MSK PROTOCOL COVER SHEET

An Open-Label Phase II Study of Mocetinostat in Selected Patients with Mutations of Acetyltransferase Genes in Relapsed and Refractory Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

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Table of Contents

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Title: An Open-Label Phase II Study of Mocetinostat in Selected Patients with Mutations of Acetyltransferase Genes in Relapsed and Refractory Diffuse Large B-Cell Lymphoma and Follicular Lymphoma

Objectives: The purpose of this trial is to determine the therapeutic efficacy of mocetinostat in selected patients with CREBBP/EP300 alterations in relapsed and refractory DLBCL and FL.

Patient Population: Patients with histologically confirmed relapsed or refractory diffuse large B cell lymphoma and follicular lymphoma with mutations of CREBBP or EP300.

Study Design: This is an open label phase II study in patients with relapsed and refractory NHL in 2 histologic subgroups: diffuse large B cell lymphoma and follicular lymphoma. Patients with mutations of CREBBP and/or EP300 will be eligible for the trial. Eligible patients will be be treated by mocetinostat and monitored for overall response, event free survival, and duration of response.

Treatment Plan: Patients who harbor mutations for CREBBP and/or EP300 will be started on mocetinostat 70 mg orally three times per week on a 28 day schedule in cycle 1. The dose will be escalated in cycle 2 to 90 mg orally three times per week on a 28 day schedule if there are no grade 3 or higher drug related toxicities. Therapy will continue until disease progression, intolerable toxicities or death.

Time to Completion: We anticipate that this study will enroll 10 patients in each cohort of follicular lymphoma and diffuse large B cell lymphoma. If 2 or more patients in each cohort show a response, we will enroll an additional 15 patients in that cohort for the second stage of the trial. Assuming a dropout rate of 10%, we plan to enroll 56 patients total, 28 patients in each cohort over 48 months.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1. PRIMARY OBJECTIVES

- Determine the efficacy as defined by overall response rate of Mocetinostat at one year in patients with relapsed/refractory DLBCL and FL who have inactivating mutations of acetyltransferase genes.

2.2. SECONDARY OBJECTIVE

- Assess the event free survival of mocetinostat in this selected population
- Assess the duration of response of mocetinostat in this selected population
- Assess the safety and tolerability of mocetinostat in this selected population

2. 3. EXPLORATORY ASSESSMENTS

- Correlation of myc and Bcl-2 positivity for treatment response
- Assessment of mechanisms of resistance to mocetinostat via genetic mutation analysis
- Assay T cell activation and exhaustion in the peripheral blood

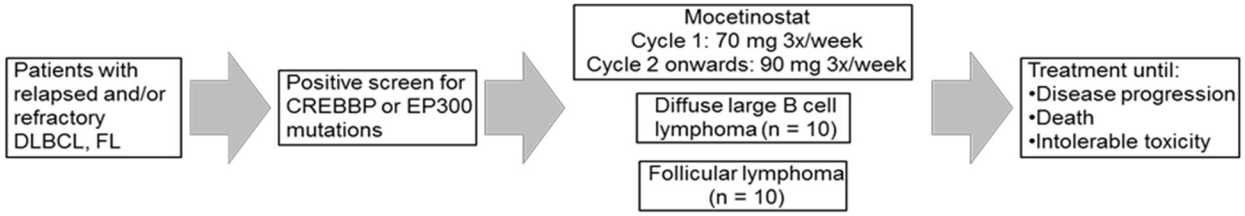

Figure 2-1. Study design overview

3.0 BACKGROUND AND RATIONALE

3.1 Rationale

This is a single center, open label, single arm single step phase II study of mocetinostat in patients with relapsed and refractory DLBCL and FL harboring mutations in CREBBP and EP300 (Figure 2-1). The integrated assessment of CREBBP and EP300 mutations were chosen based on preclinical data suggesting patients harboring CREBBP or EP300 mutations may be more sensitive to HDAC inhibition[1]. The purpose of this study is to determine the therapeutic efficacy of mocetinostat in selected patients with CREBBP/EP300 alterations in relapsed and refractory DLBCL and FL. Approximately 30% of patients with DLBCL and FL harbor inactivating mutations in acetyltransferase genes which may make their disease more susceptible to HDAC inhibition. Mocetinostat has been previously shown to elicit modest responses of 15-17% in unselected DLBCL and FL patients[2]. Selection for populations of DLBCL and FL patients with increased sensitivity to HDAC inhibition may identify a population of patients with a heightened response to HDAC therapy. The starting dose for mocetinostat for this study is based on the results of the prior phase II clinical trial assessing mocetinostat in DLBCL and FL. The starting dose will be 70 mg orally three times a week on a 28 day schedule on cycle 1 followed by dose increase to 90 mg orally three times a week on a 28 day schedule if there are no grade 3 or higher drug related toxicities. Dose reductions will be determined based on side effect profile.

3.2. Background

3.2.1. Overview of disease pathogenesis, epidemiology and current treatment

Non-Hodgkin lymphomas (NHL) are a heterogeneous group of lymphoproliferative malignancies with differing patterns of behavior and responses to treatment[3]. NHL is the ninth and seventh most frequent cancer in males and females, respectively, with an incidence of approximately 69,000 new patients each year and 19,000 deaths each year in the United States (US) [4]. The incidence rises with age becoming an important cause of mortality and morbidity in adults. NHL can occur at any age and is clinically marked by enlarged lymph nodes, fever, and weight loss. Though considered a curable disease, about 50% of NHL patients are not cured with available therapy. The current 5-year and 10- year survival rates for lymphoma are 68% and 57%, respectively [4].

3.2.2. Rationale for HDAC inhibition in patients with CREBBP and EP300 alterations

Diffuse Large B-cell Lymphoma (DLBCL) represents the most common form of B-cell non-Hodgkin Lymphoma (B-NHL), accounting for ~30% of the de-novo diagnoses and also arising as a frequent clinical evolution of Follicular Lymphoma (FL) [5]. The molecular pathogenesis of DLBCL is

associated with multiple genetic lesions that segregate in part with individual phenotypic subtypes, namely germinal-center B-cell-like (GCB) and activated B-cell-like (ABC) DLBCL, suggesting the involvement of distinct oncogenic pathways [6, 7]. Genome-wide efforts toward the identification and functional characterization of the entire set of structural alterations present in the DLBCL genome are required for a complete understanding of its pathogenesis [8].

Combining next generation whole-exome sequencing analysis of 7 DLBCL cases and genome-wide high-density single nucleotide polymorphism (SNP) array analysis of 72 DLBCL cases identified >450 loci that are affected by somatic point mutations and/or by recurrent, focal gene copy number (CN) aberrations[1]. The most commonly independently validated mutations involved the acetyltransferase genes CREBBP (CBP) and EP300 (p300). CREBBP encodes a highly conserved and ubiquitously expressed nuclear phosphoprotein that, together with the closely related protein EP300, belongs to the KAT3 family of histone/protein lysine acetyltransferases[9, 10] (Figure 3-1). CREBBP and EP300 function as transcriptional coactivators for a large number of DNA-binding transcription factors involved in multiple signaling and developmental pathways, by modifying lysine residues on both histone and non-histone nuclear proteins [11, 12]. CREBBP and EP300 enhance transcription by multiple mechanisms, including targeted acetylation of chromatin [11, 12], acetylation of transcriptional activators (e.g., the tumor suppressors p53 and GATA1) [13-16], and acetylation-mediated inactivation of transcriptional repressors (e.g. the DLBCL-associated oncogene BCL6) [17]. Additionally, both molecules were found to exhibit ubiquitin ligase activity [18].

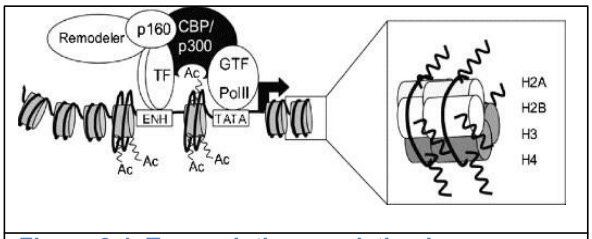

Figure 3-1. Transcription regulation by CREBBP/EP300. Schematic representation of the promoter region of a gene, with the DNA wrapped around octamer nucleosomes, the histone proteins H2A, H2B, H3 and H4. A transcription factor dimer (TF), bound to the enhancer region (ENH), recruits remodeling factors (remodeler) and HATs, like CREBBP or p300 (CBP/p300), sometimes indirectly through other coactivators like the p160 proteins. CBP and p300 can make the DNA more accessible for other regulatory proteins by acetylating the histone tails (Ac). In addition, CBP and p300 can form a physical bridge between transcription factors and the general transcription factors (GTF) and RNA polymerase II (Pol II) [9]

Previous extensive surveys in malignancies of epithelial origin have reported inactivating mutations of EP300 and CREBBP in exceedingly rare cases (<2% of primary biopsies) [19-21]. However, recurrent mutations of CREBBP are found in B-cell acute lymphoblastic leukemia [22] suggesting a specific role for CREBBP/EP300 inactivation in the pathogenesis of malignancies derived from B-lymphocytes. Overall, CREBBP/EP300 lesions are among the most frequent structural alterations yet detected in FL and DLBCL, thus representing an important feature of the pathogenesis of these common diseases. In DLBCL, CREBBP mutations and deletions typically caused the elimination or truncation of the HAT domain implicating functional significance. Of the mutations, 17 (50%) were inactivating events, including nonsense mutations (n=9), frameshift insertions/deletions (n=7) and mutations at consensus splice donor/splice acceptor sites (n=1), which generate aberrant transcripts carrying premature stop codons. The remaining variants included 3 in-frame deletions and 14 missense mutations, primarily within the HAT domain (Figure 3-2A). The lesions were predominantly monoallelic (n=33/39 cases) with rare instances of biallelic genetic lesions include the homozygous loss, a missense mutation with loss of heterozygosity (2 primary biopsies), biallelic nucleotide substitutions (2 cases), and a frameshift deletion with missense mutation of the second allele in the OCI-Ly8 cell line.

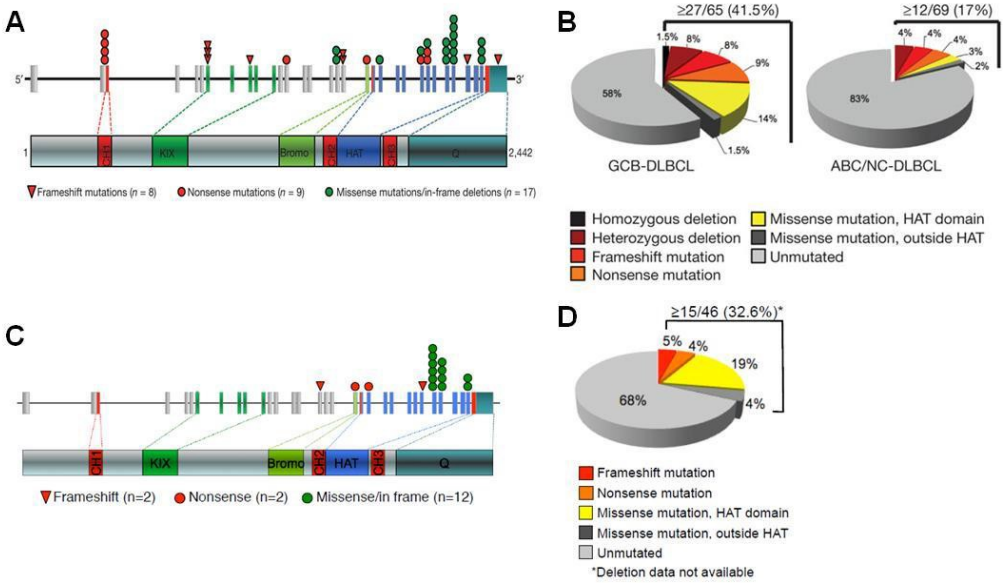

Figure 3-2. CREBBP mutations in DLBCL and FL. A. Schematic diagram of the CREBBP gene (top) and protein (bottom). Exons are colour-coded according to the corresponding protein functional domains (CH, cysteine-histidine rich; KIX, CREB-binding; Bromo, bromodomain; HAT, histone acetyltransferase; Q, polyglutamine stretch). Colour-coded symbols depict distinct types of mutations. B. frequency of CREBBP structural alterations in DLBCL subtypes (mutations and deletions, combined). C. Distribution of FL associated point mutations along CREBBP gene and protein.D. Overall frequency of CREBBP mutations according to mutation type.[1]

Cumulatively, 29% of all DLBCL patients (n=39/134), corresponding to 41.5% of GCB- and 17% of ABC-DLBCL, harbor genomic alterations affecting the CREBBP gene (Figure 3-2B). Mutations analogous to those found in DLBCL were frequent in FL (32.6%, with 16 events distributed in 15/46 cases), but not in other lymphoma types such as Burkitt lymphoma, marginal zone lymphoma, and chronic lymphocytic leukemia, suggesting a specific role in the pathogenesis of these two diseases (Figure 3-2C,D).

Mutational analysis of the EP300 gene in the same panel identified 19 sequence variants leading to frameshift mutations (n=4), nonsense mutations (n=2), missense or in-frame deletions (n=13) (Figure 3-3A). These lesions were found in 10% of DLBCL (n=13/134) and 8.7% of FL samples (n=4/46), but were virtually absent in other B-NHLs (Figure 3-3A). Seven additional DLBCLs harbored monoallelic deletions spanning, although not limited to, the EP300 locus. Notably, structural alterations of CREBBP and EP300 co-exist in only a minority of the affected cases (n=6/53 DLBCL and 0/19 FL) suggesting that inactivation of these loci is at least in part functionally equivalent.

Overall ~39% of all DLBCL and at least 41% of FL cases (based on mutations only) display structural alterations of KAT3 family genes. One key observation is that CREBBP/EP300 lesions are mostly detected in heterozygosity, suggesting a haploinsufficent role in tumor suppression. This is supported by data demonstrating congenital heterozygous mutations of CREBBP/EP300 are

sufficient to cause pathologic and developmental abnormalities including tumorigenesis [23], CREBBP heterozygote mice have de novo hematologic malignancies [24], and unlike ubiquitously expressed histone deacetylases, HAT cellular concentrations are tightly regulated therefore small dosage variations can have severe biological consequences [25].

