COLUMBIA UNIVERSITY MEDICAL CENTER

TITLE: **A Phase IbII, Open-label, Multicenter Study of the Selective HDAC6 Inhibitor, ACY-1215, for the Treatment of Patients with Relapsed or Refractory Lymphoid Malignancies**

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PROTOCOL SYNOPSIS

Title:

A Phase Ib/II, Open-label, Multicenter Study of the Selective HDAC6 Inhibitor, ACY-1215, for the Treatment of Patients with Relapsed or Refractory Lymphoid Malignancies

Study Design:

This will be an open-label, single agent, multi-institutional phase Ib/II study of ACY-1215 for the treatment of patients with relapsed or refractory lymphoid malignancies. The target population will include patients with histologically confirmed relapsed or refractory non-Hodgkin's lymphoma or Hodgkin's lymphoma, with an expansion cohort of patients with mantle cell lymphoma.

Phase Ib Objectives:

- Establish the safety of 2 dose schedules of ACY-1215 in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.

Phase II Objectives:

Primary Objectives

- Determine the overall response rates (CR plus PR) in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.
- Determine the progression free survival (PFS) and Time to Treatment Failure (TTF) in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.
- Determine the duration of response (DOR) in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.

Secondary Objectives

- Determine the safety and tolerability of ACY-1215 in patients with relapsed or refractory lymphoid malignancies.
- Evaluate the pharmacokinetic (PK) profile of ACY-1215 as a single agent in patients with lymphoid malignancies.
- Evaluate and compare pharmacodynamic (PD) endpoints with PK endpoints. Proposed PD markers of target effect in paired pre- and post ACY-1215 tissue biopsies peripheral blood, and serum samples would include: HDAC6, acetylated-α-tubulin, total

polyubiquinated proteins, GRP-78, CHOP, XBP-1, IL6, IL10, STAT3, AKT, NFkB level of expression, and Treg levels

- Conduct Magnetic Resonance Spectroscopy Imaging (MRS) for the detection of early signal of response and predict overall response.

Target Population

Patients with relapsed or refractory non-Hodgkin's lymphoma and Hodgkin's lymphoma

Inclusion Criteria

1. Patients must have histologically confirmed relapsed or refractory Non-Hodgkin's Lymphoma or Hodgkin's Lymphoma (WHO criteria), for which they are unwilling or unable to undergo an autologous stem cell transplant. Patients may have relapsed after prior stem cell transplant.
2. Must have relapsed or refractory disease. No upper limit to number of prior therapies.
3. Patients must have measurable disease
4. Patients must be age ≥ 18.
5. Patients must be ECOG performance status ≤ 2. (See definition in Appendix).
6. Patients must have adequate organ and marrow function.
7. Patients must utilize adequate contraception.
8. Patients must have the ability to understand and sign informed consent.

Exclusion Criteria

1. Prior Therapy
    a. Patients who have had chemotherapy or radiotherapy within 2 weeks of study drug treatment or those who have not recovered from adverse events due to agents administered
    b. No monoclonal antibody within 3 months unless evidence of disease progression.
2. Patients may not be receiving any other investigational agents.
3. Patients with known central nervous system metastases, including lymphomatous meningitis
4. Any known cardiac abnormalities such as:
    - Congenital long QT syndrome
    - QTc interval ≥ 500 milliseconds;
5. Uncontrolled inter-current illness
6. Pregnant or nursing women
7. Patient is known to be Human Immunodeficiency Virus (HIV)-positive

8. Patients with active Hepatitis A, Hepatitis B, or Hepatitis C infection
9. Patient has a history of surgery that would interfere with the administration or absorption of the oral study drugs

Treatment Plan

Phase Ib:

Patients will be accrued sequentially to two dose cohorts (Arm A and Arm B) of ACY1215. Upon completion of enrollment of 3 patients to Arm A and a safety assessment has occurred, patients will be allowed to be enrolled to Arm B. All patients will take the assigned dose of ACY1215 for 28 consecutive days. Patients enrolled into Arm A will take ACY1215 160mg once daily, whereas patients enrolled into Arm B will take ACY1215 160mg twice daily. ACY-1215 will be supplied as a liquid for oral administration (PO). Each dose will be administered at least 1 hour after ingestion of food followed by at least 4 ounces of water. Patients will be instructed not to ingest food or other oral medication for at least 2 hours after each ACY-1215 dose.

Phase II:

All patients will take the assigned dose of ACY1215 for 28 consecutive days. The schedule of ACY1215 will be determined based on the safety data from the Phase Ib. Recommended Phase II dose will be based on a discussion with the sponsor and collaborating investigators, with a pre-planned intent to select the schedule that allows the highest dose intensity safely. ACY1215 will be supplied as a liquid for oral administration (PO). Each dose will be administered at least 1 hour after ingestion of food followed by at least 4 ounces of water. Patients will be instructed not to ingest food or other oral medication for at least 2 hours after each ACY-1215 dose.

Duration of Treatment

There is no limit to the number of cycles of therapy. Patients may continue on treatment until they develop progressive disease (PD) or experience an unacceptable toxicity that precludes further treatment.

After discontinuation of therapy, patients will be followed on an every 3 month (+/- 1 week) basis for 1 year or until development of progressive disease or initiation of alternative therapy in order to determine the duration of response.

Patients will be treated until one of the following events:

- Disease progression
- Unacceptable adverse event(s)
- Withdrawal of consent

- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy.
- Termination of the study

Study Endpoints

Phase Ib:

The primary endpoint of the study is:
- Establish the safety and tolerability of ACY1215 in two dosing schedules.

Phase II:

The primary endpoint of the study is:
- The anti-tumor activity of ACY-1215, as measured by:
  - Objective response rate (complete response [CR] + partial response [PR]) assessed according to International Harmonization Project revised Criteria (2007)

Secondary endpoints of the study are to:
- Define the duration of response
- Define the rate of progression free survival
- Define safety and adverse events
- Define the exposure response analyses including biomarkers relating to intracellular protein acetylation.
- Describe the Single- and multiple-dose ACY-1215 pharmacokinetic profile.
- Describe changes in MRS signals with response to study drug

Sample Size

Phase Ib:

Three patients will be sequentially enrolled in one of two cohorts: Arm A and Arm B for a total of six patients (3 in each arm). If ≤33% of patients (N≤1) experiences a dose limiting toxicity (DLT) in a cohort, the cohort will be expanded to 6 patients (3+3). If there are ≤ 33% (N≤ 2 DLTs), the cohort will be further expanded to a total of 10 patients (3+3+4). The maximum total number of patients for both Arms A and B with full expansions will total of 20. If more than 1/3 or 2/6 patients experience a DLT, there will be no expansion.

Phase II:

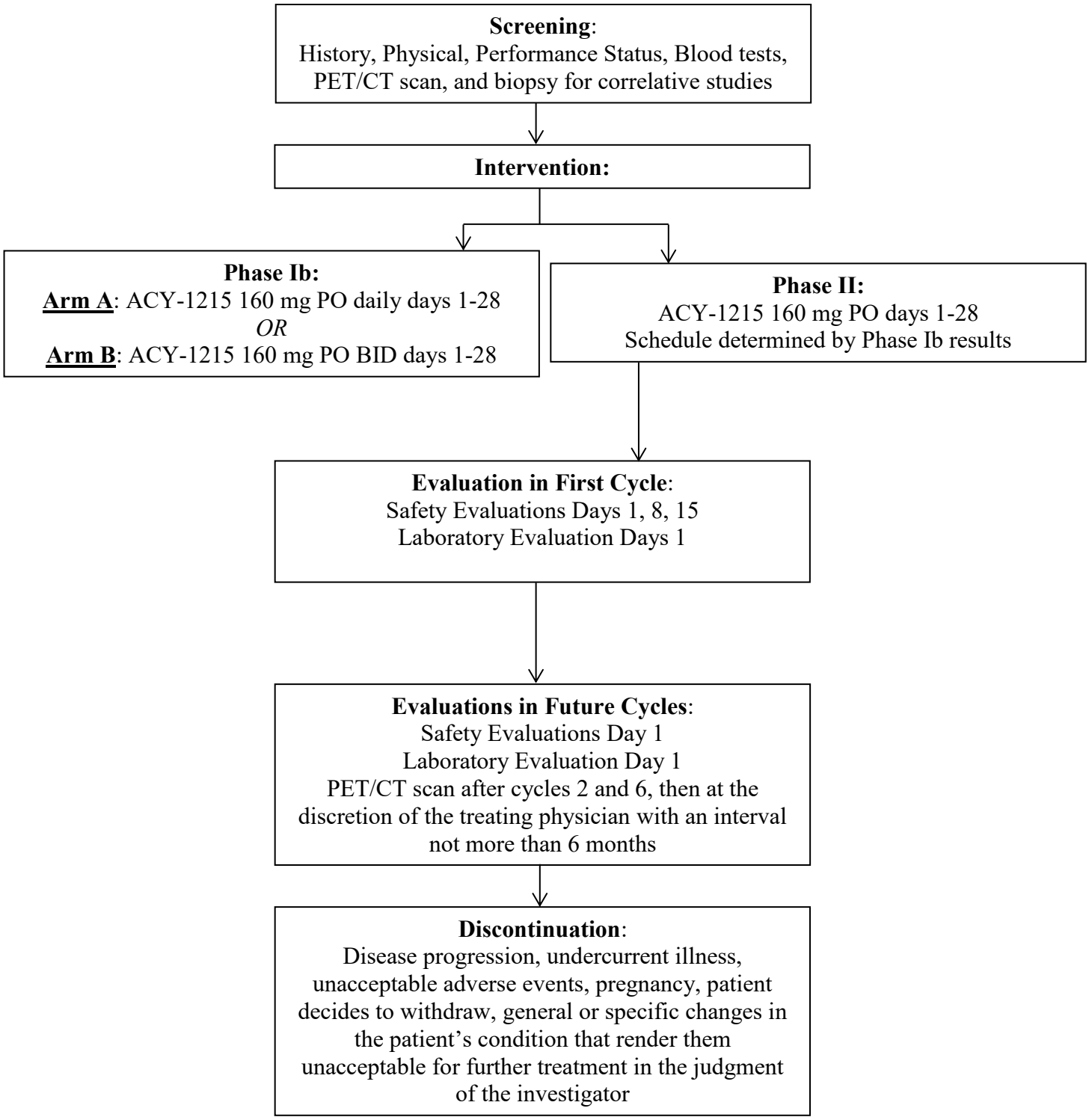
Utilizing the Simon 2 Stage Minimax design, an estimated 40 patients will be needed to determine efficacy at a power of 0.80 and type I error of 0.05. For Stage I, 22 patients

