ASSURANCE

The quality assurance process for a clinical trial research study requires verification of protocol compliance and data accuracy. As the Coordinating Center, the DF/HCC Lead Institution or designee with the aid of the QACT provides quality assurance oversight for the DF/HCC Multi-center Protocol.

9.1 Ongoing Monitoring of Protocol Compliance

All data submitted to the DF/HCC QACT will be monitored for timeliness of submission, completeness, and adherence to protocol requirements. Monitoring will begin at the time of participant registration and will continue during protocol performance and completion. The Lead Institution or designee and if applicable QACT Data Analysts assigned to the Protocol will perform the ongoing protocol compliance monitoring with the support of the participating institution's Coordinators, the Principal Investigators, and the Protocol Chair.

9.2 Evaluation of Participating Institution Performance

9.2.1 Eligibility Checklist

Eligibility criteria are checked on a protocol-specific eligibility checklist and faxed to the DF/HCC QACT prior to registration on protocol. The checklist and informed consent document are reviewed by a DF/HCC QACT Protocol Registrar before the participant can be registered on a protocol. The DF/HCC QACT cannot make exceptions to the eligibility requirements.

9.2.2 Accrual of Eligible Participants

Annual accrual rates for eligible participants enrolled onto therapeutic clinical trials is calculated for each institution. Institutions are expected to maintain the minimum annual average accrual as defined by the protocol grant or contract.

9.3 On-Site Auditing

9.3.1 DF/HCC Sponsored Trials

On-site monitoring will occur on an as-needed basis. At a minimum, the DF/HCC Lead Institute, or designee, will visit each participating twice a year while patients are receiving treatment.

The participating institutions may be required to submit subject source documents to the DF/HCC Lead Institution or designee for monitoring.

9.3.2 Participating Institution

It is the participating institution's responsibility to notify the DF/HCC Lead Institution or designee of all scheduled audit dates (internal or NCI) and re-audit dates (if applicable), which involve the DF/HCC Multi-Center Protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the DF/HCC Lead Institution or designee within 12 weeks after the audit date.

9.3.3 Coordinating Center (Lead Institution or designee)

The Protocol Chair will review all DF/HCC Multi-Center Protocol Final Audit reports and corrective action plans if applicable. The Lead Institution or designee must forward these reports to the DF/HCC QACT per DF/HCC policy for review by the DF/HCC Audit Committee. Based upon the audit assessments the DF/HCC Audit Committee could accept or conditionally accept the audit rating and final report. Conditional approval could require the Protocol Chair to implement recommendations or require further follow-up. For unacceptable audits, the Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

9.4 Sub-Standard Performance

The Protocol Chair, and the DFCI IRB is charged with considering the totality of an institution's performance in considering institutional participation in the DF/HCC Multi-Center Protocol.

9.4.1 Corrective Actions

Institutions that fail to meet the performance goals of accrual, submission of timely accurate

data, and adherence to protocol requirements will be recommended for a six- month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Institutions that fail to demonstrate significant improvement will be considered by the Protocol Chair for revocation of participation.