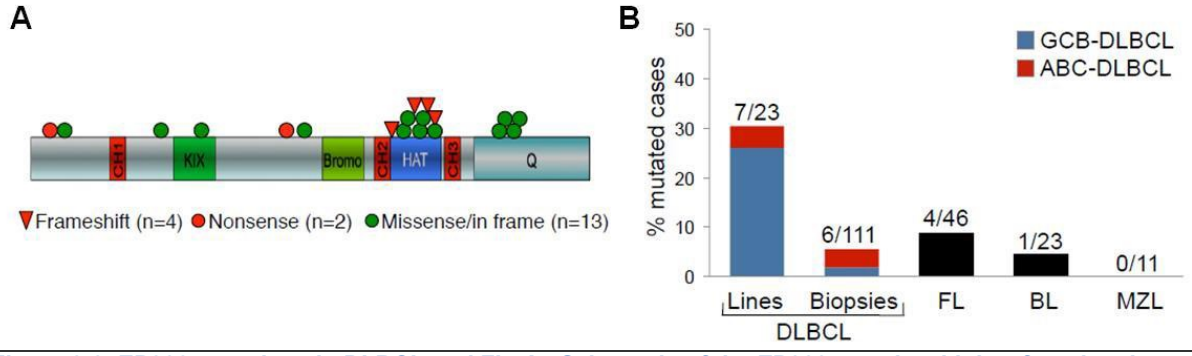

Figure 3-3. EP300 mutations in DLBCL and FL. A. Schematic of the EP300 protein with key functional domains and color coded symbols indicating distinct types of mutational events. B. Frequency of EP300 mutated samples in DLBCL, FL, Burkitt lymphoma (BL) and marginal zone lymphoma (MZL). [1]

Mutant CREBBP and EP300 proteins are deficient in acetylating BCL6 and p53, leading to constitutive activation of the oncoprotein and to decreased p53 tumor suppressor activity [1]. The balance between the activities of these two genes is critical for the regulation of DNA damage responses in mature germinal center cells during immunoglobulin gene remodeling [26, 27]. The consequences of BCL6 activity overriding p53 would be an increased tolerance for DNA damage in the context of diminished apoptotic and cell cycle arrest responses. The use of HDAC inhibitors in this HAT mutated population may contribute to re-establishing physiologic acetylation levels sensitizing the lymphoma to cellular apoptosis and cell cycle arrest [1]. Therefore, the efficacy of HDAC inhibitors should be selectively evaluated in patients with HAT mutations in CREBBP and EP300.

3.2.3. Overview of Diffuse Large B-cell Lymphoma

DLBCL comprises more than 30% of all newly diagnosed NHL cases. Majority (over 80%) are aggressive lymphomas, and more than half of these patients are older than 60 years. The advent of rituximab has significantly improved the outcomes for patients with DLBCL and approximately 50% of patients are cured with rituximab and chemotherapy. The remaining 50% of DLBCL patients, especially the poor risk patients with International Prognostic Index (IPI) ≥ 3 factors, will relapse or progress despite a good initial response to the front line immuno- chemotherapy. High-dose chemotherapy with autologous stem-cell transplantation (HDT/ASCT) is an established treatment option for poor-prognosis patients who are 65 or younger and refractory to front line therapy. Nevertheless, more than half of these patients will relapse following HDT/ASCT and die of the disease. The prognosis among patients who are not transplant candidates is even more dismal. Therefore, novel drug therapy with different mechanisms to prolong duration of disease remission in

poor risk patients and eventually to improve long term survival among these patients is a pressing need.

3.2.4. Overview of Follicular Lymphoma

FL is the second most common form of NHL prevailing in the United States representing 22% of all newly diagnosed cases of NHL. Despite an advanced stage, the clinical course of disease is usually indolent and patients are highly responsive to various combinations of standard chemotherapy drugs. The disease, however, is not curable with available treatment, and most patients tend to relapse after treatment with shorter intervals of remission in between. In approximately 30% of patients, the disease progresses more rapidly with transformation into DLBCL and early death. The molecular biology underlying this phenomenon and the factors associated with the risk of transformation are not entirely known.

The incorporation of effective and well-tolerated monoclonal antibodies, such as rituximab, into chemo-immunotherapeutic strategies provided the first evidence that survival of these patients could be prolonged. A relatively small pivotal phase II study in 166 patients with relapsed FL resulted in rituximab being the first FDA approved monoclonal antibody for the treatment of cancer. The combination of rituximab and chemotherapy (R-Chemo) has resulted in greatly improved response rates, Event free survival and also overall survival, to such an extent that R-Chemo is now worldwide the standard induction treatment in first line as well as for relapsed advanced stage FL.

Nevertheless, FL remains incurable and characterized by recurrent relapses requiring additional treatment. An increasing number of effective drugs are now being evaluated either alone or in combinations including the chemotherapy drugs bendamustine and bortezomib. More targeted agents include monoclonal antibodies and their derivatives such as drug- antibody conjugates and small molecular immunopharmaceuticals. Other agents inhibit various cellular pathways including those triggered by the B-cell receptor, including spleen tyrosine kinase (Syk) and Bruton’s tyrosine kinase, and other intracellular pathways such as the mTOR, phosphatidylinositol-3-Kinase (PI3K), and apoptosis, and drugs that target the tumor microenvironment. This abundance stresses the unremitting need for clinical trials aimed at answering the many open questions as to optimal treatment strategies in advanced FL[28].

3.2.5. Histone acetylation pathway

Epigenetic events such as acetylation, methylation, ubiquitination and phosphorylation of histones control accessibility of chromatin structure for DNA transcription, replication, repair and cellular development. Deregulation of histone acetylation is rapidly being recognized as a hallmark of cancer. Human histone deacetylases are classified into four classes: class I comprised of HDAC 1, 2, 3, and 8 are localized to the nucleus with ubiquitous tissue expression, class II comprised of HDAC 4, 5, 6, 7, 9, 10 with variable cellular localization, class III includes NAD-dependant homologues of yeast SIRT 1-7 not currently targeted by currently available HDAC inhibitors, and class IV comprised of HDAC 11 with properties of class I and class II HDAC [29]. Histone deacetylases (HDACs) remove acetyl groups from histone and non-histone proteins altering oncogenic genetic and protein expression profiles [29].

Decreased major histocompatibility class II (MHCII) expression on the tumors in both DLBCL subtypes directly correlates with significant decreases in patient survival. One common mechanism accounting for MHCII downregulation in DLBCL is reduced expression of the MHC class II transactivator (CIITA), the master regulator of MHCII transcription. Furthermore, reduced CIITA expression in ABC DLBCL correlates with the presence of the transcriptional repressor positive regulatory domain-I-binding factor-1 (PRDI-BF1). Treatment of CIITA(-) or CIITA(low) GCB cells with several different histone deacetylase inhibitors (HDACi) activated modest CIITA and MHCII expression. However, CIITA and MHCII levels were significantly higher in these cells after exposure to the HDAC-1-specific inhibitor MS-275. These results suggest that CIITA transcription is repressed in GCB DLBCL cells through epigenetic mechanisms involving HDACs, and that HDAC inhibition can alleviate repression [30].

HDAC inhibition induces large scale epigenetic changes to multiple cancer signaling networks[31-33]. Thus far, two HDAC inhibitors, vorinostat and romidepsin, have been approved by the Federal Drug Administration (FDA) for treatment of cutaneous T cell lymphoma and peripheral T cell lymphoma. Clinical activity has also been observed in Hodgkin lymphoma [34-37], DLBCL [38], multiple myeloma [39, 40], and acute myeloid leukemia [41].

3.2.6. Overview of mocetinostat

Mocetinostat (MGCD0103) is an oral second generation benzamide HDAC inhibitor that selectively inhibits HDAC 1, 2, 3 and 11 [42, 43]. Mocetinostat, an isotype selective HDAC inhibitor against HDAC1, HDAC2, HDAC3, HDAC11, has broad spectrum antitumor activity in vitro and in vivo. Mocetinostat induced hyperacetylation of histones, selectively induced apoptosis, and caused cell cycle blockade [43]. Mocetinostat exhibited potent anti-proliferative activity in cancer cell lines, but not in normal human cells, consistent with its proposed mechanism of action. In in vivo xenograft studies, mocetinostat inhibited tumor growth in prostate, NSCLC, colon cancers [42].

As of April 2013, mocetinostat has been evaluated in 13 clinical trials, including 440 clinical trial patients with the following malignancies: Hodgkin lymphoma (HL), non-Hodgkin lymphoma (NHL) [including diffuse large B-cell (DLBCL) and follicular lymphoma], acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), chronic myelogenous leukemia (CML) and advanced solid tumors including adenocarcinoma of the pancreas.

The safety profile of mocetinostat has been defined based on clinical studies. Fatigue has been observed consistently throughout the mocetinostat clinical evaluation program and has been deemed a drug-related toxicity. Gastrointestinal (GI) toxicities such as anorexia, nausea, vomiting and diarrhea have been reported as related to mocetinostat. Associated conditions, including, but not limited to, dehydration, electrolyte abnormalities such as hypokalemia (in a few cases concomitant with QTc prolongation), hypotension, and syncope, also have been observed. Less frequently, cystitis symptoms (e.g., dysuria, pollakiuria, hematuria, urgency and bladder spasm) have been reported in some subjects that received multiple cycles of treatment. In addition, a potential association of mocetinostat treatment with pericardial events has been investigated. Consequently, current studies will include echocardiogram and ECG monitoring and will exclude patients at higher risk of pericardial events. Neutropenia and thrombocytopenia have been observed more frequently in subjects with a diagnosis of MDS, leukemia or lymphoma than in patients with

other types of cancer, or in combination with a myelosuppressive agent such as gemcitabine. Patients experiencing GI toxicity, cystitis symptoms, or pericardial events should be monitored appropriately.

3.2.7. Preclinical Data

Pharmacodynamics

Mocetinostat was shown to be a selective, potent, and dose-dependent inhibitor of human Class I HDACs (isoforms 1, 2, and 3) and Class IV (isoform 11) (Table 3-1). There was weak or no activity against Class II HDACs or HDAC 8. A kinetic analysis using HDAC 1 demonstrated that mocetinostat is a potent competitive inhibitor, with a Ki of 645 nM. Binding was reversible, with high affinity and slow kinetics. In addition, mocetinostat induced acetylation of core histones H4 and H3 in human bladder carcinoma (T24) cells, with an EC50 of 0.4 μM and 0.2 μM, respectively. Acetylation of histones was also observed in A549 human non-small cell lung carcinoma cells and A2780-S human ovarian carcinoma cells. Core histone acetylation was dose-dependent and was correlated with HDAC inhibition.

Mocetinostat induced cell cycle arrest of HCT116 human colon carcinoma cells in a dose-dependent manner. G2/M and sub-G1 accumulation was also observed in HeLa human cervical cancer cells and A549 human non-small cell lung carcinoma cells. These effects were shown to occur via a mechanism independent of tubulin polymerization. Exposure of HCT116 cells to mocetinostat at concentrations of 1 to 25 μM resulted in the dose-dependent induction of apoptosis. Dose-dependent apoptosis also was observed in both A549 human lung carcinoma cells and HeLa human cervical carcinoma cells at concentrations of 1 μM (the lowest concentration tested). Mocetinostat also induced significant apoptosis in several hematologic cancer cell lines, including Jurkat T-cell leukemia cells, MV-4-11 acute myeloid leukemia cells, U266B1 multiple myeloma cells, and HL60 promyelocytic leukemia cells. Induction of apoptosis in all four hematologic cancer cell lines was dose-dependent. Expression of the tumor suppressor $p21^{waf1/Cip1}$ was upregulated both at the level of transcription and at the level of translation. A concentration of 1 μM mocetinostat induced $p21^{waf1/Cip1}$ expression at least 2-fold in HCT116 colon carcinoma cells. This effect was independent of p53 status: p21waf1/Cip1 induction was observed both in HeLa cervical cancer cells, which are p53-null, and in A549 lung carcinoma cells, which express wild type p53.

Table 3-1. Biochemical inhibition of HDAC activity by mocetinostat

Parameter	Class I HDAC Isoforms				Class II HDAC Isoform				Class IV HDAC Isoforms
	1	2	3	8	4	5	6	7	11
Inhibition (+/-)	+	+	+	-	-	-	-	-	+
IC_{50} (μM)	0.15	0.29	1.66	>20	15	>20	>20	>20	0.59

Mocetinostat had anti-proliferative pharmacodynamic activity against A549 lung cancer cells and Du145 prostate cancer cells (IC_{50} 1.0 μM), but not against normal human cells (IC_{50} > 20 μM). Inhibition was independent of p53 status as A549 cells express p53, whereas Du145 cells are p53-null. The anti-proliferative activity of mocetinostat was assessed against a variety of other human cancer cells with IC_{50} in lymphoma cell lines ranging 0.15 – 0.5 μM (Table 3-2).

Table 3-2. In Vitro Anti-proliferative Activity Against Various Human Lymphoma Cancer Cell Lines

Lymphoma Cell Lines	Subtype	IC_{50} (μM)
U937	Histiocytic lymphoma	0.15
HDLM-2	Hodgkin lymphoma	0.25
SP53	Lymphocytic lymphoma	0.32
L428	Hodgkin lymphoma	0.47
MINO	Mantle cell lymphoma	0.48
KM-H2	Hodgkin lymphoma	0.50

Nonclinical pharmacokinetics and metabolism

Pharmacokinetic studies of orally administered mocetinostat (or its dihydrobromide salt) were carried out in female CD-1 mice, female Sprague−Dawley rats, and male beagle dogs. The oral bioavailability was 12% in mice and 47% in rats. Pharmacokinetic parameters in mice and rats were linear with the dose administered and independent of vehicles used. In dogs, pharmacokinetic parameters were nonlinear with the dose and dependent on the vehicles used. A wide range of bioavailability (1−92%) was observed in dogs. It was noted that a lower pH resulted in higher bioavailability. The compound was quickly absorbed, with a short Tmax across all species tested. The terminal phase elimination half-life for 8 administered iv was 0.6 h in mice, 0.7 h in rats, and 1.3 h in dogs. The clearance in the mice (4.3 (L/h)/kg) was high, but the clearance in rats (1.7 (L/h)/kg) and dogs (2.0 (L/h)/kg) was reasonable. Steady state volume of distribution was low in mice (0.34 L/kg) and higher in rats (0.91 L/kg) and dogs (0.80 L/kg)20.

In vitro experiments also showed that mocetinostat binds to plasma proteins, and is relatively stable in the presence of liver microsomes (80 to 90% recovery). Mocetinostat was shown to be metabolized by CYP 3A4, and possibly CYP 2E1 and CYP 2C8, and to be a strong inhibitor of CYP 2C9 and a weak inhibitor of CYP 3A4. In addition, mocetinostat induced CYP 1A2 (only at the highest concentration tested, 5 μM), but did not induce CYP 3A4. Mocetinostat was also shown to be transported by P-gp, as well as to be a P-gp inhibitor.

Mocetinostat showed dose proportional PK except at very high doses and variable bioavailability across species. There was evidence of higher bioavailability with lower pH vehicles. In rats, females had higher exposure than males, but no gender differences were seen in dogs. Further information concerning the pharmacokinetic and pharmacodynamic properties of mocetinostat may be found in the Investigator Brochure.