will be enrolled of which 2 must achieve a response to allow for recruitment of patients into Stage 2. Stage 2 will enroll 18 patients of which 8 responses would be needed to attain an efficacy of 25%. An expansion cohort of 20 patients with relapsed or refractory mantle cell lymphoma patients will be assessed to evaluate efficacy in this subtype. The total number of patients accrued to the Phase II component of the study will equal 60.

Safety

Patients will be monitored carefully for the development of adverse events as well as clinical and/or radiographic evidence of disease response. Adverse events will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

Figure 1: Schema



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1. OBJECTIVES

1.1 Phase Ib:

1.1.1 Primary Objectives

- Establish the safety of 2 dose schedules of ACY-1215 in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.

1.2 Phase II:

1.2.1. Primary Objectives

- Determine the overall response rates (CR plus PR) in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.
- Determine the progression free survival (PFS) and time to treatment failure (TTF) in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.
- Determine the duration of response (DOR) in patients with relapsed or refractory lymphoid malignancies treated with ACY1215.

1.2.2 Secondary Objectives

- Determine the safety and tolerability of ACY-1215 in patients with relapsed or refractory lymphoid malignancies.
- Evaluate the pharmacokinetic (PK) profile of ACY-1215 as a single agent in patients with lymphoid malignancies.
- Evaluate and compare pharmacodynamic (PD) endpoints with PK endpoints. Proposed PD markers of target effect in paired pre- and post ACY-1215 tissue biopsies peripheral blood, and serum samples would include: HDAC6, acetylated-α-tubulin, total polyubiquinated proteins, GRP-78, CHOP, XBP-1, IL6, IL10, STAT3, AKT, NFkB level of expression, and Treg levels.
- Conduct Magnetic Resonance Spectroscopy Imaging (MRS) for the detection of early signal of response and predict overall response.

2. BACKGROUND

2.1 Background on Lymphoid Malignancies

Lymphoma is a heterogeneous group of malignancies that are derived from lymphocytes at different stages of development. The 2008 World Health Organization (WHO) now recognizes nearly 70 subtypes of lymphoma, with many of these subtypes being further subdivided [1]. These diseases include some of the fastest growing cancers known to science (Burkitt's lymphoma, lymphoblastic lymphoma/leukemia) as well as some of the most indolent (small lymphocytic lymphoma, follicular lymphoma, and marginal zone lymphoma). This diversity of biology poses challenges in diagnosis, as well as identifying drugs that might be particularly

active in specific subtypes.

In the United States, non-Hodgkin lymphomas represent 4-5% of all new cancer cases, and are the fifth leading cause of cancer death. According to Surveillance Epidemiology and End Results(SEER) registries, it is estimated that nearly 80,000 men and women will be diagnosed and over 20,000 will die of lymphoma in 2012[2]. It is estimated that about 9,000 of these cases with be diagnosed with Hodgkin lymphoma, while the remaining 70,000 will be diagnosed with non-Hodgkin lymphoma. The overall survival in patients with Hodgkin lymphoma is approximately 90%, whereas for non-Hodgkin lymphoma is less than 70%. An evaluation of the distribution of non-Hodgkin lymphoma subtypes was performed on the 114,548 cases of lymphoid neoplasms diagnosed between 1992-2001 in the SEER registries, of which 87,666 were B-cell lymphoid neoplasms, 6,228 were considered T/Natural Killer (NK) cell neoplasms, and about 10,042 were attributed to Hodgkin's disease [1]. As a group, the diffuse, large-cell lymphomas (DLBCL) account for approximately one-third of all NHLs.

The International Prognostic Index, and subtype specific prognostic scores (for example FLIPI, MIPI, and IPSS) are used for prognostic purposes to risk stratify patients. Despite many advances in the care of patients with lymphoma, many subtypes still carry a poor prognosis, and advances in treatment are still needed. Patients with relapsed or refractory disease often develop resistance and do not respond to standard chemotherapy. Novel therapies are needed to overcome this resistance, increase complete response rates, thus increase the chances to potentially bridge some patients to definitive therapy, like stem cell transplant. For those patients where there is no curative option, an increasing number of patients are living with quiescent or stable disease due to the use of targeted therapies.

2.2 ACY-1215

2.2.1 Overview

The HDACs are a family of enzymes consisting of 4 distinct classes. Class I (HDAC1, 2, 3, and 8), Class IIa (HDAC4, 5, 7, and 9) and Class IIb (HDACs 6 and 10), Class III (sirtuins 1-7) and Class IV (HDAC11). Classes I, II, and IV are zinc-dependent deacetylases, whereas Class III are dependent on the co-factor nicotinamide adenine dinucleotide (NAD). The function of HDACs has been largely attributed to their effects on gene transcription through modification of histone tail acetylation and regulation of chromatin condensation [3-5]. More recently, it has become apparent that HDACs play a critical role in the regulation and function of lysine acetylation of non-histone proteins through post-translational modifications affecting many cellular functions [6-8]. The breadth of post-translational regulation in many proteins of diverse functional roles is on a par with that achieved through phosphorylation/dephosphorylation of hydroxyl groups by kinases/phosphatases. Additionally, several HDACs, including HDAC6, are localized to the cytoplasm of cells while others can "shuttle" between the nucleus and cytoplasm [9-11]. HDACs are thus substantially more diverse in their intracellular mechanisms of action than is implied by the "histone" in their name.

The development of small-molecule HDAC inhibitors has previously focused on the antiproliferative effects of HDAC inhibition by modification of gene transcription. This initial focus has led to the approval of 2 HDAC inhibitor drugs for the treatment of cutaneous T-cell lymphoma and peripheral T-cell lymphoma (vorinostat and romidepsin) [12-14]. Vorinostat, which belongs to the structurally class of HDACs referred to as hydroxamic acids, were

previously considered to be nonselective across Class I and Class II, while the ortho aminoanilide inhibitors (e.g., MS-275, Syndax Pharmaceuticals) are relatively more semi-selective for Class I. Recently, it has been demonstrated that the hydroxamate-based inhibitors are relatively more selective for Class I and the Class IIb enzyme HDAC6, while having relatively less activity against Class IIa HDAC enzymes[3].

HDAC6 has been shown to be crucial in the degradation of misfolded proteins aggregates as an alternative to the ubiquitin-proteasome degradation pathway[15]. Failure of a cell to remove accumulated misfolded protein aggregates leads to apoptosis. HDAC6 mechanistically has two direct roles in aggresome formation[16,17]. The deacetylase activity of HDAC6 directly binds misfolded protein aggregates and tubulin, along which protein complexes are transported to the microtubule organizing center where aggresomes form. HDAC6 acts as an adaptor protein binding polyubiquitinated proteins and dynein, an ATP dependent component of the motor complex that transports protein along the microtubules.

Additionally, HDAC6 modulates the acetylation state of a number of other important proteins, one of which is GRP78, a molecular chaperone required for stability and function of numerous proteins[11, 17-19]. The unfolded protein response (UPR) is a critical mechanism employed by all cells to recognize the misfolded protein burden, and either chaperone these proteins to the aggresome or proteasome for processing, or alternatively, if the misfolded protein burden is too high, to initiate apoptosis. Inhibition of HDAC6 leads to activation of the UPR and ultimately programmed cell death. Increased acetylation of GRP78, enforced by inhibition of HDAC6, leads to its dissociation from its cognate inhibitors PERK, p-IRE-1, and ATF6, leading to the induction of CHOP-mediated cell death. GRP78 (a heat shock protein and chaperone), PERK, p-IRE-1, ATF6, and CHOP are thus all potential biomarkers of activity given their role as molecular regulators of the UPR. HDAC6 appears to have a similar role in modulating the acetylation state of Hsp90, Hsp70 and other members of the heat shock protein family.

In theory, the therapeutic index for compounds modulating protein disposal is influenced, at least to some extent, by the metabolic states and increased protein dynamics of the target cells. Malignancies derived from cells of the lymphoid lineage appear to be particularly sensitive to these types of strategies, given the approval of drugs like bortezomib in lymphoma and multiple myeloma. Lymphocytes undergo somatic hypermutation and class switch recombination to generate specific antibodies. These cells physiologically produce a large volume of proteins compared to other tissue types given their role in producing immunoglobulins. As such, the development of HDAC6 and other drugs affecting protein dynamics have had the most significant impact on diseases like myeloma and B-cell lymphomas.