Safety pharmacology and toxicology

The nonclinical safety profile of mocetinostat has been evaluated in a cardiovascular safety pharmacology study in dogs, in repeated dose toxicology studies in rats and dogs (for durations of 7 days, 28 days, 13 weeks, and 26 weeks), and in genotoxicity studies.

No evidence of mocetinostat-induced changes in cardiovascular or hemodynamic function was observed in the cardiovascular safety pharmacology, as well as in the repeated-dose toxicity studies. No adverse central nervous system (CNS) or respiratory effects have been observed in the repeated-dose toxicity studies.

Test article-related effects observed across the repeated-dose toxicology studies with mocetinostat in rats and dogs include reduced body weights and clinical pathology changes indicative of bone marrow suppression. Microscopic findings were observed in the liver, pancreas, spleen, thymus, and lung following daily administration. Histopathological changes were observed in the liver and corpora lutea of the rat and in the pancreas of the dog following administration 3 times a week.

Mocetinostat was mutagenic in vitro in the bacterial reverse mutation assay only in 1 of the conditions tested (TA98 with S9 activation), but not in the in vitro mouse lymphoma forward mutation assay. Mocetinostat increased the incidence of micronucleated erythrocytes when orally administered to rats at doses of 500 to 2000 mg/kg..

3.2.8. Clinical Data

Mocetinostat monotherapy and mocetinostat in combination with other anticancer agents have been evaluated as part of the clinical development program. Mocetinostat has been investigated in 440 clinical trial patients with the following malignancies: Hodgkin Lymphoma, Non-Hodgkin Lymphoma (including DLBCL or follicular lymphoma), acute myeloid leukemia, myelodysplastic syndrome, chronic lymphocytic leukemia, acute lymphocytic leukemia and advanced solid tumors including adenocarcinoma of the pancreas.

Pharmacodynamic biomarker

Pharmacodynamic effects of mocetinostat have been examined by analyzing HDAC activity in peripheral blood WBCs from patients treated with mocetinostat. HDAC enzyme activity has been measured using a novel whole-cell enzyme activity assay. Briefly, in this assay, patients' peripheral WBCs are incubated with a membrane-permeable HDAC substrate for 1 hour at 37ºC. The reaction is then stopped, cells are lysed, and the deacetylated product is cleaved, releasing a fluorescent moiety that can be quantified by fluorometry. Data obtained from a total of 25 patients with solid tumors in a phase I study of mocetinostat in advanced metastatic solid tumors or aggressive Non-Hodgkin Lymphoma showed HDAC activity is inhibited in a time- dependent and dose-dependent manner. Prolonged HDAC inhibition (48 to 72 hours after dosing) was observed for doses 56 mg/m2. Similarly, prolonged HDAC inhibition was observed in peripheral blood mononuclear cells (PBMCs) from 9 patients with Hodgkin Lymphoma treated with 110 mg of mocetinostat.

Human safety and tolerability data

Four Phase I trials have evaluated mocetinostat monotherapy. Mocetinostat was not tolerated well by patients with advanced solid tumors when given daily as single oral dose of up to 17 mg/m2 for 14 days followed by a 7-day rest period. The DLT at 17 mg/m2 administered daily was fatigue. Dose-limiting fatigue, as well as nausea, vomiting, and diarrhea also appeared to be the major adverse effects observed to date in the other Phase I, Phase I/II, and Phase II studies with one of the following treatment schedules: 3 times weekly dosing for 2 weeks followed by a 7-day rest period; 3-times-weekly dosing for 3 weeks with no rest period; or 3 times weekly dosing for 4 weeks with no rest period.

The 3-times-weekly schedule appears to have improved tolerability compared with daily dosing, as higher MTDs have been observed with the former schedule. Studies with mocetinostat have escalated to a single-agent dose of 83 mg/m2 (average total daily dose = 160 mg) administered 3

times weekly without interruption. Treatment at this dose level was limited by GI toxicity. However, evaluation at 60 mg/m2 (average total daily dose = 110 mg) was initially determined to be the MTD according to protocol-defined criteria.

In patients with relapsed or refractory NHL (DLBCL and FL), safety data is reported for 69 patients, 41 patients with DLBCL and 28 patients in the FL cohort. The median age of these patients was 61 (range: 31 to 80). All patients had received prior cancer therapy. Mocetinostat was administered orally 3 times weekly for 4 consecutive weeks (28-day cycles). The starting dose was initially 110 mg, and it was reduced to 85 mg for non-life-threatening toxicities (e.g., fatigue, GI effects). Following an interruption to enrolment due to investigation of a possible relationship between treatment with mocetinostat and the observation of pericardial events in some patients, enrolment was resumed at a dose of 70 mg three times weekly. The study was subsequently closed for administrative reasons. In an attempt to consolidate the multiple dosing regimens of mocetinostat, the MTD will be specified as 90 mg three times weekly.

In addition to Phase I studies, the safety profile of mocetinostat has been evaluated as a single agent in Phase II studies. Four Phase II studies have evaluated mocetinostat as a monotherapy in the following populations: 1) Elderly, previously untreated patients with AML or MDS or adults with relapsed/refractory AML or high-risk MDS; 2) Patients with relapsed or refractory NHL; 3) Patients with refractory CLL; and 4) Patients with relapsed or refractory HL. The safety profile of mocetinostat has also been investigated in combination with other anticancer agents in Phase I/II and Phase II studies. Mocetinostat has been evaluated with Vidaza® (azacitidine) in patients with MDS, AML, HL, or NHL, with Gemzar® (gemcitabine) in patients with refractory solid tumors or pancreatic cancer, and with docetaxel in patients with solid malignancies. As of April 2013, mocetinostat has been evaluated in 440 patients in 13 clinical trials (analyses were performed based on 435 patients for whom sufficient information was captured in the database at the time of data cut).

System organ classes (SOCs) with the most frequently reported AEs (≥20% of all patients for an SOC) across all studies are summarized in Table 3-3; individual events occurring in ≥10% of all patients in a preferred term category within those SOCs are also presented. Overall, the percentage of patients experiencing any AE was 99.3%. The most frequent AEs (occurring in ≥20% of patients in a preferred term category) were nausea (71%), fatigue (70%), diarrhea (57%), vomiting (49%), anorexia (36%), anemia (26%), constipation (25%), pyrexia (25%), thrombocytopenia (24%), decreased weight (23%), abdominal pain (22%), cough (21%), dyspnea (21%), and peripheral edema (20%).

The most frequent AEs (occurring in ≥10% of patients in a preferred term category) considered related to study drug were the following: nausea (66%), fatigue (63%), diarrhea (50%), vomiting (44%), anorexia (31%), weight decreased (21%), anemia (21%), thrombocytopenia (20%), neutropenia (16%), abdominal pain (14%), decreased appetite (13%), asthenia (13%), constipation (12%), pyrexia (12%), dyspepsia (12%), headache (11%), dizziness (10%), and peripheral edema (10%).

SOCs with the most frequently reported Grade 3/4 AEs (≥10% of all patients for an SOC) across all studies are summarized in Table 3-4; individual events occurring in ≥5% of all patients in a preferred term category within those SOCs are also presented.

Overall, the percentage of patients experiencing any Grade 3/4 AE was 81%. The most frequent Grade 3/4 AEs (occurring in ≥10% of all patients in a preferred term category) were fatigue (25%), thrombocytopenia (17%), neutropenia (16%), anemia (14%), and febrile neutropenia (12%).

The most frequent Grade 3/4 AEs (occurring in ≥5% of all patients in a preferred term category) considered related to study drug were the following: fatigue (23%), neutropenia (14%), thrombocytopenia (14%), anemia (9%), nausea (8%), febrile neutropenia (7%), vomiting (5%), and anorexia (5%).

SOCs with the most frequently reported SAEs (≥10% of all patients for an SOC) across all studies are summarized in Table 3-4; individual events occurring in ≥5% of all patients in a preferred term category within those SOCs are also presented.

Overall, the percentage of patients experiencing any SAE was 59%. The most frequent SAEs (occurring in ≥5% of all patients in a preferred term category) were pneumonia (9%), febrile neutropenia (7%), AML (7%), dehydration (6%), fatigue (6%), and vomiting (5%).

Pericarditis and pericardial effusion, with or without cardiac tamponade, have been reported following treatment with mocetinostat. These events have been associated with SAEs in approximately 4% of patients. The incidence is higher in populations with greater predilection for pericardial abnormalities, including Hodgkin lymphoma, but also AML and NHL. Bladder toxicity resulting in dysuria and rarely hemorrhagic cystitis has been described in a few patients receiving mocetinostat.

Table 3-4. Most commonly reported grade 3/4 adverse events across all studies

System Organ Class/Preferred Term	All Patients (N=435)
Patients with at least one AE	350 (80.5)
Blood and lymphatic system disorders	**175 (40.2)**
Thrombocytopenia	72 (16.6)
Neutropenia	69 (15.9)
Anemia	59 (13.6)
Febrile neutropenia	52 (12.0)
General disorders and administration site conditions	**159 (36.6)**
Fatigue	108 (24.8)
Asthenia	21 (4.8)
Gastrointestinal disorders	**103 (23.7)**
Nausea	39 (9.0)
Vomiting	23 (5.3)
Abdominal pain	21 (4.8)
Diarrhea	20 (4.6)
Infections and infestations	**96 (22.1)**
Pneumonia	35 (8.0)
Metabolism and nutrition disorders	**93 (21.4)**
Anorexia	24 (5.5)
Hypokalemia	22 (5.1)
Dehydration	21 (4.8)
Investigations[a]	**58 (13.3)**
Respiratory, thoracic and mediastinal disorders	**57 (13.1)**
Dyspnea	28 (6.4)

a No individual event occurred at a percentage ≥5%.
Note: If the same event term was recorded multiple times for a patient, the patient was only counted once.

Table 3-4. Most commonly reported serious adverse events across all studies

System Organ Class/Preferred Term	All Patients (N=435)
Patients with at least one AE	255 (58.6)
Infections and infestations	**99 (22.8)**
Pneumonia	37 (8.5)
Gastrointestinal disorders	**66 (15.2)**
Vomiting	21 (4.8)
General disorders and administration site conditions	**65 (14.9)**
Fatigue	25 (5.7)
Blood and lymphatic system disorders	**58 (13.3)**
Febrile neutropenia	30 (6.9)
Neoplasms benign, malignant and unspecified	**53 (12.2)**
Acute myeloid leukemia	29 (6.7)

Note: If the same event term was recorded multiple times for a patient, the patient was only counted once.

Toxicity

Cardiac Arrythmias

Grade 3 AEs of QTc prolongation (> 500 msec) were reported in 4 of 435 patients in clinical trials with mocetinostat; 3 of those 4 events were also reported as part of SAEs. Three of the 4 patients already had a prolonged QTc at baseline. Three of the events of QTc prolongation occurred in a setting of GI disturbances associated with dehydration and/or hypotension. In 2 cases, there was definite hypokalemia, with concomitant low magnesium in one patient, and in both cases, the QTc values decreased quickly to baseline levels after IV administration of potassium and magnesium.

Concomitant treatment with drugs identified as having the potential to cause QTc prolongation may have been a factor in 2 patients.

Although therapy with mocetinostat does not appear to be an obvious risk factor for development of QTc prolongation, ECG monitoring may be warranted in the settings of GI disturbances associated with dehydration and/or electrolyte abnormalities.

Pericardial Events

MethylGene/Mirati identified pericardial AEs by searching the SAE database, the clinical database for each study, searching CT scan reports, and prospective ECHOs. The total number of patients with pericardial findings was 45 (10.3%), with 19 patients having serious adverse events (4.3%) (Table 3-5). An additional 26 on-study non serious pericardial findings (for a total of 45 pericardial findings) were identified by the Sponsor, including 6 incidental cases from database searches, 7 incidental cases from CT scan review, and 13 cases from prospective echocardiographic monitoring. A fourteenth pericardial finding was identified through echocardiographic monitoring (non-serious trivial pericardial effusion), subsequent to the complete analysis of pericardial events. There were also 14 patients identified with pericardial findings at baseline.

All retrospective review findings except 2, as well as all of the 13 prospective echocardiographic monitoring cases were reported as minimal, trivial, or small effusions, not requiring treatment or medical intervention. The information presented below is based on the initial 45 pericardial findings. These additional pericardial findings are of uncertain clinical relevance, because minimal (or trivial) effusions typically represent the normal amount of pericardial fluid in a disease-free state [44]; however, they were included in the analyses as a conservative measure.

The types of pericardial events included pericarditis, pericardial effusion, and cardiac tamponade, with many patients having more than one of these three adverse events (Table 3-6). Of the pericardial adverse events, pericardial effusion was the most common. The occurrence of pericardial AEs was similar for patients with NHL as it was for the overall population treated with mocetinostat (Table 3-7). Most of the pericardial AEs (54.8%) and SAEs (73.7%) occurred during the first cycle of treatment.

Table 3-5. Summary of Pericardial SAEs and Pericardial Findings Identified

Method of Identification	No. of Cases Identified		
	Total No. of Patients	Pre-Treatment	On-Study
		No. Patients (%)	No. Patients (%)
Pharmacovigilance			
SAEs	437	-	19 (4.3)
Retrospective Review Findings			
Database Searches	-	-	6 (1.4)
Radiographic Review	199	14 (7.0)	7 (3.5)
Prospective Echocardiographic Monitoring Findings			
Echocardiograms	35	-	13(37.1)
Total			
Total Pericardial SAEs	437	-	19 (4.3)

Total Pericardial Findings[1]	437	14 (3.2)	45 (10.3)

Table 3-6. Nature of Pericardial Event

	Pericardial SAEs (N = 19)			All Pericardial Findings (N = 44)		
	No.	% of Pericardial SAE Patients	% of Evaluable Population	No.	% of Patients with Pericardial Findings	% of Evaluable Population
Total No. of Patients with any Pericardial Term[1]	19	100	4.4	34[2]	77.3	7.8
No. of Patients with Pericarditis	6	31.6	1.4	6	13.6	1.4
No. of Patients with Pericardial Effusions	16	84.2	3.7	31[2]	70.5	7.1
No. of Patients with Cardiac Tamponade	8	42.1	1.8	8	18.2	1.8
Total No. of Pericardial Terms[1]	30	-	-	45	-	-

[1]Includes the following terms: pericarditis, pericardial effusion, and cardiac tamponade. More than one event term could be attributed to the same patient.
[2] Pericardial effusion terms for 3 patients with pericardial effusion findings identified through echocardiographic monitoring were not available from the database at the time of this analysis. There were 12 terms of pericardial effusion for the other pericardial findings captured in the database.

Table 3-7. Summary of Pericardial Findings by Type of Malignancy

Specified Patient Population by Type of Malignancy	Study Nos.	No. of Patients	Pericardial SAEs (N = 19)		All Pericardial Findings (N = 44)	
			N	% of Specified Patient Population	N	% of Specified Patient Population
Solid Tumors	0103-001, 0103-002, 0103-006, CL001	114	1	0.9	5	4.4
MDS, AML, & Other Leukemia	0103-003, 0103-004, 0103-005, 0103-007, 0103-009, CL003	177	8	4.5	17	9.6
Hodgkin Lymphoma	0103-010, CL002	63	6	9.5	13	20.6
Non-Hodgkin Lymphoma	0103-008, CL002	80	3	3.8	8	10.0
Other	0103-006	1[1]	1	N/A	1	N/A
Total Population		**435**	**19**	**4.4%**	**44**	**10.1%**

[1] Although Study No. 0103-006 was performed with solid tumor patients, 1 patient was exceptionally admitted with cutaneous T-cell lymphoma (and had a pericardial SAE).

Fatigue

Fatigue has been observed consistently throughout the mocetinostat clinical evaluation program and has been deemed a drug-related toxicity. The etiology of fatigue is not yet understood.

Gastrointestinal Toxicities

GI toxicities such as anorexia, nausea, vomiting and diarrhea have been reported as related to mocetinostat. Dehydration, electrolyte abnormalities (such as hypokalemia), hypotension and syncope also have been observed in connection with GI toxicity.

Cystitis

Cystitis symptoms (e.g., dysuria, pollakiuria, hematuria, urgency, and bladder spasm) have been reported in some subjects, most commonly after multiple cycles of treatment.

Human pharmacokinetics and product metabolism

The PK profile of mocetinostat has been evaluated in clinical trials, after both single or repeated dose administration. Plasma samples for PK analyses were collected over a 24-hour period following single and multiple doses. Plasma drug concentrations were determined using a validated, sensitive, LC-MS/MS assay. High PK variability was noted in initial studies with mocetinostat (administered with water). This variability was partly reduced through administration of mocetinostat with a low pH beverage. In general, mocetinostat was rapidly absorbed following administration with 200 mL of a low pH beverage, with Cmax occurring 0.5 to 1.5 hours after dosing. Drug concentrations in plasma declined biphasically and remained quantifiable for 24 hours after dosing. The elimination half- life ranged from approximately 7 to 12 hours. As determined from Cmax and AUC values, exposure to mocetinostat following oral dosing appears to increase with doses up to 110 mg. Some saturation of absorption may occur at higher doses. Mocetinostat did not appear to accumulate following multiple dosing, and its elimination half-life was approximately 10 hours.

Pharmacodynamic effects of mocetinostat have been examined by analyzing HDAC activity in peripheral blood WBCs from patients treated with mocetinostat. HDAC enzyme activity has been measured using a novel whole-cell enzyme activity assay. Briefly, in this assay, patients' peripheral WBCs are incubated with a membrane-permeable HDAC substrate for 1 hour at 37ºC. The reaction is then stopped, cells are lysed, and the deacetylated product is cleaved, releasing a fluorescent moiety that can be quantified by fluorometry. Data obtained from a total of 25 patients with solid tumors showed HDAC activity is inhibited in a time- dependent and dose-dependent manner. Prolonged HDAC inhibition (48 to 72 hours after dosing) was observed for doses • 56 mg/m2. Similarly, prolonged HDAC inhibition was observed in peripheral blood mononuclear cells (PBMCs) from 9 patients with Hodgkin Lymphoma treated with 110 mg of mocetinostat.

Clinical Efficacy Data

An open label phase II study evaluated mocetinostat as a monotherapy in non-Hodgkin lymphoma study (Table 3-8). The phase II study enrolled patients with DLBCL and FL with patients receiving mocetinostat at doses ranging from 70-110 mg three times per wk every 28 days. Sixty-nine patients were enrolled for treatment at starting doses of 85-110 mg with 41 patients with DLBCL and 28 patients with FL. Median age was 62 years (range 32 to 81). Median duration of treatment was ~3 months (range: <1 to 24). Objective response rate in DLBCL and FL, respectively, was 7/41 (17%; including 2 unconfirmed PRs) and 3/28 (11%; including 1 CR). Median time to response was 2.0 mos (range 1.7-21.0) and 5.3 mos (range 4.3-6.0) respectively. Stable disease was achieved by 13/41 (32%) and 14/28 (50%), respectively, for a disease control rate of 49% and 61%, respectively. Mean duration of SD in patients with DBLCL was ~4.5 mos (range 2-12 mos), with 10 patients

remaining stable for ≥3 mos. Among FL patients, mean duration of SD was approximately 4.1 mos (range 1.7-13 mos), with 9 patients remaining stable for ≥3 mos. The FL CR occurred in a 62-year-old female with paratracheal, subcarinal and portal target lesions who achieved a PR after 4 cycles and CR after 12 cycles that persisted through the remaining 4 mos on study. Study drug was discontinued for adverse events in 19/69 (28%). Fatigue, weight loss or anorexia were most common (n=4 each). A total of 26 drug-related SAEs were reported among 12 patients (17%; 1-6 events per pt). There were no drug related deaths.

Table 3-8. Efficacy of Mocetinostat in DLBCL and FL

Clinical Trial/Study	Population	Dosing Regimen	Efficacy
NCT00359086 Phase II Study of MGCD0103 in Patients With Relapsed and Refractory Lymphoma	Relapsed or refractory DLBCL or follicular lymphoma	3 times/week for 4 weeks Starting dose: 110 mg, reduced to 85 mg 28 day cycles	ORR: DLBCL 17% (7/41) FL 10% (3/28) Disease control: DLBCL 49% (20/49) FL 61% (17/61)

ORR (CR+PR), Disease control (CR+PR+SD)

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This is a phase II single center single stage clinical trial evaluating the efficacy of mocetinostat in a population of patients with DLBCL or FL with inactivating mutations of acetyltransferase genes CREBBP and/or EP300.

A pre-screening evaluation of archival tumor biopsies from current relapse or fresh tumor biopsies is required for CREBBP and EP300 analysis. Potential eligible patients will be asked to sign a "Molecular Pre-screening Informed Consent." The patient's archival tumor from the current relapse or a fresh tumor biopsy will be obtained. This will ensure that the CREBBP/EP300 molecular status of the tumor is known when the potential patient is screened for enrollment into the study.

Twenty-eight patients will be enrolled in each cohort with an anticipated analysis of 25 patients in each cohort for a total of 50 evaluable patients. Patients will be started on mocetinostat and monitored for response by physican exam and imaging. Treatment will be organized into cycles of 28 days in all cohorts and patients will receive mocetinostat orally three times a week at 70 mg for cycle one and increased to 90 mg for cycle 2 onwards barring any grade 3 or higher drug related toxicities. Treatment will continue until disease progression, intolerable toxicity, withdrawal of consent, or until other criteria for discontinuation are met, whichever comes first.

4.3 Intervention

Mocetinostat will be administered as an oral therapeutic three times a week on a 28 day cycle. The starting dose will be 70 mg orally three times per week in cycle 1. The dose will be escalated in cycle 2 to 90 mg orally three times per week on a 28 day schedule if there are no grade 3 or higher drug related toxicities. Therapy will continue until disease progression, intolerable toxicities or death. Toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for

Adverse Events (NCI CTCAE) Version 4.0. Response to treatment will be determined according to Cheson criteria[45] initially every 8 weeks for 6 months, then every 12 weeks for 6 months and every 4 months thereafter, until disease progression or prohibitive toxicity develops, whichever comes first. All patients benefiting from treatment at the time of final analysis will be permitted to continue study drug at investigator's discretion until disease progression, intolerable toxicity or withdrawal of consent.Give a detailed explanation of the intervention to be conducted, the treatment plan and the rationale for its use.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. Mocetinostat

Mocetinostat will be supplied by MethylGene/Mirati Therapeutics. The mocetinostat IND will be cross referenced between MSKCC and MethylGene/Mirati. IND approval and activation is pending at MSKCC.

5.2. Study drug preparation and dispensation

Mocetinostat will be dispensed by an authorized person at MSKCC. Investigator staff will add the patient number on the label. Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that patient's unique patient number.

5.3. Study drug packaging and labeling

Mocetinostat Finished Drug Product is supplied by MethylGene/Mirati in hard gelatin capsules. Initially, 10 mg and 25 mg unit dose strength capsules will be provided, each containing either 10 mg or 25 mg of Mocetinostat, calculated as free-base corrected for purity. Additional unit dose strengths may be added in the future.

Medication labels comply, or will comply, with the legal requirements of the United States and will be printed in English. The storage conditions for study drug will be described on the medication label (currently 2-8°C – refrigerated storage).

Mocetinostat, 10 mg and 25 mg unit dose strengths will be supplied in bulk bottles (48 count) for patient dispensing at clinical sites. The pharmacist will repackage bottles for each subject's dose for dispensation.

5.4. Study drug ingredients

Study drug contains the free-base form of Mocetinostat (MGCD0103), mocetinostat dihydrobromide salt and inert excipients: microcrystalline cellulose, sodium starch glycolate, colloidal silicon dioxide, non-bovine magnesium stearate.

5.5. Study drug disposal and destruction

Study drug destruction at the investigational site will only be permitted if authorized by MethylGene/Mirati in a prior agreement and if permitted by local regulations.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

Patients eligible for inclusion in this study have to meet **ALL** of the following criteria:

- Patient has provided a signed study Informed Consent Form prior to performance of any study related procedurePatient is ≥ 18 years of age
- Patient has histologically confirmed diagnosis of diffuse large B cell lymphoma or follicular lymphoma harboring mutations in CREBBP or EP300 with relapsed or refractory disease
- Patients with diffuse large B cell lymphoma must have received at least two prior therapies and have received, declined or be ineligible for autologous or allogeneic stem cell transplant.
- Patients with follicular lymphoma must have received at least two prior therapies.
- Patients with either diffuse large B cell lymphoma or follicular lymphoma will be allowed to enroll after receiving only 1 prior therapy if they are felt to not be a candidate for further systemic chemotherapy.
- Patient has at least one measurable lesion (≥ 2 cm) according to Cheson criteria [45]. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1
- Patient has adequate bone marrow and organ function by:
  - Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L
  - Platelets ≥ 75 x 10^9/L (no platelet transfusion within past 14 days)
  - Hemoglobin (Hgb) ≥ 9.0 g/dL (no RBC transfusion within past 14 days)
  - International Normalized Ratio (INR) ≤ 1.5
  - Serum Creatinine ≤ 1.5 x upper limit of normal (ULN)
  - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) within 2.5 x ULN, or ≤ 5.0 x ULN for patients with documented hepatic involvement
  - Serum bilirubin ≤ 1.5 x ULN or ≤ 3.0 x ULN for patients with Gilbert Syndrome or documented hepatic involvement.
- Patients must have fully recovered from major surgery and from the acute toxic effects of prior chemotherapy and radiotherapy (residual grade 1 toxicity, e.g. grade 1 peripheral neuropathy, and residual alopecia are allowed)

6.3 Subject Exclusion Criteria

Patients eligible for this study must **NOT MEET ANY** of the following criteria:

- Patient has received previous treatment with HDAC inhibitors
- Patient has evidence of graft versus host disease (GVHD)
- Patient has active or history of central nervous system (CNS) disease
- Patient has impaired cardiac function including any of the following:
  - Presence or history of pericardial effusion (definitions are provided in Section 9.3.4) and/or pericarditis.
  - Acute myocardial infarction, symptomatic angina pectoris ≤ 6 months prior to starting study drug
  - Presence of congestive heart failure ≥ NYHA class 3

  - QTc > 480 ms on a screening ECG
  - Screening LVEF < 45% by echocardiography or MUGA
  - Uncontrolled cardiac arrhythmia including uncontrolled atrial fibrillation/atrial flutter/sinus tachycardia, complete left bundle branch block, congenital long QT syndrome
  - Presence of permanent cardiac pacemaker
  - Other clinically significant heart disease
- Subject is taking warfarin at start of treatment or within 6 months prior to start of study treatment.
- Patient has a concurrent malignancy or has a malignancy within 3 years of study enrollment (with the exception of adequately treated basal or squamous cell carcinoma or non-melanomatous skin cancer)
- Patient is concurrently using other approved or investigational antineoplastic agent
- Patient has received chemotherapy, targeted anticancer therapy, pelvic and/or para-aortic radiotherapy or has had major surgery ≤ 4 weeks (6 weeks for nitrosourea, monoclonal antibodies or mitomycin-C) prior to starting study drug or who have not recovered from side effects of such therapy
- Patient has impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of mocetinostat (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome, or small bowel resection)
- Patient is currently receiving increasing or chronic treatment (> 10 days) with corticosteroids or another immunosuppressive agent. The following uses of corticosteroids are permitted: single dose, topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular).
- Patient has a history of non-compliance to medical regimen or inability to grant consent.
- Concomitant medications causing prolonged QT which cannot be discontinued or changed to a different medication prior to initiating study
- Patient is currently being treated with drugs known to be moderate or strong inhibitors or inducers of isoenzyme CYP3A, and the treatment cannot be discontinued or switched to a different medication prior to starting study drug. Patients must have discontinued strong inducers for at least one week and must have discontinued strong inhibitors before the start of treatment. Note: the oral anti-diabetic drugs troglitazone and pioglitazone are CYP3A inducers. Refer Appendix A, Table 20-1 to 20-5
- Patient has a known history of HIV (testing not mandatory), active Hepatitis B or C infection
- Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum hCG laboratory test (> 5 mIU/mL)
- Women of child bearing potential and men with reproductive potential, if they are unwilling to use adequate contraception while on study therapy and for 3 months thereafter

7.0 RECRUITMENT PLAN

Patients will be recruited by the treating team of physicians and medical professionals. Patients will be treated by the lymphoma service at MSKCC. Given the diverse population of patients at MSKCC, we expect that minorities and women patients will have full access to this study and will be

fairly represented in the accrual. The study procedures and requirements will be clearly presented in the molecular prescreening consent form and the consent form and explained to all patients at the time the consent is obtained. The principle investigator, Dr. Andrew Zelenetz, MD, PhD, will be available to all patients for further questions and information through a contact number provided on the molecular prescreening consent and the therapeutic consent.

7.1 Molecular pre-screening

Only patients with mutations in CREBBP or EP300 will be eligible for enrollment into this study. For patients with documented mutation of CREBBP or EP300, molecular pre-screening will not be needed. For patients with unknown CREBBP or EP300 status, tumor biopsies will be tested. Tumor mutational testing will be performed in the MSK Department of pathology Diagnositc Molecular lab using protocol 12-245. Mutational testing performed via the MSK-DMP on the IMPACT panel will require normal tissue/blood for germline comparision to identify mutations.