While the mechanisms of action of a drug like bortezomib are considered broad and at times difficult to precisely define, it is clear that the proteasome inhibitor appears to enhance the activity of virtually every drug it has been studied with. One example is the incorporation of bortezomib with the regimen EPOCH for the treatment of activated B-cell like (ABC) diffuse large B-cell lymphoma, as recently demonstrated by Wilson et al[20]. Bortezomib has also been shown to be synergistic with pan-class HDAC inhibitors such as vorinostat in DLBCLand multiple myeloma [21,22] and in combination with romidepsin and belinostat in mantle cell lymphoma [23]. The evidence of anticancer activity of HDAC6 inhibitors in animal disease models, coupled with the evidence that HDAC6 -/- genetic knockout animals have a normal life span [24] whereas Class I -/- animals are nonviable, suggests that selective HDAC6 inhibitors have the potential for a substantially reduced side-effect profile versus current HDAC inhibitor drugs and drug candidates, while retaining the inhibition of the aggresome pathway and

potentiating the UPR leading to marked anticancer effectiveness.

It has been shown ACY-1215, an HDAC6-selective, orally active small-molecule enzyme inhibitor has had single agent activity in a panel of lymphoma cell lines and mouse models, and marked synergistic activity with several agents such as bortezomib, carfilzomib, and ibrutinib, unpublished data. ACY-1215 has been studied *in vivo* in models of multiple myeloma and lymphoma with marked activity both as a single agent and in combination with bortezomib [17]. Therefore ACY-1215 will be investigated for treatment of lymphoma as a single agent leading to future studies evaluating its effects in combination with other targeted agents known to be active in lymphoma and synergistic with ACY-1215.

2.2.2 Rationale for the Study

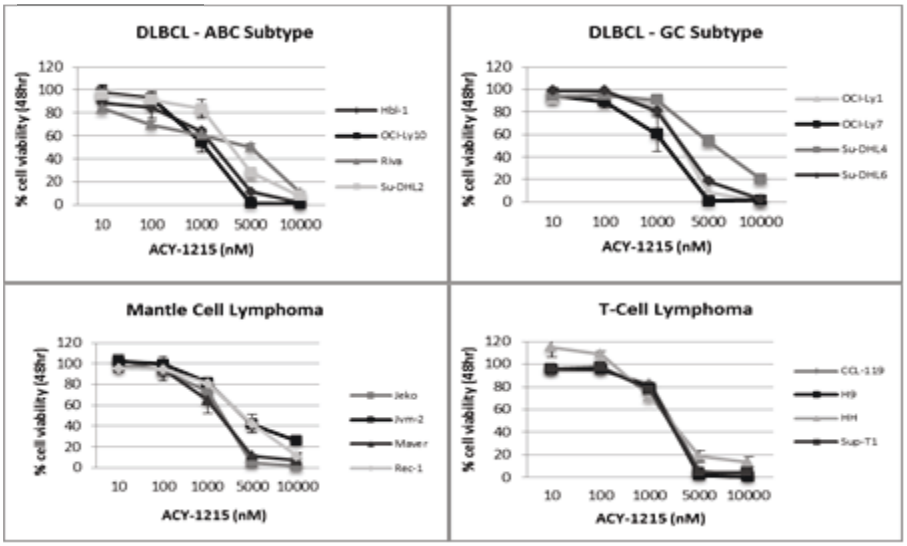
Hypothesis and Preliminary Data

The emergence of epigenetic therapies has identified pan-class deacetylase (DAC) inhibitors as effective therapeutic agents for the treatment of lymphoma. While pan-class DAC inhibitors have led to FDA indications, clinical activity has been limited to the T-cell derived malignancies. The mechanism of action remains largely unknown and off-target effects lead to side effects including fatigue, gastrointestinal disturbances, and cytopenias. Recently, the development of isoform selective DAC inhibitors have opened the opportunity to investigate their mechanism. It is now recognized that DAC inhibitors not only have epigenetic properties, but have direct effects on transcription factors (p53), oncogenes (Bcl6), and protein degradation pathways (aggresome) [5-8]. Proteolysis occurs primarily through the ubiquitin-proteosome pathway. In states where this pathway is physiologically overwhelmed or therapeutically inhibited, the aggresome sequesters proteins for degradation. DAC6 is a class IIb deacetylase that facilitates misfolded protein transport to the aggresome for proteosome-independent proteolysis. Inhibition of the aggresome activates the unfolded protein response (UPR) pathway, a cellular quality control mechanism with two primary functions: (1) to promote survival during cellular endoplasmic reticulum (ER) stress by chaperoning proteins back for re-folding and halting further transcription until homeostasis is restored and (2) to signal CHOP (C/EBP-homologous protein) mediated apoptosis when homeostasis cannot be reestablished[9]. While most cells depend on both branches of the UPR to coordinate protein folding, lymphocytes physiologically down-regulate the UPR-apoptosis pathway, specifically CHOP, to allow for generation of high affinity antibodies. In addition to initiating genetic abnormalities (translocations and point mutations) lymphomas inherit this biology, and thus gain a survival advantage. Given these principles, our hypothesis is: ***If lymphomas generate high levels of misfolded proteins, then pharmacologic up-regulation of the UPR through DAC6 inhibition, could lead to accumulation of misfolded proteins and ultimately increased apoptosis.***

ACY1215 is currently being evaluated in the clinical setting for the treatment of multiple myeloma. Little is known about its effectiveness in lymphoma. In preclinical models of lymphoma, we have demonstrated that selectively targeting DAC6 with ACY1215 inhibits sequestration of misfolded proteins by disrupting transport to the aggresome through acetylation of α-tubulin. It also leads to the acetylation of the key ER-resident chaperone protein, GRP78. This releases and activates the UPR signaling protein, PERK, which in turn promotes transcription of the pro-apoptotic transcription factor, CHOP. This dynamic process, under the influence of ACY1215, shifts toward the pro-apoptotic pathway and ultimately cell death. Interestingly, cells most sensitive to ACY1215 expressed higher baseline levels of pro-apoptotic

proteins CHOP and BIM, and lower levels of pro-survival proteins GRP78 and Bcl2. These findings may serve as potential biomarkers of response for this drug in patients with lymphoma. *In vivo* experiments of ACY1215 in a xenograft model of lymphoma (OCI-Ly10) led to delayed tumor growth equal to that seen with single agent bortezomib. ACY1215 given 50 mg/kg intraperitoneal days 1-5, 8-12, 15-19 alone, or in combination with bortezomib 0.5 mg/kg days 1, 8, 11. The combination led to statistically significant tumor growth delay and median overall survival after one cycle of therapy.

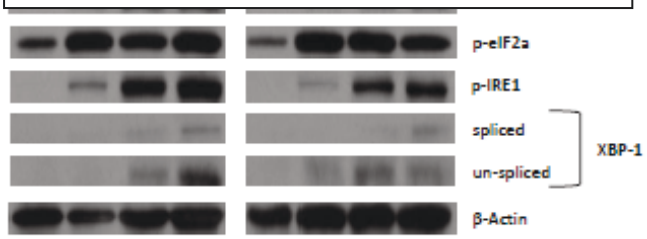
Figure 2



DLBCL - ABC		DLBCL - GC	
Cell Line	IC_{50}	Cell Line	IC_{50}
Hbl-1	366 nM	OCI-Ly1	570 nM
OCI-Ly10	365 nM	OCI-Ly7	307 nM
Riva	1411 nM	Su-DHL4	6198 nM
Su-DHL2	1447 nM	Su-DHL6	1395 nM

MCL		TCL	
Cell Line	IC_{50}	Cell Line	IC_{50}
Jeko	842 nM	CCL-119	601 nM
Jvm-2	3958 nM	H9	341 nM
Maver	899 nM	HH	2634 nM
Rec-1	2271 nM	Sup-T1	798 nM

Figure top left represents concentration : effect curves for 16 lymphoma cell lines. Figure top right displays the calculated IC50 for these cell lines. Figure left shows modulation of the UPR pathway as a function of treatment with ACY1215, Bortezomib, or the combination.



Targeting of protein degradation pathways may represent a novel approach for the treatment of select lymphoma subtypes. It is well established that mantle cell lymphoma is sensitive to this approach as bortezomib is active in this lymphoma subtype. Additionally DLBCL has demonstrated the greatest sensitivity to ACY1215 *in vitro*. Evaluating the clinical impact of ACY1215 in these lymphoma subtypes will define its activity in this population and allow for a better understanding of the UPR pathway in lymphoma. Utilizing paired tissue samples will define both baseline levels and effects of ACY1215 on the UPR and apoptosis, such as GRP78, PERK, XBP-1, CHOP, BIM and Bcl2, and may lead to predictions of which patients may respond to therapy. Dual targeting of

protein degradation pathways with both ACY1215 and bortezomib has synergistic antitumor activity *in vitro* and enhanced all effects on modulation of the UPR and apoptosis.

In addition, MRS imaging will be compared to biomarker and clinical response data. Tumor metabolism has long been of interest as a potential predictor of response to chemotherapy. The intra-tumoral content of the phospholipid-related metabolites phosphoethanolamine (Etn-P) and phosphocholine (Cho-P) has been shown to be increased in clinically aggressive malignant disease and to decrease with clinical response to anticancer therapy, suggesting that phospholipid metabolism may be an intrinsic component of oncogenesis [25, 26] This is significant because molecular changes can be detected at a significantly earlier time points than clinical or standard radiologic response. Novel radiation-free imaging represents an opportunity to detect early signals of response. Once validated, this modality could compliment standard imaging modalities adding another dimension of information.