Only patients that exhibit a CREBBP/EP300 mutation as described below (in addition to all other inclusion/exclusion criteria) will be eligible for subsequent study enrollment. We anticipate pre-screening approximately 100 patients in order to enroll 27 in each cohort.

CREBBP and EP300 mutation is confirmed if:

Direct sequencing results confirm the presence of a CREBBP or EP300 mutation (deletion, frameshift, nonsense, missense) affecting CREBBP or EP300 as previously described [1] or via corroboration with the COSMIC database.

OR

Should mutations be identified that have not been previously described, patients may be enrolled following discussion and agreement of the principle investigator on consultation with MethylGene/Mirati. The method used and the result should be entered into CRDB.

8.0 PRETREATMENT EVALUATION

8.1. Screening

After signing the main study informed consent form for the study, the remaining screening assessments will be done generally within 7 to 28 days prior to start of treatment (Table 8-1). Please note that the screening period must not exceed 28 days.

- Medical history and demographics
- Complete history and physical exam (including weight, pulse, blood pressure, temperature, ECOG performance status)
- Medication review
- Bloodwork 14 days prior to starting therapy:
  - CBC with differential
  - Comprehensive metabolic panel, LDH, magnesium, phosphorus
  - Liver function tests
  - Uric acid

  - Coagulation tests with PT/PTT and INR
  - HIV testing
  - Hepatitis B and C testing
- ECG
- Pregnancy test will be performed for women of child bearing potential
- Echocardiogram at baseline
- Evidence of disease evaluation within 28 days prior to starting treatment
  - CT scan with contrast, unless contraindicated, of the chest, abdomen, and pelvis
  - CT scan with contrast, unless contraindicated, of the neck as clinically indicated
  - PET scan for patients with DLBCL
  - MRI may be substituted for CT scan if patients are intolerant of CT scans with contrast
  - Archival or fresh tumor biopsy for confirmation of CREBBP and/or EP300 mutation

9.0 TREATMENT/INTERVENTION PLAN

9.1. Mocetinostat administration

Mocetinostat will be administered on a three times per week dosing schedule. There will be no breaks between dosing cycles. Mocetinostat will be initiated at 70 mg orally three times per week for cycle 1. The dose will be increased to 90 mg orally three times per week

The following general guidelines should be followed for mocetinostat administration:

- Patients should be instructed to take the dose of mocetinostat three times a week in the morning, at approximately the same time each day
- Mocetinostat should be taken at least 1 hour following a light breakfast.
- Patients should not eat for 2 hours after the administration of each mocetinostat dose.
- Mocetinostat should be taken with a low pH beverage (Table 9-1). Patients should swallow the capsules as a whole and not chew them.
- If vomiting occurs during the course of treatment, no re-dosing of the patient is allowed before the next scheduled dose. The occurrence and frequency of any vomiting during a treatment cycle must be noted in the adverse events section of CRDB.

Table 9-1. List of low pH beverages	
Coca cola, diet cola	Lime juice
Cranberry juice	Lemon juice
Hawaiian Fruit Punch	Orange juice
Dr. Pepper Soda	Orange soda
Gatorade	Pepsi cola, +/- caffeine

9.2. Mocetinostat dose modification

Patients will be initiated at 70 mg mocetinostat three times per week for 1 cycle and observed for toxicities. If there are no grade 3 or higher drug related toxicities, the dose will be increased to 90 mg starting cycle 2 if thre are no grade 3 or higher treatment related toxicities.

Mocetinostat dose reduction will be administered at 20 mg below the current dose. For each patient, a maximum of 3 dose reduction (minimum dose of 35 mg three times per week) will be allowed after which the patient will be discontinued from treatment with mocetinostat (Table 9-2). Once a dose has been reduced during a treatment cycle, re-escalation will not be permitted during any subsequent cycle. If the administration of mocetinostat is interrupted for reasons other than toxicity, then treatment with the study drug may be resumed at the same dose. The same applies if the patient experienced an unacceptable toxicity not specifically described in Table 3-3 or Section 9.3, provided this toxicity resolved to ≤ CTCAE grade 1, unless otherwise specified.

If treatment with the study drug is withheld for ≥21 consecutive days, then study drug must be permanently discontinued. Patients who permanently discontinue the study drug should have follow-up for 30 days after discontinuation of all study treatment or resolution of the AE to ≤ grade 1, whichever occurs first, that includes all study assessments appropriate to monitor the event.

Table 9-2. Dose modifications for mocetinostat

Mocetinostat dose levels and reductions*	
Starting dose 0	70 mg three times per week
Escalation dose +1	90 mg three times per week
Dose level 0	70 mg three times per week
Dose level –1	50 mg three times per week
Dose level –2	35 mg three times per week**

*Dose reduction should be based on the worst preceding toxicity
**Dose reduction below 35 mg 3x/week is not allowed. If a dose reduction below 35 mg 3x/week is required, the patient should be permanently discontinued from mocetinostat.

9.3. Guidelines for dose reduction based on toxicities

9.3.1. Management on non-hematologic toxicities

In the case of drug-associated grade 3 non-hematologic toxicities experienced by the subject, hold treatment (one or both drugs if applicable) until toxicity is resolved to ≤ grade 1 or to baseline value. If further treatment is desired, treatment should then be resumed at the next lower dose level for the applicable drug(s). If the toxicity can be managed by routine supportive care, such as anti-emetics or electrolyte supplementation, then a dose reduction is not required. If there is no recovery within 21 day the subject will go off protocol treatment, unless the clinical investigator in discussion with MethylGene/Mirati deems that it is in the best interest of the subject to resume treatment. If grade 3 non-hematologic toxicity recurs following the first dose reduction, a second dose reduction of one dose level may be implemented following recovery to ≤ grade 1 or to baseline. However if grade 3 non-hematologic toxicity again recurs, then the subject should be removed from protocol therapy. Subjects who experience grade 4 non-hematologic toxicities should have study treatment discontinued, unless the Investigator and the sponsor agree that the subject is benefiting from study treatment, in which case, treatment may be resumed at a lower dose level as described above following recovery. Dose reductions for lower-grade toxicities may also be implemented based on Investigator discretion; however the sponsor should be notified of such an event (Table 9-3).

Table 9-3. Dose Modifications – Non-Hematologic Drug Related Toxicities[1]

Occurrence	Toxicity	Treatment Delay	Dose Modification
1st Occurrence	< Grade 3	May be implemented based on Investigator and subject discretion; Sponsor should be notified	
	Grade 3	Hold until ≤ Grade 1 or return to baseline	Then, resume at next lower dose level
	Grade 3 toxicity manageable with routine supportive care	Hold until ≤ Grade 1 or return to baseline	Not required
	Grade 4	--	Remove from Therapy
2nd Occurrence	Grade 3	Hold until ≤ Grade 1 or return to baseline	Then, resume at next lower dose level (e.g., 2nd dose reduction)
3rd Occurrence	Grade 3	--	Remove from Therapy[2]

1For pericardial toxicity, see Section 6.2.2.
2 Unless the Investigator and the sponsor agree that the subject is benefiting from study treatment, in which case, treatment may be resumed at the next lower dose level as described above following recovery.

9.3.2. Management of Gastrointestinal Toxicity

GI toxicities, such as anorexia, nausea, vomiting and diarrhea have been reported as probably related to mocetinostat. Associated conditions, including, but not limited to, dehydration, electrolyte abnormalities such as hypokalemia (sometimes with associated QTc prolongation), hypotension, and syncope have also been observed. Subjects experiencing GI toxicity should be closely monitored and treated as per guidelines mentioned below.

For anorexia, dehydration, nausea, vomiting, or diarrhea that is grade 3 or 4, or is prolonged grade 2 (more than 3 days), manage per institutional standard. Hold study treatment until resolution to grade 1 or better.

9.3.3. Management of Mocetinostat associated Cystitis

In the event of a subject experiencing symptoms of cystitis (dysuria, pollakiuria, hematuria, urgency or bladder spasm) suspected to be mocetinostat related:

- Encourage adequate hydration.
- Conduct urinalysis, urine culture, blood urea nitrogen (BUN), creatinine and complete blood count (CBC).
- If clinically significant symptoms persist despite a negative work-up or treatment of an associated condition, hold study drug until resolution of clinically significant symptoms.
- Resume dosing of mocetinostat when medically appropriate at the same or a reduced dose level as per the Investigator's judgment.

9.3.4. Management of Pericardial toxicity

Subjects will be assessed for evidence of pericardial events during scheduled visits according to the schedule in Table 10-1. The following findings would heighten suspicion of pericardial effusion or pericarditis and prompt immediate evaluation by ECHO:

Symptoms: shortness of breath, orthopnea, chest pain, dizziness, rapid pulse

- Clinical exam: hypotension, jugular venous distension, pulsus paradoxus, faint heart sounds, friction rub, and/or arrhythmia
- ECG: sinus tachycardia, atrial fibrillation, atrial flutter, low voltage with non specific ST-T wave changes and ST elevation or PR depressions, arrhythmia
- Chest X-ray: widening cardiac silhouette

ECHOs will categorize pericardial fluid as minimal (or trivial), small, moderate or large and will assess for hemodynamic compromise.

Pericardial effusions will be assessed as follows (Table 9-4):

- Minimal (or trivial): A small echo-free space in the posterior atrioventricular groove that is visible only in systole when the heart has pulled away from the pericardium. Typically represents a normal amount of pericardial fluid in a disease-free state.

- Small: <1 cm of posterior echo-free space, with or without fluid accumulation elsewhere, present throughout the cardiac cycle, including diastole (and not only systole).
- Moderate: 1 to 2 cm of echo-free space. Moderate effusions tend to be seen along the length of the posterior wall but not anteriorly.
- Large: >2 cm of maximal separation. Large effusions tend to be seen circumferentially.
- Hemodynamic compromise: RV compression, IVC dilation without respiratory variation, abnormal flow variation across the AV valves without respiratory variation, enlarged or collapsed ventricles. RA diastolic collapse in isolation is too non-specific to signal hemodynamic compromise, but should be considered consistent with this diagnosis when accompanied by other findings

Table 9-4. Pericardial Effusion Echocardiographic Assessment and Subject Management Guidelines

Category	Definitions	Subject Management
Minimal (or trivial)	A small echo-free space in the posterior atrioventricular groove that is visible only in systole when the heart has pulled away from the pericardium. Typically represents a normal amount of pericardial fluid in a disease-free state.	Increased ECHO and ECG monitoring[1]: -Weekly until the minimal (or trivial) effusion is no longer present or has not progressed (to a small or greater effusion) over a period of 2 weeks to validate the findings as non-pathologic or until the effusion has regressed (if sooner); - Regular schedule afterwards (i.e., prior to each subsequent cycle).
Small	<1 cm of posterior echo-free space, with or without fluid accumulation elsewhere, present throughout the cardiac cycle, including diastole (and not only systole).	Increased ECHO and ECG monitoring: -Weekly for the first month after the new pericardial effusions are first noted or until the effusion has regressed (if sooner). - Treatment for the effusion may be administered at the discretion of the Investigator. - Study drug will not be discontinued in these subjects, at the discretion of the investigator, unless the effusion progresses.
Moderate	1 to 2 cm of echo-free space. Moderate effusions tend to be seen along the length of the posterior wall but not anteriorly.	Remove from study treatment; refer to cardiologist for follow up as clinically indicated, until resolution or stabilization.
Large	>2 cm of maximal separation. Large effusions tend to be seen circumferentially.	
Hemodynamic Compromise	RV compression, IVC dilation without respiratory variation, abnormal flow variation across the AV valves without respiratory variation, enlarged or collapsed ventricles. RA diastolic collapse in isolation is too non-specific to signal hemodynamic compromise, but should be considered consistent with this diagnosis when accompanied by other findings	Remove from study treatment; refer to cardiologist for follow up as clinically indicated, until resolution or stabilization.

[1] Subjects with ECHO findings of minimal (or trivial) effusion may be discontinued from the study at any time if judged in the subject's best interest, following discussion between the Investigator and the Medical Monitor.

Subjects who are found to have moderate or large pericardial effusions (as defined above) and/or evidence of hemodynamic compromise (regardless of the size of the pericardial effusion) will be immediately removed from study treatment and will be managed according to the accepted standard of care at the discretion of the Investigator. Subjects should be referred to cardiologist for follow up as clinically indicated, until resolution or stabilization.

Subjects who are found to have de novo (i.e. not present at baseline) small pericardial effusions on study will be followed with weekly ECHOs and ECGs for the first month after the new pericardial effusions are first noted or until the effusion has regressed (if sooner). Treatment for the effusion may be administered at the discretion of the Investigator. Study drug will not be discontinued in these subjects, at the discretion of the investigator, unless the effusion progresses.

Subjects presenting with de novo (i.e. not present at baseline) minimal or trivial pericardial effusions visualized by ECHO will be permitted to stay on study treatment since these findings would be considered to represent physiological levels of fluid and typically represents a normal amount of pericardial fluid in a disease-free state. However, such subjects will have increased safety monitoring, including weekly ECHOs and ECGs for 2 weeks to validate the finding as non-pathologic or until the effusion has regressed (if sooner), followed by a return to the regular schedule.

In patients who develop a significant pericardial toxicity, blood will be collected and tested for anti-nuclear antibody (ANA) and anti-histone antibody testing.

In exceptional circumstances where ECHO is not considered a technically optimal assessment of pericardial space (e.g., overweight subject), other methods (e.g., MRI) should be used for pericardial assessments. In such cases, the guidelines provided in Table 9-4 would not apply, and the evaluation should be performed in consultation with the Medical Monitor. In the event that a pericardial effusion is first identified by a method other than ECHO, efforts should be made to obtain an ECHO for assessment of effusion size.

9.3.5. Management of chest pain

Subjects who report chest pain, even without other complaints suggestive of pericarditis, effusion, hemodynamic compromise, or tamponade, will require careful questioning to characterize this symptom. Pericarditis typically presents with dull or sharp precordial or substernal pain that may radiate to the neck, trapezius ridge (especially the left), or shoulders. This pain ranges from mild to severe. Unlike ischemic chest pain, pain due to pericarditis is usually aggravated by thoracic motion, cough, breathing, or swallowing food and may be relieved by sitting up and leaning forward. Tachypnea and nonproductive cough may be present. Fever, chills, and weakness are common.

If the subject's symptoms suggest pericarditis, history and physical exam including careful auscultation for pericardial friction rub and an ECG should be performed. In the first stages of pericarditis, pericardial effusion may or may not be found on ECHO. ECHO in a week or two may be more useful.