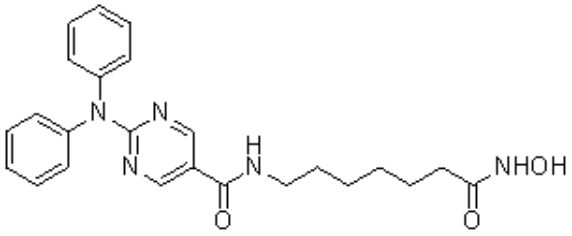
The approval of bortezomib in MCL provides a basis for further study of these approaches in this disease, potentially establishing future regulatory approaches combining ACY1215 plus bortezomib verses alone. The proposed study will establish important single agent activity of ACY1215, and will pave the way for thinking about future combination studies, how to power them from a statistical perspective, and how to design potential regulatory studies in diseases like MCL. Establishing biomarkers for response to this isoform selective DAC6 inhibitor will help elucidate the mechanism of action of ACY-1215 in lymphoma and might lead to understanding of the optimal patient populations to benefit from this therapy.

2.2.3 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.

2.2.4 ACY-1215 Chemical Structure

Figure 3: Chemical Structure



The molecular formula of ACY-1215 is $C_{24}H_{27}N_5O_3$, its molecular weight is 433.5, and its chemical name is: 2-(Diphenylamino)-N-(7-(hydroxyamino)-7-oxoheptyl)-pyrimidine-5-carboxamide.

2.2.5 Product description:

ACY-1215 is a histone deacetylase (HDAC) inhibitor that has not been assigned either an International Nonproprietary Name (INN) or a United States Adopted name (USAN). The active pharmaceutical ingredient is a white to off white crystalline solid with a melting point of

approximately 192°C. ACY-1215 is highly soluble in dimethyl sulfoxide, soluble in methanol, and poorly soluble in acetone, chloroform, and water at less than 1 mg/mL. The label attached to each vial contains the appropriate information, including product name and amount, lot number, directions for storage, date of manufacture, name of Sponsor, and the following statement:

"Caution: New Drug--Limited by Federal (or United States) law to investigational use."

Study drug labels will not contain any statement that is false or misleading in any manner or represent that the study drug is safe or effective for the purposes for which it is being investigated.

2.2.6 Solution preparation:

ACY-1215 will be supplied by Acetylon Pharmaceuticals as a liquid for oral administration in 20mL clear type I glass vials. Each vial will contain 15 mL of a 12 mg/mL solution for a total of 180 mg per bottle.

2.2.7 Storage requirements:

ACY-1215 will be stored at -20ºC. Additional storage conditions and dose preparation instructions will be provided in detail within the Pharmacy Manual. All study drug must be stored in a safe and locked place with no access by unauthorized personnel.

2.2.8 Administration

ACY-1215 should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

2.2.9 Supplier

Acetylon Pharmaceuticals, INC will supply ACY-1215 to study participants at no charge.

2.2.10 Agent Accountability

Accountability for ACY-1215 at the study center is the responsibility of the Investigator. The Investigator will ensure that the study drug is used only in accordance with this protocol. Where allowed, the Investigator may choose to assign some of the drug accountability responsibilities to a pharmacist or other appropriate individual. Drug accountability records indicating the drug's delivery date to the study center, inventory at the study center, use by each patient, and return to Sponsor or designee (or disposal of the drug, if approved by Sponsor) will be maintained by the study center. These records will adequately document that the patients were provided the doses as specified in the protocol and should reconcile all study drug received from Acetylon. Accountability records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and patient numbers. The Sponsor or its designee will review drug accountability at the study center on an ongoing basis during monitoring visits.

All unused and used study drug will be retained at the study center until inventoried by the monitor. All used, unused or expired study drug will be returned to Acetylon or if authorized, disposed of at the study site and documented. All material containing ACY-1215 will be treated and disposed of as hazardous waste in accordance with governing regulations.

2.2.11 Pre-Clinical Pharmacology

2.2.11.1 *In Vitro* Activity

ACY-1215 is a potent inhibitor of HDAC6 activity (50% inhibitory concentration [IC_{50}] 5.7 nM) and is ~10-fold less active against Class I HDAC enzymes, HDAC1, HDAC2 and HDAC3 and has minimal activity against other HDAC enzymes including HDAC4, 5, 7, 9, 11, and sirtuin 1 and 2. In addition the two major metabolites of ACY-1215 have minimal activity against HDAC6. ACY-1215 in the submicromolar (μM) concentration range increases the level of acetylated α-tubulin, a key therapeutic target of HDAC6 inhibition in multiple myeloma and lymphoma cells. ACY-1215 can also increase the level of acetylated α-tubulin in human peripheral mononuclear cells (PMBCs) in a dose-dependent and time-dependent manner.

ACY-1215 can inhibit the growth of lymphoma cell lines (OCI-Ly1, OCI-Ly7, OCI-Ly10, Su-DHL2, Su-HDL4, Su-DHL6, HBL-1, Jeko, JVM-2, Rec-1, Maver, HH, H9, Sup-T1, CCL-119), in the 0.3-2 μM concentration range. The antiproliferative activity of ACY-1215 can overcome the growth supportive activity of growth factors such as Il-6 and IL-10, while having minimal impact on normal cells such activated PBMCs. In addition ACY-1215 (0.2 -1.5 μM) displays synergistic antiproliferative activity in lymphoma cells with the proteosome inhibitor bortezomib (1 – 5nM). At the molecular level the synergistic activity is demonstrated by the increase in molecular markers of apoptosis such as cleaved PARP and caspases, and increased levels of polyubiquitinated proteins, as well as substantially increasing the proportion of lymphoma cells in apoptosis (determined by propidium iodide and Annexin V staining). In addition, there is modulation of the UPR response with increase of GRP78, PERK, p-eIF2a, p-IRE1, spliced XBP-1 in cells treated with ACY-1215 alone and in combination with bortezomib.

2.2.11.2 *In Vivo* Activity

In the plasmacytoma mouse model of human MM, bortezomib was administered intravenously twice weekly and ACY-1215 was administered daily for 5 days each week over a period of two weeks to maintain exposure of the HDAC6 inhibitor during and after administration of bortezomib. ACY-1215 at 50 and 75 mg/kg (once daily [QD] × 5) in combination with bortezomib at 0.5 mg/kg (2 × week), demonstrated significant suppression of tumor growth and increased median survival than either agent alone. Further, ACY-1215 showed single agent activity in suppression of tumor growth at 50 mg/kg. ACY-1215 as a single agent or in combination with bortezomib was well-tolerated and the MTD level of ACY-1215 is equal to or greater than 75 mg/kg in the plasmacytoma model.

In a disseminated skeletal disease mouse model of multiple myeloma bortezomib was administered once per week and ACY-1215 was administered daily for 5 days each week with bortezomib delivered on Day 2 of each week over a two week period. The combination of ACY-1215 (10 – 75 mg/kg, QD × 5) and bortezomib (1 – 1.5 mg/kg, 1 × week) demonstrated significant suppression of tumor growth and increased median survival compared to either agent alone or vehicle. Single agent activity of ACY-1215 was observed, but at a higher dose level of 200 mg/kg compared to 50 mg/kg in the plasmacytoma model. ACY-1215 was well-tolerated as a single agent in tumor bearing animals and in combination with bortezomib in preliminary safety studies in non-tumor bearing animals. Variable incidence of toxicity resulting in premature death was observed in tumor bearing animals at higher dose levels of ACY-1215 (≥30 mg/kg) in combination bortezomib (1 or 1.5 mg/kg). These effects were observed in the first and

second treatment cycles and only when disseminated tumor was present in animals, suggesting the toxicity may in part be related to the significant suppression of tumor growth. Preliminary results comparing tumor bearing to non-tumor bearing animals suggest a greater impact on renal function in the former when treated with a high dose of ACY-1215 in combination with bortezomib. Overall ACY-1215 had an MTD dose level of ~200 mg/kg as a single agent and MTD level of ≥10 mg/kg and <30 mg/kg in combination with bortezomib in animals bearing disseminated tumor.

In a lymphoma xenograft model of diffuse large B-cell lymphoma (OCI-Ly10) mice treated with ACY-1215 50 mg/kg days 1-5, 8-12, 15-19 exhibited decreased tumor burden compared to control miceand equal delay of tumor growth compared to single agent bortezomib 0.5 mg/kg days 1, 8, 11.. Mice tolerated the therapy well with weight loss exceeding 10% within the first 5 days of therapy which quickly resolved to baseline. Mice treated with the combination of ACY1215 in combination with bortezomib had statistically significant synergistic tumor growth delay and a survival advantage after one cycle of therapy.

2.2.12 Safety Pharmacology

In an extensive survey of diverse enzyme functions, including kinases, receptors and ion channels, no significant interactions (inhibition > 50% at 10 μM) were noted, with the exception of a mild to moderate inhibition (IC_{50} 1.3 μM) of the enzyme 5-lipoxygenase.

ACY-1215 has no activity against the human ether-à-go-go related gene (hERG) channel in vitro at 10 μM and showed 18% inhibition at the solubility limit of ~62 μM, i.e. 12 – 60 fold higher than the expected efficacious concentration.