9.4. Concomitant therapy

9.4.1. Permitted concomitant therapy

Supportive care/Palliative care: Supportive and palliative care for disease related symptoms may be administered at the investigator's discretion including the use of analgesics.

Anti-emetics: Subjects should be premedicated for nausea and vomiting as these have been associated with the administration of mocetinostat.

Transfusions: Subjects may receive transfusions as necessary.

9.4.2. Cautioned concomitant therapy

CYP450 substrates: In vitro human liver microsome assays demonstrated that mocetinostat had differing inhibitory effect on the metabolism of medications by cytochrome P450 CYP2C9 (strong inhibition for diclofenac but no inhibition for tolbutamide). In in vitro assays using specific chemical inhibitors and individual human recombinant CYP enzymes (cDNA expressed supersomes), mocetinostat was found to be metabolized mainly by CYP2E1 and to a lesser extent by CYP3A4 and CYP2C8. Caution should be used when mocetinostat is administered to Subjects taking medications metabolized by CYP2C9 or that inhibit or induce metabolism by CYP2E1. See Appendix A, Table 20-1 and Table 20-2, for examples of medications of interest. If a subject is taking a drug on one these lists, it is encouraged to substitute a different medication if possible.

Gastric acid inducers: Medications that directly increase gastric pH such as short-acting antacids should be avoided 4 hours before and 1 hour after administration of mocetinostat. Medications that affect gastric acid secretion, such as H2 antagonists or proton pump inhibitors will be allowed.

QTc Prolongating medications: Patients currently receiving treatment with risk of prolonging QTc or inducing torsade de pointes are recommended to either discontinue or switch to a different medication prior to study enrollment. Prohibited QTc prolonging medications are listed in Table 20.4. Concomitant use of potential QTc prolonging agents should be discussed with the sponsor and evaluated based on a case by case basis.

Substrates and inhibitors of P-gp: Mocetinostat was shown to be a substrate and an inhibitor of P-gp. Therefore, P-gp sensitive substrates and strong inhibitors of P-gp should be used with caution (Table 20.3).

Anti-coagulation: At the discretion of the investigator and under medical supervision, Subjects may continue to receive prophylactic dose levels of anti-coagulants (except warfarin and coumarin derivatives) and chronic supportive care agents (e.g. ESAs) established at least 4 weeks or more prior to first dose of study treatment and used in a consistent regimen unless reduced or discontinued. The investigator should take into consideration the use of anticoagulants in subjects at risk of bleeding due to low platelet count.

9.4.3. Prohibited concomitant therapy

Other anticancer treatments: Other anti-cancer treatment including chemotherapy and radiotherapy are prohibited during this study. If such agents are required, then the patient must be discontinued from the study.

Growth factor support: Prophylactic use of growth factor support to avoid anticipated study treatment side effects or as a substitute for a scheduled dose reduction. However they may be used in case of severe anemia (hemoglobin < 80 g/L or 8 g/dL) or neutropenia (< 1.0 x 109/L or 1000/ mm3) at discretion of the Investigator. Use of growth factors must be documented in CRDB.

Warfarin or coumarin derivatives: Therapeutic doses of warfarin or other coumadin derivatives anticoagulants are not permitted. Warfarin has a narrow therapeutic range and mocetinostat is possibly affected by CYP2C9, the main metabolizing enzyme of warfarin.

Drugs with QTc prolonging activity: As listed in Table 20.4. This list is not comprehensive and any questions should be reviewed with the pharmacist and discussed with the sponsor.

CYP3A4 inhibitors and inducers: As listed in Table 20.5. This list is not comprehensive and any questions should be reviewed with the pharmacist and discussed with the sponsor.

Herbal medications/preparations: Hernal medications and preparations are not allowed throughout the study, as a potential drug- drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using these herbal medications at least 7 days prior to first dose of study treatment.

Contraceptives: Hormonal contraceptives may be affected by cytochrome P450 interactions, and are therefore not considered effective for this study, since induction of CYP3A4 may not be excluded in patients receiving mocetinostat.

Gastric acid inducers: Medications that directly increase gastric pH such as short-acting antacids should be avoided 4 hours before and 1 hour after administration of mocetinostat. Medications that affect gastric acid secretion, such as H2 antagonists or proton pump inhibitors will be allowed.

Immunosuppressants: Chronic administration of corticosteroids (>10 days), patients receiving increasing corticosteroids or another immunosuppressive agent will be prohibited. The following uses of corticosteroids are permitted: single dose, topical applications (e.g., rash), inhaled sprays (e.g., obstructive airways diseases), eye drops or local injections (e.g., intra-articular).

10.0 EVALUATION DURING TREATMENT/INTERVENTION

10.1. Evaluation Summary Chart.

Table 10-1 lists all of the assessments and indicates with an "X", the visits when they are performed. All data obtained from these assessments must be supported in the patient's source documentation. All visits can take place 3 days before or 3 days after the specified study visit (total window of 7 days) except for the time window for the end of treatment and safety follow-up visit which is +7 days.

Table 10-1. Study flow and evaluation

Evaluation Summary								
Day of Cycle	Cycle 1 Day 1 (- 3 days)	Cycle 1 Day 8 (+/- 1 day)	Cycle 1 Day 15 (+/- 1 day)	Cycle 1 Day 22 (+/- 1 day)	Cycle 2 Day 1 (+/- 3 days)	Cycle 2 Day 15 (+/- 1 day)	Cycle 3 Day 1 + onward (+/- 3 days)	End of Study
Treatment								
Mocetinostat	Continuous dosing, three days per week by mouth							
Pill Diary Review					X		X	X
History+ Physical								
Toxicity Assessment[a,]	X	Continuous Assessment						X
Medication review	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X
ECOG	X		X		X		X	X
Vital signs[b]	X		X		X		X	X
Laboratory assessments								
Hematology[c]	X (- 7 days)		X		X	X	X	X
Chemistry[c]	X(-7 days)		X		X	X	X	X
DLBCL arm only: Chemistry specific to tumor lysis syndrome[d]		X(day 2, 3, 4 of cycle 1 only)						
Coagulation (PT/PTT)	X (-7 days)	As clinically indicated						X
Pregnancy test (serum); for WOCBP only	X (-7 days)				X		X	X
Tumor assessments								
Radiographic assessment[e]	X (-28 days)						X Q 8 wks for 0-6 mo; Q 12 wk for 6-12 mo; Q16 wk after 1 yr	X Q 8 wks for 0-6 mo; Q 12 wk for 6-12 mo; Q16 wk after 1 yr
Bone Marrow biopsy	As clinically indicated	** At time of complete response if BM involved prior						
Safety assessments								
ECG	X (-28 days)		X		X (predose)	X	As clinically indicated	X
Cardiac imaging (ECHO)	X (-28 days)		X		X (predose)	X	As clinically indicated	X
Biomarkers								
CREBBP/EP300 screening	Pre-screening							
Collection of fresh tumor from biopsy/resection			X (optional)				X (optional)	X (optional at relapse)

Research blood sample	X (-7 days)		X		X			

a. Assessed including type, severity, timing and relationship to study drug using NCI common Toicity Criteria version 4.0
b. Weight, blood pressure, pulse
c. CBC with differential, Chemistry (Potassium, sodium, calcium, magnesium, chloride, inorganic phosphorus, ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, Gamma GT, Serum creatinine, urea or blood urea nitrogen (BUN), lipase, albumin, uric acid)
d. Uric acid, potassium, sodium, calcium, inorganic phosphorus and serum creatinine
e. CT scan with contrast, unless contraindicated, of the chest, abdomen, and pelvis, neck; PET scan for patients with DLBCL (combination PET/CT may be used); MRI may be substituted for CT scan if patients are intolerant of CT scans with contrast

10.1.4. End of treatment evaluation (within 30 days of last dose of mocetinostat)

- MD visit, with history and physical exam including weight, blood pressre, pulse, ECOG performance status, and updated medication list. Concurrent medications will be reviewed for potential drug-drug interactions with study medications.
- Patient drug diary review
- Toxicity will be assessed and the type, severity, timing, and relationship of each adverse event to therapy will be determined as ther NCI Common Toxicity Criteria version 4.0.
- Blood work to be obtained will include:
  - CBC with differential, Comprehensive metabolic panel, LDH, phosphorus, uric acid
  - PT/PTT
  - Serum pregnancy test for females of reproductive age
- ECG
- Echocardiogram
- Optional tumor biopsy

10.2. Evidence of disease evaluation

Patients will have evidence of disease evaluation at baseline using modified criteria for malignant lymphoma [45]. Response criteria will generally follow the CT scan recommendations as per the revised response criteria for malignant lymphoma [45]. Further clarification on these criteria has been published by [46]. MRI will be allowed only in those cases when CT scan cannot be performed.

Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 10-1, based on physical examination, radiological evaluation and core bone marrow biopsy (only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment). Tumor assessments will be performed every 2 cycles/8 weeks for the first 6 months, every 3 cycles/12 weeks for the following 6 months, and every 4 cycles/16 weeks thereafter. Clinical suspicion of disease progression at any time will require a physical examination and radiological

confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule from baseline.

10.2.1. Physical Exam

Tumor assessment by physical examination and evaluation of disease related B symptoms (unexplained fever of ≥ 38°C; unexplained, recurrent drenching night sweats; or unexplained loss of >10% body weight within the previous 6 months) will be performed and recorded following the schedule for radiological tumor assessments.

10.2.2. Radiographic tumor assessment

At screening, all patients must have a PET/CT scan with contrast of the Chest, Abdomen and Pelvis. The same type of PET/CT scan used at screening must be used for all subsequent assessments. CT scan with contrast of the Neck, Chest, Abdomen and Pelvis is allowed in lieu of PET/CT for patients with follicular lymphoma at the discretion of the treating physician. MRI with contrast will be allowed only in those cases when CT scan cannot be performed and will be used at baseline and all subsequent assessments in these patients. No modality change would be allowed during the study. Only in exceptional cases when a patient is known to have or determined during the study, to have intolerance to the CT scan contrast medium, a CT scan without contrast will be acceptable to avoid modality change. At screening, tumor assessments should preferably be performed ≤ 7 days prior to the first dose of mocetinostat, however tumor assessments ≤ 21 days prior to first dose of study drug will be acceptable.

PET and CT Scans of the Chest/Abdomen and Pelvis will be performed every 8 weeks for the initial 6 months, every 12 weeks for the subsequent 6 months and every 16 weeks thereafter. It may also be performed as clinically indicated.

A sum of the product of diameters (SPD) for lesions measured prior to study treatment will be calculated and reported at baseline. Conventional CT and MRI should be performed with contiguous cuts of 7.5 mm or less in slice thickness. Spiral CT should be performed using a 5 mm or less contiguous reconstruction algorithm (this specification applies to tumors of the chest, abdomen and pelvis).

If a very small lesion cannot be reliably measured because of its size, it is recommended to enter the minimum lesion size (i.e., 5 mm for spiral CT). In other cases where the lesion cannot be reliably measured for reasons other than its size (i.e., borders of the lesion are confounded by neighboring anatomical structures), no measurement should be entered and the lesion cannot be evaluated.

Any measurable extranodal lesions (organs other than lymph nodes) that resolves from baseline (disappear completely) must be assigned a size of 0 mm when documenting in CRDB. An extranodal lesion must be ≥ 1 cm x 1 cm to be considered measurable.

10.2.3. Bone marrow assessment

Information on the patient bone marrow involvement prior to study entry must be present in his/her source documents. Prior tumor bone marrow involvement should be entered in CRDB.

Core bone marrow biopsy is required to confirm Complete Responses (at the first occurrence of radiological and clinical evidence of CR) in patients with bone marrow tumor involvement prior to study treatment who achieve Complete Response based on clinical and radiological evidence. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). Bone marrow biopsy should be obtained no later than at the next visit immediately following clinical and radiological evidence of CR (i.e. < 28 days ± 7 days from the date of the radiological assessment, on which the CR is based on).

10.3. Laboratory assessments

The standard clinical laboratory analyses described below are to be performed by the study site's local laboratories according to the Visit Schedule, outlined in Table 10-1.

The investigator is responsible for reviewing all laboratory reports for patients in the study and evaluating any abnormalities for clinical significance. At any time during the study, abnormal laboratory parameters that are clinically relevant (e.g., require dose modification and/or interruption of study drug, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, must be recorded in CRDB. Laboratory data will be summarized using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Local laboratory tests will be collected and analyzed on the scheduled day, even if study medication is being held. More frequent examinations may be performed at the investigator's discretion if medically indicated; those results should be recorded in CRDB.

Laboratory assessments performed as part of the screening evaluations and within 7 days of the first dose of study drug, will not be required to be repeated on Day1 of Cycle 1.

In the event of grade 2, grade 3 or grade 4 hematological toxicities that require study drug dose modifications or interruptions, hematological tests must be repeated until recovery to the baseline value or grade 1.

Hematology

Hematology includes the following parameters: complete blood count consisting of a white blood cell (WBC) count with differential (total neutrophils [including bands], lymphocytes, monocytes, eosinophils, basophils), hemoglobin (Hgb), and platelet counts.

Hematological tests will be performed at screening, on Cycle 1 Day 1 (prior to administration of the study drug) and repeated on Day 1 of every subsequent treatment Cycle and at the End of Treatment. Hematology test may also be performed as medically necessary.

Clinical chemistry

Clinical chemistry includes the following parameters:

- Potassium, sodium, calcium, magnesium, chloride, inorganic phosphorus
- ALT/SGPT, AST/SGOT, alkaline phosphatase, total bilirubin, direct bilirubin, LDH, Gamma GT
- Serum creatinine, urea or blood urea nitrogen (BUN), lipase, albumin, uric acid

Clinical chemistry will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug), repeated on Day 1 of every subsequent treatment cycle and at End of Treatment. Chemistry tests may also be performed as clinically indicated. Patients with diffuse large B-cell lymphoma will require additional evaluations of the following parameters on days 2, 3 and 4 in the first treatment cycle to monitor for TLS:

- Uric acid, potassium, sodium, calcium, inorganic phosphorus and serum creatinine

Coagulation

The coagulation profile includes partial thromboplastin time (PTT) and either prothrombin time (PT) or International normalized ratio (INR). Coagulation profile will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug) and as clinically indicated.

Pregnancy and assessment of fertility

Pregnancy tests are indicated for all females of childbearing potential. Serum tests are required at screening, on Cycle 1 Day 1 (prior to administration of study drug) and repeated on Day 1 of every subsequent treatment cycle and at End of Treatment. Additional serum pregnancy tests should be performed as soon as indicated in case the patient is suspected to be pregnant.

In case of pregnancy, the patient must immediately be withdrawn from study treatment.