In beagle studies, dose levels of 10, 30, and 60 mg/kg of ACY1215 produced a moderate and transient rise in heart rate (19 – 24 bpm)with a modest decrease in systolic pressure (5 - 15 mm Hg) observed at 0.5 - 11 hours post-dose for all 3 dose levels. One beagle in the highest dose group (60 mg/kg) with the highest exposure and maximum concentrations (C_{max}) levels of ACY-1215 exhibited a QTcR prolongation 15 – 24 hours post-dose, with a maximal excursion of 32 ms (13.4%), and an average excursion for the time period of 20 ms (8.3%) compared to pre-dose values. Plasma levels of ACY-1215 during this period were at least 100-fold below the concentration of ~62 μM, where a minimal 18% inhibition of the hERG channel was observed.

ACY-1215 did not elicit any changes in respiratory or central nervous system function.

2.2.13 Pre-Clinical Pharmacokinetic Studies

ACY-1215 is rapidly absorbed (time to maximum concentration [T_{max}] ≤1 hour) following oral administration in the mouse, rat, and dog, with an oral bioavailability of 11% to 19% in rodents and approximately 45% in dogs. Allometric scaling between species suggests the pharmacokinetic profile of ACY-1215 in humans will be similar to that observed in dogs. Pharmacodynamic studies in mice with ACY-1215 demonstrated a reversible increase in levels of acetylated α-tubulin, a biomarker of HDAC6 inhibition, in peripheral blood mononuclear cells (PBMCs). ACY-1215 is classified as moderately permeable and is stable in human liver microsomes (half-life [$t_{1/2}$] >45 minutes).

Two major metabolites were identified in human S9 liver and intestinal microsomes, which were also present in plasma samples from toxicological studies rat and dog. ACY-1215 and the

2 major metabolites have minimal potential to cause drug-drug interactions through inhibition or induction of CYP450 enzymes.

2.2.14 Pre-Clinical Toxicology

ACY-1215 administered by the oral route has been extensively studied in toxicological studies including pivotal 28 Day repeat-dose studies in rats and dogs. Exposure in the dog for ACY-1215 was considerably higher than in rats by 21- to 31-fold due to higher bioavailability in the dog. Severe toxicity has not been observed at any dose level after administration of ACY-1215 in rats and dogs.

In the rat, a 28 Day repeat-dose study, which included a neurobehavioral functional observation battery and motor assessment, no significant findings were observed after administration of ACY-1215 at dose levels of 30, 60, and 120 mg/kg. The no observed adverse effect level (NOAEL) in rat for the nominal dose is considered to be 120 mg/kg. The NOAEL in the rat for the exposure level is considered to be 30 mg/kg due to the slight increase in exposure with increasing dose on Day 28.

Significant toxicological findings were restricted to the pivotal dog 28 Day repeat-dose study and were generally minimal to mild in nature. The findings were partially or fully recoverable following a 14-day recovery phase. Slight decreases in body weight and minimal to mild decreases in red blood cell mass was observed at all 3 dose levels of 30, 60, and 120 mg/kg, while decreases in white blood cells, lymphocytes, and monocytes were observed in males. The decreased red blood cell mass may reflect decreased hematopoiesis and/or increased turnover of red blood cells suggested by minimal to slight pigment deposition in the liver of some dogs. Marginal, non-adverse, though statistically significant from the control group, clinical chemistry changes were noted in both genders in all dose groups, including a decrease in hepatic enzyme activities (alanine transaminase, alkaline phosphatase, and gamma-glutamyl transferase) and increases in triglyceride (males), total bilirubin (high dose male), albumin and total protein. Administration ACY-1215 at all dose levels was associated with decreased thyroid/parathyroid weights by 27-49% (males) and decreased thymus gland weights by 59-65% (females). There were no histological correlates for the organ effects. A NOAEL in the dog was not established due to the hematological findings and slight but statistically significant body weight effects, which were present at all dose levels.

The mutagenic potential for ACY-1215 appears to be low. ACY-1215 did not exhibit mutagenicity in either the Ames test or Chinese hamster ovary (CHO) micronucleus test. ACY-1215 did not display a mutagenic potential in the mouse lymphoma mutation assay, except with metabolic activation at concentrations 46- to 460-fold above the therapeutic range in cellular assays with MM cells.

Detailed descriptions of findings from nonclinical studies of ACY-1215 are summarized in the Investigator's Brochure.

2.2.15 Clinical Data

ACY-1215 monotherapy was administered at doses to 360 mg without any observed dose limiting toxicities.. Across all dose levels, the most common treatment-emergent adverse events reported among 15 patients treated with ACY-1215 monotherapy were elevated creatinine (5 patients; 33%), anemia, fatigue, hypercalcemia, and upper respiratory infection (4 patients each;

27%), and cough, diarrhea, dizziness, and low white blood cell count (WBC) (3 patients each; 20%). Of these events, diarrhea and low WBC only occurred at doses ≥160 mg. Grade 3 adverse events that were considered by the investigator to be at least possibly related to study drug occurred at doses of 160 mg and 360 mg, and included anemia and decreased WBC and absolute neutrophil count; no Grade 4 events were reported.

Pharmacokinetic analysis of ACY-1215 monotherapy revealed measurable levels of ACY-1215 in all patients, with maximum plasma concentration (C_{max}) levels ranging from 85±39 to 503±195 ng/mL (0.2 to 1.2 μM) and area under the concentration curve from time 0 to the last time point of quantifiable drug concentration (AUC_{last}) values ranged from 170±61 ng•h/mL to 1093±357 ng•h/mL at dose levels of 40 to 360 mg.[1] Maximal plasma (C_{max}) and exposure (AUC) levels were observed in patients treated at 160 mg (C_{max} 626±150 ng/mL, and AUC_{last} 1074±439 ng•h/mL) and 240 mg (C_{max} 719±329 ng/mL, and AUC_{last} 1231±430 ng•h/mL), suggesting an exposure plateau was reached at dose levels ≥160 mg.[1]

The drug was rapidly absorbed (T_{max} ~1 hour) from the gastrointestinal tract. The apparent elimination half-life was ~3 hours. By 24 hours post-dose, drug levels ranged from ~1 ng/mL to below the lower limit of quantification (0.5 ng/mL). There was no accumulation of drug observed over multiple days of administration [28] Overall drug exposure was similar for all doses greater than 160 mg..

Pharmacodynamic analyses in peripheral blood mononuclear cells (PBMCs) revealed acetylation of tubulin at starting at the 40mg dose and that this peaked to a 2-fold increase in acetylated tubulin, the pharmacological marker of HDAC6 inhibition, in all patients at doses of ≥160 mg. At doses higher than 160 mg, a modest increase in acetylated histones was demonstrated with ACY-1215 monotherapy.

Taken together, the data show that exposures observed at ACY-1215 doses ≥160 mg achieve the target change in pharmacodynamic markers such as acetylated tubulin, while sparing acetylation of H3 (an off-target effect), and attain drug levels in the range where efficacy was observed in nonclinical studies[28] These drug levels plateaued at 160 mg so further increases in dosing did not lead to increased in drug exposure.

Further information about ACY-1215 can be found in the investigator brochure.

2.3 Rationale for Phase Ib Study Design

Given that the experience of ACY-1215 monotherapy is limited and restricted to patients with multiple myeloma, a Phase Ib study will be performed exclusively in patients with lymphoma. In addition, in the previous Phase I myeloma experience the dosing schedule was on days 1-5, 8-12 of a 21day cycle. In the prior Phase I study, DLTs were never reached at the dose of 360 mg daily, although pharmacodynamics endpoints were met and the maximum plasma concentrations plateaued at 160 mg daily dosing. This current study is designed to evaluate two dosing schedules of the recommended dose (see above Section 2.2.14) for safety and tolerability while maximizing intensity of exposure to the study drug. Given the half-life of elimination ranges from 3-4 hours, dosing every 12 hours will be explored. Patients of all lymphoma subtypes will be enrolled in order to broaden the experience with ACY-1215 monotherapy. Three patients will be sequentially enrolled in one of two cohorts: Arm A and then after a safety assessment has occurred, Arm B for a total of six patients (3 in each arm). If ≤33% of patients (N≤1) experiences a dose limiting toxicity (DLT) in a cohort, the cohort will be expanded to 6 patients

(3+3). If there are ≤ 33% (N≤ 2 DLTs), the cohort will be further expanded to a total of 10 patients (3+3+4). The total number of patients for both Arms A and B with full expansions will total 20. If more than 1/3 or 2/6 patients experience a DLT, there will be no expansion. Safety data obtained from this Phase Ib will be analyzed by the sponsor and collaborating investigators to recommend a Phase II dose and schedule.

3. PATIENT SELECTION

3.1 Inclusion Criteria for Lymphoma

Patients meeting all of the following criteria will be considered eligible for enrollment in the study:

1. Patients must have histologically confirmed relapsed or refractory non-Hodgkin's lymphoma or Hodgkin's lymphoma (WHO criteria), for which they are unwilling or unable to undergo an autologous stem cell transplant. Patients may have relapsed after prior stem cell transplant.
2. Must have received first line chemotherapy. No upper limit to number of prior therapies.
3. Patients must have measurable disease.
4. Patients must be age ≥ 18.
5. Patient has a Karnofsky Performance Status score of ≥70 or ECOG ≤2
6. The patient or the patient's legal representative is able to understand the risks of the study and provide signed informed consent and authorization to use protected health information (in accordance with national and local privacy regulations).
7. Patient has adequate bone marrow reserve, as evidenced by:
   - Absolute neutrophil count (ANC) of $\geq 1.0 \times 10^9$/L.
   - Platelet count of $\geq 50 \times 10^9$/L.
8. Patient has adequate renal function, as evidenced by a CR within the institutional limits of normal or a calculated creatinine clearance of ≥30 mL/min according to the Cockroft-Gault equation.
9. Patient has adequate hepatic function, as evidenced by serum bilirubin values <2.0 mg/dL and serum alanine transaminase (ALT) and/or aspartate transaminase (AST) values <3 × the upper limit of normal (ULN) of the local laboratory reference range. (Patients with isolated elevations in alkaline phosphatase [ALP] <5 × ULN in the presence of bony disease are not excluded from participating in the study.)
10. Females of childbearing potential must have a negative urine or serum pregnancy test within 7 days of (C1D1) and have adequate contraception. (A female is considered to be NOT of childbearing potential if she has undergone bilateral oophorectomy or if she has been menopausal without a menstrual period for 12 consecutive months.)

3.2 Exclusion Criteria

1. Prior Therapy
    a. Patients who have had chemotherapy or radiotherapy within 2 weeks of study drug treatment or those who have not recovered from adverse events due to agents administered
    b. No monoclonal antibody within 3 months unless evidence of disease progression.
2. Patients may not be receiving any other investigational agents.
3. Patients with known central nervous system metastases, including lymphomatous meningitis
4. Any known cardiac abnormalities such as:
    - Congenital long QT syndrome
    - QTc interval ≥ 500 milliseconds;
5. Uncontrolled inter-current illness
6. Pregnant or nursing women
7. Patient is known to be Human Immunodeficiency Virus (HIV)-positive
8. Active Hepatitis A, Hepatitis B, or Hepatitis C infection
8. Patient has a history of surgery that would interfere with the administration or absorption of the oral study drugs

3.3 Inclusion of Women and Minorities

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

3.4 Source of Patients

This will be a multi-center study. Each study center is required to obtain Institutional Review Board (IRB) approval to conduct the study before enrollment of patients may commence. Patients meeting the entrance criteria who are known or referred to the study center will be eligible for enrollment.

4. REGISTRATION PROCEDURES

4.1 General Guidelines

Eligible patients will be entered on study by the coordinating center study team at Columbia University Medical Center (CUMC). Subsites will fax or PDF/e-mail their signed eligibility checklist to the coordinators at CUMC. Once received, CUMC will confirm eligibility, enter the patient into the CUMC Cancer Center database and assign a study ID number to each patient. CUMC will provide the subsite with the information and the patient will be enrolled to the study.

Following enrollment, patients should begin protocol treatment within 10 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a

patient does not receive protocol therapy within the specified timeframe, the patient's enrollment on the study may be canceled.

4.2 Screening

All potential study patients will be screened and eligibility determined prior to enrollment. Unless otherwise specified, the following procedures and evaluations will be performed as noted in the study calendar (Section 9) prior to the start of study drugs (cycle 1, dose 1):

1) Obtain written informed consent and privacy authorization prior to initiating any protocol-required procedure that is not considered standard of care
2) Review eligibility criteria
3) Review medical chart for past medical/surgical history
4) Record medications and prior treatment regiments
5) Record response to prior treatment regimen
6) Document histopathology from:
    i. Original diagnosis
    ii. Tumor biopsy in the relapsed setting (if applicable)
7) Documentation of known measurable disease parameters by the following procedures:
    i. CT of neck, chest, abdomen, and pelvis (PET/CT optional)
    ii. Skin exam
    iii. Other imaging techniques documenting disease site other than neck, chest, abdomen, and pelvis, if applicable
8) Obtain a 12-lead electrocardiogram (ECG) and calculate the QTc interval.
9) Perform a comprehensive physical examination
10) Assess and record ECOG or Karnofsky Performance Status
11) Local laboratory: Collect blood for hematology (CBC with differential counts), chemistry (Na, K, Cl, HCO3, BUN, creatinine, glucose, calcium, magnesium, including serum β-human chorionic gonadotropin [β-hCG] pregnancy test for women who are not postmenopausal or surgically sterile [within 7 days prior to cycle 1, dose 1 and again within 24 hours prior to first dose of the study drugs.), liver function tests (total protein, Albumin, AST, ALT, total bilirubin, direct bilirubin, alkaline phosphate).
12) Calculate creatinine clearance using the glomerular filtration rate (GFR) according to the Cockroft and Gault Equation, only if screening serum creatinine is > Upper Limit of Normal: GFR* = (140 – age [years]) x actual body weight (kg)72 x serum creatinine *For female patients, multiply by 0.85
13) Urinalysis

4.3 Informed Consent

4.3.1 Study Informed Consent

Study personnel must obtain documented consent from each potential patient prior to conducting any study related procedures and enrolling the patient to the clinical study. Any procedures/tests performed prior to giving written informed consent may be used provided that these tests are considered part of standard care. Consent must be documented on the IRB approved consent form by obtaining the dated signature both of the patient and of the investigator conducting the consent discussion. If the patient is unable to sign the consent form, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., study staff personnel).

The information from the consent form should be translated and communicated to the subject in language understandable to the subject. When the study participant is non-English the consent form must be read accurately in its entirety by a qualified professional translator. The translator will provide a written statement indicating that the consent form has been accurately translated from the accompanying English version, and that the study participant consents to participation. The professional translator will sign the consent form as an impartial witness.

A copy of the signed and dated consent form should be given to the patient before participation in the study.

The initial informed consent form and any subsequent revised written informed consent form, and written information will receive IRB approval prior to implementation. The patient or his/her legally acceptable representative will be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the trial. The communication of this information will be documented.

4.4 Registration Process

To register a patient, the following documents should be completed by a member of the research staff and sent to the study coordinator at CUMC:

- Eligibility Screening Worksheet
- Copy of required laboratory and imaging tests

The Study Coordinator will verify eligibility. To complete the registration process, the Coordinator will:

- Assign a patient study number
- Register the patient on the study
- Confirm registration with the Principal Investigator

No patient may be enrolled or begin treatment prior to registration and assignment of a patient number. Patients who are registered but not treated will be replaced. Investigators will be notified by CUMC when enrollment in the initial part of the study(stage 1) is closed and enrollment into the next parts of the study (stage 2 and expansion cohort) can begin. Investigators will be notified by CUMC or the Sponsor if the study is placed on administrative hold, when it is completed, or is closed to further patient enrollment.

4.5 Withdrawal and Replacement of Patients

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator also has the right to withdraw patients from the study for any of the following reasons:

- Progression of Disease.
- Occurrence of an unacceptable adverse event.
- Patient requires use of an unacceptable concomitant medication.
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the Investigator.
- Non-compliance.
- Patient withdrawal of consent.
- Patient no longer meets the protocol entrance criteria.
- Sponsor request.

At the time of withdrawal, all study procedures outlined for the End of Study Visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the patient's chart and the CRF.

Patients who discontinue from the study will not be replaced.

Patients who miss >10% of planned dose will be censored for response assessment, but not for toxicity, and will be replaced for adequate response assessment.

5. TREATMENT PLAN

5.1 Overall Design and Plan of the Study

5.1.1 Phase Ib:

This is a Phase Ib two-arm multicenter, open-label study in patients with relapsed/refractory lymphoma. The phase Ib will be conducted to determine the safety and tolerability of two dosing schedules of ACY-1215 monotherapy in patients with lymphoid malignancies. Patients will be accrued sequentially to two dose cohorts (Arm A and then after a safety assessment has occured, Arm B) of ACY1215. All patients will take the assigned dose of ACY1215 orally for 28 consecutive days. Patients enrolled into Arm A will take ACY1215 160 mg daily, whereas patients enrolled into Arm B will take ACY1215 160 mg twice daily. ACY-1215 will be supplied as a liquid for oral administration (PO). Each dose will be administered at least 1 hour after ingestion of food followed by at least 4 ounces of water. Patients will be instructed not to ingest food or other oral medication for at least 2 hours after each ACY-1215 dose. Three

patients will be sequentially enrolled in one of two cohorts: Arm A and then after a safety assessment has occurred, Arm B for a total of six patients (3 in each arm). If ≤33% of patients (N≤1) experiences a dose limiting toxicity (DLT) in a cohort, the cohort will be expanded to 6 patients. If there are ≤ 33% (N≤ 2 DLTs), the cohort will be further expanded to a total of 10 patients (3+3+4). The total number of patients for both Arms A and B with full expansions will total of 20. If more than 1/3 or 2/6 patients experience a DLT, there will be no expansion. Safety data obtained from this Phase Ib will be analyzed by the sponsor and collaborating investigators to recommend a Phase II dose.

5.1.2 Phase II:

This is a phase II, single-arm, multicenter, open-label study in patients with relapsed or relapsed/refractory lymphoma. Utilizing the Simon 2 Stage Minimax design, an estimated 40 patients will be needed to determine efficacy at a power of 0.80 and type I error of 0.05. Using this design, there will be an early stopping rule if <10% achieve a response in Stage 1. Twenty-two (N= 22) patients will be accrued to Stage 1, of which 2 patients are required to achieve a response to allow accrual to Stage 2. Patients accrued to Stage 1 of the Phase II will be of all lymphoid malignancy subtypes including those with mantle cell lymphoma (MCL). Eighteen patients (N=18) will be treated in Stage 2, of which 8 responses would be needed to attain an efficacy of at about 25%. The safety, tolerability, single- and multiple-dose PK, pharmacodynamics, and anti-tumor activity of ACY-1215 also will be evaluated. Simultaneously in Stage 2, an additional cohort of 20 mantle cell lymphoma patients will be assessed to evaluate for a signal of efficacy in this subtype. These patients will be enrolled in parallel to the phase II study. Assuming success in Stage I, enrollment to Stage 2, and expansion of MCL cohort, the total number of patients will be 60 (Stage 1 N=22, Stage 2 N=18, MCL focused Expansion Phase N=20).