Note: Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

10.4. Cardiac assessments

Electrocardiograms

The study requires standard 12-lead digital ECG as indicated in Table 10-1. Pre-dose ECGs must be performed prior to any study drug administration on the respective days. ECGs may be repeated more frequently at the investigator's discretion if signs and symptoms of cardio-toxicity exist. If an ECG is performed for screening ≤ 7 days before the first dose of study treatment, it does not need to be repeated on Day 1 of Cycle 1. Single ECG should generally be done prior to any blood draws.

Clinically significant findings must be discussed with the principle investigator prior to enrolling the patient in the study. New or worsened clinically significant findings occurring after informed consent must be recorded in CRDB.

Echocardiograms

Echocardiogram (ECHO) will be used to assess LVEF at screening and obtain baseline presence of pericardial effusion at start of study.

Echocardiograms will be performed at screening, on Cycle 1 Day 1 (prior to administration of study drug), cycle 1 day 15, cycle 2 day 1, cycle 2 day 15 and repeated as clinically indicated and at End of Treatment. Echocardiograms may be repeated more frequently at the investigator's discretion if signs and symptoms of cardio-toxicity exist. Alternatively, cardiac MRI may be utilized as clinically indicated. If an echocardiogram is performed for screening ≤ 7 days before the first dose of study treatment, it does not need to be repeated on Day 1 of Cycle 1.

LVEF assessment and evaluation of pericardial effusions may be performed as clinically indicated at the investigator's discretion if there are signs or symptoms of cardiotoxicity. In case of clinically significant abnormalities, they should be reported in CRDB.

10.5. Biomarkers and exploratory assessments

Tumor tissue samples will be collected pre-treatment with the purpose of investigating the effects of CREBBP/EP300 mutations in treatment response to HDAC inhibition. In addition, we will also identify risk factors for treatment response, and disease relapse.

- Correlation of myc and Bcl-2 positivity for treatment response
    - Concurrent expression of Myc and Bcl-2 in DLBCL portends an overall poorer prognosis largely the results of double hit biology [47, 48]. Concurrent expression of myc and Bcl-2 occurs in both germinal center and activated B cell DLBCL suggesting heterogenous molecular pathways may be responsible for myc deregulation. Modulation of epigenetic landscape with mocetinostat may provide a route to deregulate the dependent myc signaling via alteration of gene expression. The immunohistochemistry staining of the pre-treatment samples for myc (defined as ≥40% of tumor cells staining positive) and Bcl-2 (defined as ≥ 70% of tumor cells staining positive) will be correlated to response to mocetinostat [47].
- Determination of mechanisms of resistance to mocetinostat via mutational analysis
    - Inhibition of HDAC activity results in accumulation of acetylated proteins including histones, transcription factors, and heat shock proteins which alter their function leasing to global cellular changes to transcription, mitosis, and protein stability. These changes interfere with tumor cell proliferation, survival and cellular homeostasis contributing to an anti-tumor effect. As cancer cells adapt to this insult, several mechanism of resistance may develop including the increased rug efflux, HDAC overexpression or desensitization, alterations of stress response mechanisms and increased anti-apoptotic signaling[49]. We plan to compare pretreatment, on-treatment and post relapse samples for alterations in key genes known to be frequently mutated in B cell lymphomas. The genes are tabulated in Table 10-2.

Table 10-2. Genetic mutations common in B cell lymphoma

CREBBP	CD79B
EP300	Beta-2-microglobulin
MLL2/3	TNFAIP3
EZH2	CARD11
TP53	BCL-6
KDM2B	PIM-1
KIT	FOXO1
PDGFRA	NOTCH2
MYC	CDKN2A
MyD88	REL

- During the study: The pre, during, and post- treatment tumor biopsy should be collected with patient's consent as appropriate for patient safety. At the end of treatment, collection of optional post-relapse tumor sample will provide a unique opportunity to investigate the potential mechanisms of resistance of mocetinostat in patients. If the patient consents and the circumstances are favorable, it is encouraged to collect a fresh frozen tumor biopsy at initial screening biopsy and tumor progression .This tumor biopsy should be collected regardless whether the pre-treatment tumor sample was collected or not. The tumor sample at disease progression should only be obtained as a core biopsy, if feasible. During collection of the fresh biopsy, if the treating physician collects enough tumor tissue, the tumor should be divided into 2 passes. The first pass is formalin fixed and the second pass is snap frozen and will be used for biomarker analysis.

- Assay T cell activation and exhaustion in the peripheral blood
  - Peripheral blood samples from three timepoints (Cycle 1 Day 1 (pretreatment), Cycle 1 Day 15, and Cycle 2 Day 1) will be used to perform preliminary analysis of T cell activation and exhaustion. Four vials of peripheral blood will be drawn into CPT (Cell Preparation Tubes) with Sodium Heparin (each tube is 2 ml tubes for a total of 8 ml) and banked at the Immune Monitoring Core Facility.

11.0 TOXICITIES/SIDE EFFECTS

11.1. Adverse events

11.1.1. Definitions and reporting

An adverse event is defined as the appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s), or medical condition(s) that occur after patient's signed informed consent has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (e.g. hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication(s).

Adverse events that begin or worsen after informed consent should be recorded in CRDB. Conditions that were already present at the time of informed consent should be recorded in the Medical History in CRDB. Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment. Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate Adverse Event.

Adverse events will be assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading does not exist for an adverse event, the severity of mild, moderate, severe, and life-threatening, corresponding to Grades 1 - 4, will be used. CTCAE Grade 5

(death) will not be used in this study; rather, information about deaths will be collected though a Death form.

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

1. The severity grade (CTCAE Grade 1-4)

2. Its duration (Start and end dates)

3. Its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes) or its relationship to the study treatment (Reasonable possibility that AE is related: No, Yes, investigational treatment, Yes, the study treatment (non-investigational), Yes, both and/or indistinguishable)

4. Action taken with respect to study or investigational treatment (none, dose adjusted, temporarily interrupted, permanently discontinued, unknown, not applicable)

5. Whether medication or therapy taken (no concomitant medication/non-drug therapy, concomitant medication/non-drug therapy)

6. Outcome (not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown)

7. Whether it is serious, where a serious adverse event (SAE) is defined as in Section 11.2.1

All adverse events should be treated appropriately. If a concomitant medication or non-drug therapy is given, this action should be recorded in CRDB.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (Cheson criteria), should not be reported as a serious adverse event.

Adverse events separate from the progression of malignancy (example, deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

11.1.2. Laboratory test abnormalities

Laboratory abnormalities that constitute an Adverse event in their own right (are considered clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment), should be recorded in CRDB. Whenever possible, a diagnosis, rather than a symptom should be provided (e.g. anemia instead of low hemoglobin). Laboratory abnormalities that

meet the criteria for Adverse Events should be followed until they have returned to normal or an adequate explanation of the abnormality is found. When an abnormal laboratory or test result corresponds to a sign/symptom of an already reported adverse event, it is not necessary to separately record the lab/test result as an additional event.

Laboratory abnormalities, that do not meet the definition of an adverse event, should not be reported as adverse events. A Grade 3 or 4 event (severe) as per CTCAE does not automatically indicate a SAE unless it meets the definition of serious as defined below and/or as per investigator's discretion. A dose hold or medication for the lab abnormality may be required by the protocol in which case the lab abnormality would still, by definition, be an adverse event and must be reported as such.

11.2. Serious adverse events

11.2.1. Definitions and reporting

Serious adverse event (SAE) is defined as one of the following:

- Is fatal or life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above
- Requires inpatient hospitalization or prolongation of existing hospitalization. Hospitalization is defined as admission to the Emergency Room for more than 24 hours or hospital admission.

Events not considered to be serious adverse events are hospitalization for:

- Hospitalization of subjects to receive study treatment
- Subjects admitted to a hospice or nursing home for elective non-specific, general care or social reasons/respite care
- Hospital admissions purely for the evaluation and treatment of febrile neutropenia
- Hospitalization for prescheduled or elective procedures (such as for pain management, disease staging/restaging procedures, or protocol-specific procedures) Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
- Treatment on an emergency outpatient basis that does not result in hospital admission and involves an event not fulfilling any of the definitions of a SAE

The following Special Reporting Events will be reported in the same manner as SAEs using the dedicated reporting forms:

- Overdose of mocetinostat is defined as any increase in dose (> 20%) or frequency (>20% increased frequency over one month period) over the planned dose and frequency. In the case of overdose, further administration of Investigational Product(s) will be suspended, the subject will be followed closely for potential side effects until resolution and a decision regarding resumption of dosing will be made in conjunction with MSKCC.

- Pregnancy - Pregnant women are excluded from this study. In the case of an identified pregnancy of a female participant or female partner of a male participant, study treatment will be immediately discontinued and follow-up reports on the safety of the fetus and mother will be provided for the duration of the pregnancy. If the fetus is brought to term, information regarding its development may be requested up to 3 months after birth.

Protocol specific SAE

- Drug-induced liver toxicity should be reported as an SAE, even when assessed non-serious by the investigator.

Protocol exempt SAEs

- Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (Cheson criteria), should not be reported as a serious adverse event.

To ensure patient safety, every SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until at least 30 days after the patient has stopped study treatment must be reported to the IRB/PB and MethylGene/Mirati as soon as possible but no later than 5 calendar days.

The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE office at sae@mskcc.org. The report should contain the following information:

- Subject name (report generated with initials if it will be sent outside MSKCC)
- Medical record number
- Disease/histology
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
    - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols: The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report.

11.3. Documentation and reporting of Pericardial Events

Since pericardial abnormalities (e.g., pericarditis, pericardial effusion and hemodynamic compromise) exist along a continuum with overlap between the clinical symptomatology and diagnoses, each pericardial AE (including grading of severity for each individual event) along the continuum should be captured separately (Table 11-1).

Table 11-1. Definitions of Pericardial Events

Event Term	Definition	Characteristics/Diagnosis
Pericarditis	Inflammation of the pericardium	The major clinical manifestations of acute pericarditis include: 1) chest pain, 2) pericardial friction rub, 3) ECG changes (with new widespread ST elevation or PR depressions), and 4) pericardial effusion. At least 2 of these features are usually considered necessary to make the diagnosis.
Pericardial effusion	Excess exudate, or fluid, in the pericardium	Once a pericardial effusion is suspected, the diagnostic approach consists of 3 steps: 1) establish the presence of effusion, 2) assess the hemodynamic impact, and 3) establish the cause. Clinical evaluation and ECG findings may suggest the presence of a pericardial effusion, but imaging, usually ECHO, is required to establish a diagnosis.
Hemodynamic Compromise	Mechanical compression of the heart by large amounts of fluid or blood within the pericardial space that limits the normal range of motion and function of the heart	The diagnosis of hemodynamic compromise is based upon clinical and imaging evidence. The following physical findings 1) sinus tachycardia, 2) elevated jugular venous pressure, and 3) pulsus paradoxus are suggestive of frank tamponade. ECHO or other imaging of the pericardium is essential to the diagnosis of hemodynamic compromise.

All pericardial findings, regardless of seriousness and relationship to study medication, should be reported to the IRB/PB and MethylGene/Mirati. When reporting pericardial events, available ECHO results/reports (or other means of diagnosis if available) should also be provided. All cardiac events, including pericardial findings will be reported to the DSMB to facilitate their ongoing evaluation of safety in subjects treated in this study. Serious pericardial AEs are to be reported according to the standard procedure for reporting of SAEs.

11.4. Pregnancies

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to the IRB/PB and MethylGene/Mirati within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the oncology MethylGene/Mirati Drug Safety and Epidemiology Department (DS&E). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the MethylGene/Mirati study treatment of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The objective of this study is to determine the efficacy of mocetinostat in selected patients with CREBBP/EP300 mutations with DLBCL and FL. The primary efficacy endpoint is the overall

response rate at 1 year, defined as the proportion of patients with a best overall response of CR or PR according to Cheson criteria per Section 12.1. Secondary efficacy endpoints are duration of response and event free survival. Duration of response is defined as the time from the date of first occurrence of CR or PR whichever is recorded first to the date of the first objectively documented progressive disease (PD) or death due to any cause. Event free survival (EFS) is defined as the time from the date of treatment start to the date of the first documented progressive disease (PD) or death due to any cause

12.1. Criteria for evaluation of response

Response will be evaluated, using modified criteria for malignant lymphoma [45]. Response criteria will generally follow the CT scan recommendations as per the revised response criteria for malignant lymphoma [45]. Further clarification on these criteria has been published by [46]. MRI will be allowed only in those cases when CT scan cannot be performed.

Clinical evaluation and tumor assessments will be performed periodically, as is indicated in Table 10-1, based on physical examination, radiological evaluation and core bone marrow biopsy (only to confirm complete responses in patients with bone marrow tumor involvement prior to study treatment). Clinical suspicion of disease progression at any time will require a physical examination and radiological confirmation to be performed promptly, rather than waiting for the next scheduled tumor assessment. In case of an unscheduled or delayed tumor assessment for any reason, subsequent tumor assessments must be performed according to the originally planned schedule from baseline.

12.1. Measurability of lesion for objective response

- Measurable disease: lesions that can be accurately measured in two dimensions by CT, MRI, plain x-ray of other conventional technique and have a greatest transverse diameter of 2 cm or greater. Splenomegaly alone is not sufficient to qualify as measurable disease. PET scans alone are insufficient for evaluation of measurable disease.
- Non-measurable disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusions, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed by CT of disease documented only by indirect evidence (e.g. lab values).

12.2. Objective disease response assessment

Objective status is to be recorded at each evaluation according to the 2007 revised Cheson criteria [45]. All measurable lesions up to a maximum of 6 lesions (largest) should be identified as target lesions at baseline. If there are more than 6 measurable lesions, the remaining will be identified as non-target lesions and included as non-measurable disease. The 6 lesions should be selected according to the following features: they should be from disparate regions of the body and they should include mediastinal and retroperitoneal areas of disease if these sites have measurable lesions. Measurements must be provided for target lesions, while presence or absence must be noted for non-target measurable and non-measurable lesions.