5.1.3 Treatment plan common to both Phase Ib and Phase II:

After executing written informed consent, patients will be evaluated for study eligibility during the Screening period within the Screening period before Cycle 1, Day 1 [C1D1]. Patients determined to be eligible will be treated on study. Patients will be evaluated on Days 1, 8, and 15 of Cycle 1.

On study drug administration days that coincide with scheduled study center visits, ACY-1215 will be administered at the study center.

- One cycle of therapy is comprised of 28 or 56 doses of ACY-1215.
- Administration of the study drugs will be allowed within 48 hours of the scheduled dates.
- Missed doses will not be made up.

Patients will be evaluated for disease response with CT or PET/CT after cycles 2 and 6, then at the investigators discretion with intervals no more than 6 months. Patients who withdraw from the study will be required to have an End of Study Visit 4 weeks (+/- 7 days) after the last study drug dose. After discontinuation of therapy, patients will be followed on an approximately every 3 month basis (+/- 1 week) until development of PD or initiation of alternative therapy in order to determine the duration of response.

Safety will be evaluated during the study by documentation of AEs and SAEs, clinical laboratory tests (hematology, clinical chemistry, and urinalysis), physical examinations, vital sign measurements, and 12-lead ECGs.

The anti-tumor activity of ACY-1215 will be determined by CT or PET/CT and assessment of disease response will be evaluated using the International Harmonization Project revised Criteria (2007) [27].

Exposure-response of ACY-1215 including biomarkers relating to intracellular protein acetylation, IL6 and IL10 secretion, and markers of the UPR will be analyzed as a function of treatment and response.

Serial blood samples will be collected for determination of the single- and multiple-dose PK of ACY-1215. Patients will receive ACY-1215 160mg orally (PO) for 28 consecutive days per cycle according to schedule determined by the Phase Ib. There will be no limit to the number of cycles patients will receive.

Table 1: Regimen Description

	REGIMEN DESCRIPTION					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Frequency***	***Schedule***	***Cycle Length***
ACY-1215	None	160mg (1 vial)	PO	Once daily vs. Twice daily	Days 1-28	*28 days*

5.1.2 Regimen Description and Guidelines for Drug Administration

Treatment will be administered on an outpatient basis. All patients will take the oral ACY-1215 160mg for 28 consecutive days on a 28-day treatment cycle. Frequency in phase II will be determined based on Phase Ib results. ACY-1215 will be supplied as a liquid for oral administration (PO). Each dose will be administered at least 1 hour after ingestion of food and followed by at least 4 ounces of water. Patients will be instructed not to ingest food or other oral medication for at least 2 hours after each ACY-1215 dose. Reported adverse events and potential risks for oral ACY-1215 are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the patient's malignancy.

5.1.2.1 Rationale for the Dose Selected

In this study, ACY-1215 will be examined as a single agent administered by the oral route 28 consecutive days of a 28 day cycle in patients with relapsed and/or relapsed-refractory lymphoma to assess clinical response, safety, tolerability, PK and PD of ACY-1215.

The rationale of the dosing schedule of ACY 1215 is based on results from a Phase I monotherapy trial in which no maximally tolerated dose (MTD) was established when ACY-1215 was dosed once daily on days 1-5 and days 8-13 of a 21 day cycle up to a dose of 360 mg. Pharmacokinetics were similar at doses of 160 mg (C_{max} 626 +/- 150 ng/mL and $AUC_{0-\infty}$ 1300 +/- 533 ng*h/mL) to higher doses. The half-life of elimination ranged from 3-4 hours and no

accumulation of drug was observed. Dosing at 160 mg and above demonstrated acetylation of tubulin, the pharmacodynamic marker of HDAC6 inhibition, in peripheral mononuclear cells for all patients in these cohorts. Doses above 160 mg lead to off target effects demonstrated by acetylation of histone 3 and increased toxicities. Given the relatively short half-life (~3 h) and safety profile of ACY-1215, twice daily dosing will also be explored to maximize the dose intensity while limiting the toxicity. Twice daily administration of ACY-1215 at 160 mg is expected to approximately double the daily exposure (AUC) to ~4000 ng·h/mL with a minimal impact on maximal plasma levels and no anticipated accumulation, since >95% of the administered dose will have been cleared before the next dose administration. 28-day repeat dose GLP toxicology studies in dogs showed that exposure levels of 15,000-26,800 ng·h/mL were attained with minimal to mild changes in blood cell parameters and minimal changes in body weight that were partially to fully recoverable. Twice daily dosing is therefore not anticipated to change the safety profile of ACY-1215. Accordingly, once daily and BID dosing at 160 mg will be explored in the Phase 1b section of the trial.

5.1.2.2 Rationale and Justification of the Study Design

The trial design is based on existing data recently obtained from a Phase 1-2 study of ACY1215 in patients with multiple myeloma. In nonclinical studies, ACY-1215 has been shown to induce cellular cytotoxicity in MM and lymphoma cells as a single agent. Thus, the anti-tumor activity of ACY-1215 will be studied in patients with lymphoma.

Given that the experience of ACY-1215 monotherapy is limited and restricted to multiple myeloma patients only, a Phase Ib study will be performed. In prior Phase I study, dose limiting toxicities were never reached, although pharmacodynamics endpoints were met and pharmacokinetic profile plateaued at 160 mg daily dosing. This current study is designed to evaluate two dosing schedules of the recommended dose (160 mg see above Section 2.2.14) for safety and tolerability while maximizing intensity of exposure to the study drug. It will inform the final dosing schedule to be used in the Phase II. The total possible number of patients to be accrued to the Phase Ib is 20 if each cohort is expanded to 10 patients.

The Phase II study will be designed to determine the efficacy of ACY-1215 in lymphoid malignancies and incorporated an expansion cohort of patients with mantle cell lymphoma. The minimum number of patients to be treated in stage 1 of the Phase II part is consistent with this standard minimax Simon-2stage design. In order to ensure the safety of patients, the Sponsor personnel, the Study Chair, and Investigators will review all safety data from the first stage before enrollment of additional patients into stage 2 and the expansion cohort. The expansion cohort of patients with mantle cell lymphoma was chosen to obtain early activity and response data in this specific subtype. This subtype was chosen given its sensitivity to bortezomib, a drug which inhibits catabolism of unfolded proteins and which has single agent activity in mantle cell lymphoma.

5.1.3 Required Blood Parameters and Other Investigations Prior to Each Treatment

Before the start of each treatment cycle, patients should be reassessed and the following criteria must be fulfilled:

- Karnofsky Score $\geq$ 70 or ECOG Performance Status $\leq$ 2

- ANC > 1000/dL
- Platelet count ≥ 50,000
- Serum creatinine concentration ≤ 2.0 × ULN or ≤ baseline, or creatinine clearance >30 ml/min
- AST (SGOT) and ALT (SGPT) ≤3.0 × ULN or ≤3.0 × ULN in presence of demonstrable liver metastases
- Bilirubin concentration ≤2.0 × ULN
- Recovery of any drug-related non-hematological toxicity to Grade 1 or less, unless otherwise indicated

5.1.4 Dose-Limiting Toxicity

A dose limiting toxicity (DLT) is defined as any toxicity not specifically included in section 5.1.4 that occurs within cycle 1. DLT is also defined as any toxicity, occurring up to 7 days after completion of cycle 1 that results in a delay of initiating cycle 2. For patients who discontinue study drug administration after Cycle 1, DLT will be defined as any toxicity not specifically included in section 5.1.4 that occurs within 30 days of the last dose of drug on study, in cycle 1 that is not related to disease progression.

DLTs include:

Hematologic dose-limiting toxicity will be defined as either Grade 4 neutropenia that does not resolve to ≤ Grade 2 within ≤ 7 days, any Grade 4 thrombocytopenia, or any Grade 5 hematologic toxicity. At least three patients in each cohort must be evaluable for hematologic toxicity.

Non-hematologic dose-limiting toxicity will be defined as any Grade 3, 4 or 5 non-hematologic toxicity, with the exception of:

- Grade 3 nausea or Grade 3 vomiting that occurs in the setting of inadequate compliance with supportive care measures specified in Section 5.1.7 and lasts for less than 48 hours.
- Grade 3 diarrhea that occurs in the setting of inadequate compliance with supportive care measures specified in Section 5.1.7 and lasts for less than 48 hours.
- Grade 3 dehydration that occurs in the setting of inadequate compliance with supportive care measures specified in Section 5.1.7 and lasts for less than 48 hours.
- Grade 3 acidosis or alkalosis that responds to medical intervention by returning to ≤ Grade 2 within 48 hours.
- Isolated (i.e. no other abnormalities) Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 5 days in duration.
- Isolated (i.e. no other abnormalities) Grade 3 elevation of amylase without associated clinical symptoms, lasting ≤5 days
- Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hypophosphatemia that responds to medical intervention.

- Grade 3 hypercholesterolemia.
- Grade 3 hypertriglyceridemia
- Grade 2 Alopecia
- Grade 3 Constipation
- Grade 3 Fatigue

Management and dose modifications associated with the above adverse events are outlined in Section 6.3.

5.1.5 Prophylactic Medicines and Supportive Care

All prescription and non-prescription medications including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken from thirty days prior to the first dose of ACY-1215 through the End of Study Visit must be recorded in the CRF.

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhea:** Diarrhea should be treated promptly with appropriate supportive care, including loperamide. Loperamide should not be taken prophylactically. Patients should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. The daily dose of loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities of clear fluids.