- Complete response (CR): Complete disappearance of all measurable and non-measurable disease with the exception of the following. In patients with positive PET prior to therapy, a post treatment residual mass of any size is permitted as long as it is PET negative. If the PET scan was negative prior to therapy, all nodal masses > 2 cm in greatest transverse diameter (GTD) at baseline must have regressed to ≤ 2 cm in GTD and all nodal masses > 1 cm and ≤ 2 cm in GTD and > 1 cm in their short axis before treatment must have regressed to ≤ 1 cm in their short axis. No new lymphoma lesions should be visible on PET scan or by any other imaging studies. The spleen and/or liver, if considered enlarged at baseline based on physical examination or imaging study (other than PET), must have regressed in size and must not be palpable. If bone marrow was positive at baseline, it must be negative based on biopsy and aspirate at the same site. Normalization of markers (i.e. LDH) definitely assignable to DLBCL or FL. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline unless clinically contraindicated.
- Partial response (PR): Applies to patients with at least one lesion that does not qualify for a CR. For patients with measurable disease, ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 dominant lesions identified at baseline. No new lesions and in increase in the size of extranodal disease. Extranodal disease (splenic and hepatic lesions) must have regressed by ≥ 50% in SPD. In patients with a positive PET scan prior to therapy, PET should be positive in at least one previously involved site. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline unless clinically contraindicated. Patients who meet all other criteria but have new lesions observed on PET scan only (not confirmed on CT or other imaging studies) are considered partial responders.
- Stable disease (SD): Does not qualify for CR, PR, or relapsed/progressive disease. Tumor measurements must be obtained by an imaging modality other than PET. Persistent abnormalities seen on CT scans must be FDG-avid on PET scans. All disease must be assessed using the same technique as baseline unless clinically contraindicated.
- Relapsed disease (after CR)/Progressive disease (after PR or SD): At least 50% increase in the SPD of target measurable nodal lesions over the smallest sum observed (over baseline if no decrease during therapy), or ≥ 50% increase in the GTD of any node > 1 cm in shortest axis, or ≥ 50% increase in the SPD of other target measurable lesions (e.g. splenic or hepatic nodules) over the smallest sum observed. Appearance of any new bone marrow involvement. Appearance of any new lesion > 2 cm in longest axis, or ≥ 50% increase in GTD of any previously involved node with a diameter ≤ 1 cm in the short axis such that its longest axis is not > 2 cm. Lymph nodes should be considered abnormal for relapse or progressive disease only if the long axis is > 2 cm, or if both the long and short axis are > 1 cm. In patients with a positive PET scan before therapy, lesions should be PET positive. Tumor measurements must be obtained by an imaging modality other than PET and preferably consistent throughout the study unless clinically contraindicated. Appearance of any new lesion on PET alone (not confirmed by CT or other imaging modality) is NOT considered relapse or progression.

12.3. Best objective response

- CR: one objective status of CR documented before relapse
- PR: one objective status of PR documented before progression but not qualifying as a CR

- Stable: at least one objective status of stable disease documented at least 6 weeks after registration, no qualifying as a CR or PR
- Increasing disease: objective status of progression within 12 weeks of registration not qualifying as CR, PR or SD
- Inadequate assessment, response unknown: progression greater than 12 weeks after registration and no other response category applies

13.0 CRITERIA FOR REMOVAL FROM STUDY

13.1. Criterial for premature patient removal from study

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

- Progressive disease
- Unacceptable toxicities
- Protocol deviation
- Lost to follow-up
- Pregnancy
- Discovery of patient ineligibility
- Errors in treatment compliance
- Administrative problems

In addition to the general study treatment withdrawal criteria, the following study specific criteria will also require premature study treatment discontinuation:

- Study treatment modifications that result in discontinuation
- Interruption of mocetinostat treatment for more than 21 days
- Use of prohibited medication
- Start of any other anti-neoplastic therapy

If a study treatment withdrawal occurs, or if the patient fails to return for visits, the investigator must determine the primary reason for a patient's premature withdrawal from study treatment and record this information in CRDB. In case of withdrawal from study treatment, the patient needs to indicate on the informed consent form whether she is willing to continue with subsequent follow-up procedures

13.2. Patient Followup

Patients lost to follow up should be recorded as such in CRDB. For patients who are lost to follow-up, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g., dates of telephone calls, registered letters, etc.

13.2.1. Safety followup

All patients will be followed for adverse events and serious adverse events for at least 30 days following the last dose of mocetinostat. At the end of this period (between day 30 and day 37 after

last dose), the investigator should contact the patient to inquire about any AE observed/concomitant medication taken during this period. This could be done via either an office visit or a phone contact.

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. In case the patient has any abnormal lab values at end of treatment that are considered clinically significant by the investigator, the patient needs to come to the site for repeat blood analysis until resolution or stabilization including at least a site visit with respective analyses 30-37 days after end of treatment.

If patients refuse to return for safety evaluation visits or are unable to do so, every effort should be made to contact them by telephone to determine their status. Attempts to contact the patient should be documented in the source documents (e.g., dates of telephone calls, registered letters, etc.).

13.2.2. Efficacy followup

Patients who discontinue study treatment for reasons other than disease progression, death start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent to efficacy follow-up will continue to have radiological tumor assessments per Table 10-1 after end of treatment, or until disease progression, start of a new antineoplastic therapy, death, lost to follow-up, or withdrawn consent.

At the time the patient discontinues the efficacy follow-up period or starts a new antineoplastic therapy, this will be recorded in CRDB.

14.0 BIOSTATISTICS

The primary objective is to determine the efficacy of Mocetinostat in patients with relapsed/refractory DLBCL and FL who have inactivating mutations of acetyltransferase genes. To this end we will examine the endpoint of 1-yr overall response (complete response or partial response defined as per Cheson criteria further elaborated in Section 12.1). Currently this rate is around 15% for both lymphoma subtypes based on a previous study [2], and we expect to improve it to 40%. To this end we will use two parallel optimal Simon two-stage designs, one for each subtype, to test the rate of 15% (lower than which will be unacceptable) vs 40% (higher than which will be acceptable). For each subtype, in the first stage, we will enroll 10 eligible patients. If 1 or 0 patients show response in a year, no additional patients will be enrolled and the regimen will be considered not promising. If 2 or more patients show response, then an additional 15 patients will be enrolled for the second stage. Among the 25 patients, If 7 or more patients are able to show response then this treatment regimen will be declared effective. For this decision rule the type I error (declare Mocetinostat promising while it is actually not) rate is 6% and the type II error (declare Mocetinostat not promising while it actually is) rate is around 10%. The early stopping (i.e., stop after the first stage with 10 patients) probability is 0.54 when the true response rate is 15% or lower, and is 0.046 when the response rate is 45% or higher. If a patient died or progressed (and consequently received other treatments) within a year before showing any responses, or provided no information about the best response status, he/she will be recorded as a non-respondent patient. We expect the withdrawal/drop-out rate to be low (around 10%). However if such events occurred due to reasons unrelated with the disease and the patients had not shown any sign of response or progression, such patients will be replaced by new patients.

Due to the potential withdrawal we will enroll totally 56 patients (28 each subtype), and we expect to have 50 analyzable patients (25 each subtype) within 4 years. Note that only the first 25 analyzable patients, for each lymphoma subtype, will be counted towards the analysis of primary objective. For other objectives, all available patients will be used and the analysis will be done separately for each subtype.

Event free survival (defined as time from the date of treatment start to the date of the first documented progressive disease (PD) or death due to any cause) rate using mocetinostat in this selected population will be estimated by the Kaplan-Meier method. For subjects achieving objective response as assessed by investigators, their duration of response is defined as the time from the date of first occurrence of CR or PR whichever is recorded first to the date of the first objectively documented progressive disease (PD) or death due to any cause. The duration of response will be assessed based on the sub-cohort of patients who showed responses also using Kaplan-Meier. To assess the safety and tolerability of mocetinostat, all toxicities related to the treatment will be tabulated and summarized by type and severity for illustration. Adverse events requiring discontinuation of study drug will be summarized and tabulated separately.

Other exploratory objectives include correlation of myc and Bcl-2 positivity with treatment response, assessment of mechanisms of resistance to mocetinostat via information on additional gene sequencing by IMPACT and Foundation Medicine, and analysis of T cell activation and exhaustion in the peripheral blood. For the former, myc and Bcl-2 positivity will be determined by IHC as binary factors which will be correlated with treatment response by Fisher's exact test. The laboratory genetic mutation study will be mostly descriptive for future references. A panel of mutations included in Table 10-2 will be examined for their presence/absence before and after treatments. Analysis of T cell activation and exhaustion will be over 3 timepoints. Due to the expected small sub-sample size, we may only be able to summarize the T cell activation and exhaustion markers measurements. However, if there are >5 responders and >5 non-responders, then Wilcoxon rank sum tests will be used to preliminary assess the correlation between these markers and the response.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.3 Randomization

Randomization will not be necessary for this study. After meeting inclusion and exclusion criteria, patients are eligible for this single arm open label study.

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the study team.

The Clinical Research Database (CRDB) will be used for data collection. The data will be reported to the institution (IRB) and the drug manufacturer (MethylGene/Mirati) as appropriate.

Tumor slides will be stored in the pathology department. Results from laboratory studies will photomicrographs of immunohistochemical studies and computer files of sequencing data. These files will be stored on the Department of Medicine server. Documentation linking patient identifiers, patient samples, and results will be securely maintained in the CRDB with access limited to study investigators.

16.2 Quality Assurance

Routine registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates, extent, and accuracy of evaluations and followup will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action.

Random sample data quality and protocol compliance audits will be conducted by the study team at a minimum of twice a year and more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at:
http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1

The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at:
http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, and there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

17.1 PROTECTION OF HUMAN SUBJECTS

Prior to the enrollment of each patient, the risks, benefits, and objectives of the study will be reviewed with the participant, including a discussion of the possible toxicities and side effects. Alternative treatment options, including non-protocol treatment options, will be discussed with the patient. It will be reviewed that participation in this clinical trial is voluntary and that the patient may withdraw consent at any time. The study is designed with careful safety monitoring for toxicities and regular physician visits. Every effort will be made to keep study records private. Neither the patient's name nor anything else that could identify the patient will be used in any reports or publications that result from this study. Trained staff at MSKCC, the FDA, or the drug manufacturer MethylGene/Mirati, will be able to review the medical records if necessary. The financial cost of the study will be discussed with the patient and mocetinostat will be provided free of charge.

17.2 Privacy

Medical information is confidential. The participant's personal identity will not be used in reports that are written about the research. The MSKCC Institutional Review Board and Privacy Board (IRB/PB) will review all requests for research performed involving biospecimens ascertained through this protocol. Blood and tissue samples will be stored with a code linked to the patient's medical record. With the permission of the IRB/PB, research studies on cellular, genetic, immunologic or other features of tumor or normal samples may be performed with sample information linked by codes to personal identifiers and no names attached to the samples. The results of any research using blood or tissues will not be placed in the medical record. The consent also indicates that samples and research information collected may be shared with other qualified researchers after de-identification.

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization Form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization Form. The Research Authorization Form must be completed by the Principle Investigator and approved by the IRB/PB.

17.3 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form

- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Appendix A – Pharmacology

20.1. List of drugs metabolized by CYP2C9

This list of CYP2C9 metabolizers are to be used with caution is not comprehensive and any questions should be reviewed with the pharmacist and discussed with the principle investigator.

Table 20-1. List of drugs metabolized by CYP2C9

Non-steroidal anti-inflammatory	Oral hypoglycemics	Angiotensin II blockers	Others
Celecoxib	Glipizide	Losartan	Fluvastatin
Diclofenac	Rosiglitazone	Irbesartan	Phenytoin
Ibuprofen	Tolbutamide		Sulfamethoxazole
Naproxen			Tamoxifen
Piroxicam			Torsemide
			Warfarin

20.2. List of drugs inhibiting or inducing CYP2E1

This list of CYP2E1 modulators are to be used with caution is not comprehensive and any questions should be reviewed with the pharmacist and discussed with the principle investigator.

Table 20-2. List of drugs inhibiting or inducing CYP2E1

Inhibitors	Inducers
Disulfiram	Ethanol
	Isoniazid

20.3. List of P-gp substrates to be used with caution

This list of P-gp substrates to be used with caution is not comprehensive and any questions should be reviewed with the pharmacist and discussed with the sponsor.

Table 20-3. List of P-gp substrates to be used with caution

P-gp substrates
Aliskiren
Ambrisentan
Colchicine
Dabigatran
Digoxin
Everolimus
Fexofenadine
Imatinib
Lapatinib
Maraviroc
Nilotinib

Posaconazole
Ranolazine
Saxagliptin
Sirolimus
Sitagliptin
Tolvaptan

20.4. List of prohibited QT prolonging drugs

Table 20-4. List of prohibited QT prolonging drugs

Drug	QT risk(*)	Comment
Amiodarone	known risk for TdP	TdP risk regarded as low
Arsenic trioxide	known risk for TdP	
Chloroquine	known risk for TdP	
Chlorpromazine	known risk for TdP	
Disopyramide	known risk for TdP	
Dofetilide	known risk for TdP	
Haloperidol	known risk for TdP	When given intravenously or at higher-than-recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	known risk for TdP	
Methadone	known risk for TdP	
Pentamidine	known risk for TdP	
Pimozide	known risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Procainamide	known risk for TdP	
Quetiapine	possible risk for TdP	Sensitive CYP3A substrate
Quinidine	known risk for TdP	Sensitive CYP3A substrate
Sotalol	known risk for TdP	
Tacrolimus	possible risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Terfenadine	Known risk for TdP	Sensitive CYP3A substrate with narrow therapeutic index
Thioridazine	Known risk for TdP	
Vardenafil	possible risk for TdP	Sensitive CYP3A substrate

(*) Classification according to the QTdrugs.org Advisory Board of the Arizona CERT

Sensitive substrates: Drugs whose plasma AUC values have been shown to increase 5-fold or higher when co-administered with a potent inhibitor of the respective enzyme.

20.5. List of prohibited CYP3A inhibitors and inducers

This list of prohibited CYP3A inhibitors and inducers are not comprehensive and any questions should be reviewed with the pharmacist and discussed with the sponsor.

Table 20.5. List of prohibited CYP3A inhibitors and inducers

Strong CYP3A inhibitors	**Moderate CYP3A inhibitors**	**Strong CYP3A inducers**	**Moderate CYP3A inducers**
clarithromycin	amprenavir	carbamazepine *	bosentan
conivaptan	aprepitant	fosphenytoin *	efavirenz
grapefruit juice	diltiazem	nevirapine	etravirine
indinavir	atazanavir	oxacarbazepine*	felbamate *
itraconazole	cimetidine	phenobarbital *	modafenil
ketoconazole	ciprofloxacin	phenytoin *	nafcillin
lopinavir with ritonavir	darunavir with ritonavir	primidone *	pioglitazone
nefazodone	elvitegravir	rifabutin	rufinamide *
nelfinavir	erythromycin	rifampin	talviraline
posaconazole	fluconazole #	ritonavir	tipranavir
saquinavir	schisandra sphenanthera	St. John's Wort	topiramate * (>200 mg/day)
star fruit juice	tipranavir with ritonavir		
telithromycin	verapamil		
voriconazole			

fluconazole inhibition is dose-dependent and use may be considered on a case by case basis
* These drugs are Enzyme Inducing Anti-Epileptic drugs of Medicine's "Clinically Relevant" Table; and from [50].