- **Nausea/vomiting:** ACY-1215 is not emetogenic. Standard institutional guidelines for anti-emetics will be used. Nausea and vomiting should be treated aggressively, with agents such as prochlorperazine, metoclopramide, 5-HT-3 inhibitors, or benzodiazepines. Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy. Patients who experience indigestion or gastroesophageal reflux symptoms may be treated with Proton Pump Inhibitors (PPIs) as well as H2 blockers as clinically indicated. High dose steroids (> 10 mg QD of predisone equivalent) are to be avoided as an anti-emetic therapy.

- **Growth Factors**: Patients who have pre-existing chronic anemia prior to receiving ACY-1215 may continue to receive erythropoietin or darbepoietin. After initiating treatment, anemia may be managed with growth factors according to the ASCO guidelines: 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline http://www.jco.org/cgi/content/full/24/19/3187.

  Post cycle 1, colony stimulating growth factors (e.g., filgrastim, peg-filgrastim, and sargramostim) may be used in patients who experience hematological toxicity per

American Society of Clinical Oncology (ASCO) guidelines. Furthermore, patients who are not receiving such prophylaxis who experience febrile neutropenia (a DLT if occurring in Cycle 1) may receive treatment with colony stimulating factors at the Investigator's discretion. Neulasta should not be administered given that there is no data for co-admnistration of ACY-1215 with neulasta.

- **Thrombocytopenia:** Transfusion of platelets may be used if clinically indicated. Dose modification for thrombocytopenia is allowed in a manner consistent with the guidelines for dose modification (Section 6).

5.1.6 Excluded Medications and Substances

The following medications and supportive therapies and procedures are prohibited during the study:

- Any investigational agent other than ACY-1215, including agents that are commercially available for indications other than lymphoma that are under investigation for the treatment of lymphoma.
- Any anti-neoplastic treatment with activity against lymphoma other than study drug.

5.2 Duration of Therapy

Treatment may continue until one of the following criteria applies:

- Disease progression
- Unacceptable adverse event(s), DLTs
- Withdrawal of consent
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- An event that in the judgment of the treating physician warrant's discontinuation of therapy
- Termination of the study

5.3 Patient Adherence to Protocol Schedule

All patients are required to adhere to the protocol-specified visit schedule. If the patient misses the D1 visit of any cycle, attempts should be made to reschedule the visit within the following 2 days. Failure to attend scheduled study visits may result in discontinuation from the study.

Patients will be required to maintain a log of the precise time at which they had last ingested food prior to taking ACY-1215, the time at which they took study drug, and the time at which they next ingested food.

5.4 Criteria for Removal from Study

Patients will be removed from treatment when any of the criteria listed in Section 5.2 applies. The reason for study removal and the date the patient was removed must be documented in the patient's chart and the CRF.

Subjects/patients may withdraw at any time or be dropped from the study at the discretion of the investigator should any untoward effects occur. In addition, a subject/patient may be withdrawn by the investigator if he/she violates the study plan or for administrative and/or other safety reasons. The investigator or study coordinator will notify the appropriate parties within 2 business days when a subject has been discontinued/ withdrawn due to an adverse event (Section 7). When a subject discontinues/withdraws prior to study completion, all applicable activities scheduled for the end of study visit should be performed at the time of discontinuation. Any adverse events present at the time of discontinuation/withdrawal will be followed until resolution.

5.5 Duration of Follow Up

Patients will have an end of study visit 4 weeks +/- 7 days after their last dose of drug to evaluate safety. Patients will be further followed every three months after the 4-week safety evaluation for one year, or until they develop a POD or begin a new treatment for their disease, for evaluation of delayed toxicity. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

6.1 Dose Delays

- Study drugs will be held until adverse event returns to ≤ Grade 2.
- If interruption lasts for more than 14 days, study treatment will be discontinued.
- In patients who miss >10% of planned dose in the Phase II, but not the Phase Ib, data will be censored for response, but not for toxicity, and patients will be replaced for adequate response assessment.

6.2 Resuming Administration of Study Drug

For toxicities that can be treated or prevented, such as nausea, vomiting, diarrhea and neutropenia, mucositis, treatment may be resumed at the previous dose once supportive measures have been instituted and toxicity recovers to Grade 2 or less.

6.3 Dose Modifications

Dose escalation will not be allowed in any patient at any time. Before each scheduled study drug dose administered in the clinic, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s).

Toxicities are to be graded according to the NCI CTCAE, Version 4.0. The Investigator is to assess the relationship of a toxicity to each study drug. If a toxicity is considered to be related to a particular drug(s), then the dose of the drug(s) to which the toxicity is considered related may be modified per the applicable algorithm in the following subsections. Conversely, if the toxicity is considered unrelated to a particular drug(s), then no modification of that drug(s) is required.

6.3.1 ACY-1215 Dose Modifications

In general, if study drug has been held and the toxicity does not resolve, as defined above, then drug must be discontinued. Note: Dose reductions should not be performed for alopecia or for nausea or vomiting that was not treated with aggressive anti-emetic support. Dose modifications are described in detail in the table below.

Table 2: Dose Modifications for ACY1215

Dose Modifications for ACY1215	
CTCAE Grade or Abnormal Value	1) ACY1215
Thrombocytopenia	
Grade 1 (75×10^9/L - < LLN) Grade 2 (50 - < 75×10^9/L)	Maintain dose level 2) Maintain dose level
Grade 3 or 4 thrombocytopenia: OR Thrombocytopenia that requires platelet transfusion or recurrent Grade 3 or 4 thrombocytopenia	Hold subsequent doses of therapy until thrombocytopenia returns to ≤Grade 2 or baseline and continue at full dose Hold subsequent doses of therapy until thrombocytopenia returns to ≤Grade 2 or baseline and permanently reduce dose of ACY1215 to 75% of dose. If the same toxicity recurs despite dose reduction, reduce by an additional 25%.
Neutropenia (ANC)	
3) Grade 1 (1.5×10^9/L - < LLN) **4)** Grade 2 (1.0 - < 1.5×10^9/L)	5) Maintain dose level 6) Maintain dose level
7) Grade 3 and 4 neutropenia:	8) Hold subsequent doses of therapy until specific cytopenia returns to ≤Grade 1 or baseline and continue at full dose
9) Febrile Neutropenia	
Febrile (≥38.5ºC) Grade 4 neutropenia or recurrent Grade 3 or 4 neutropenia:	10) Hold subsequent doses of therapy until neutropenia returns to ≤Grade 1 or baseline and permanently reduce dose of ACY1215 to 75% of dose. If the same toxicity recurs despite dose reduction, reduce by an additional 25%.
11) All Other Non-Hematologic Drug Toxicities (not mentioned in previous tables)	
Grade 1 or 2: Grade 3 Grade 4	12) Maintain dose level Hold treatment with ACY1215 until toxicity returns to ≤Grade 1 or baseline, then restart therapy at full dose. If Grade 3 toxicity recurs, reduce dose of by 25%. This is a permanent dose reduction. Grade 4 toxicity: Hold treatment with ACY1215 until toxicity returns to ≤Grade 1 or baseline, and then restart therapy at 25% dose reduction. This is a permanent dose reduction

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Safety Evaluation Procedures

7.1.1 Adverse Event Reporting

An adverse event is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the study drugs, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the study drugs product, is also an adverse event.

Adverse events may occur in the course of receiving study drugs or within the follow-up period specified by the protocol, as well as from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse events will be graded and recorded throughout the study according to NCI-CTCAE, version 4.0. Toxicities will be characterized in terms including duration, intensity, and time to onset. Safety endpoints will include all types of adverse events, in addition to laboratory safety assessments, ECOG performance scale status, ECGs, and vital signs.

The investigator must assess all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

The following safety evaluations will be performed during patient screening and at defined points during the course of the study:

- Vital signs
- Laboratory studies complete blood count (CBC), serum chemistry, urinalysis, coagulation studies (PT/PTT), pregnancy test, LDH
- Electrocardiograms (ECG)
- Physical examinations
- Performance Status Evaluation using the ECOG scale
- Adverse event monitoring using the NCI CTCAEv4.0

The Study Calendar (Section 9) provides specific details on collection time points.

Serious Adverse Event (SAE) Definition
A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]

[1]"Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

[2]"Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

[3]Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

Note: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations; for example, important medical events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definition above. Any adverse event is considered a serious adverse event if it is associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Hospitalizations that do not meet these criteria are:

- Social reason in the absence of an AE
- Surgery or procedure planned prior to entry into the trial

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7) and the characteristics of an observed AE (Section 7) will determine whether the event requires expedited (via AdEERS) in addition to routine reporting.

Ongoing monitoring of the clinical safety data in this trial will be performed consistent with procedures outlined in the DSMC charter. This review will pay particular attention to Grade 3 or 4 adverse events, serious adverse events (SAEs), adverse events that lead to discontinuation and adverse events that lead to dose reduction. Should the incidence of any particular adverse event, or combination of events, rise to a level of clinical concern the DSMC will be notified for possible review of the emergent adverse events.

7.2 Pregnancy

Pregnancies occurring while the patient is receiving ACY-1215 or within 30 days after the patient's last dose of ACY-1215 will not be considered serious, but are to be reported using the same procedures as for SAEs described in Section 7.3. There are no adequate and well-controlled studies of this agent in pregnant women.

Women of child bearing potential will be advised to avoid becoming pregnant while receiving treatment with ACY-1215 . Women enrolled in this study should either be post-menopausal, free from menses for > 1 years, surgically sterilized, or willing to use 2 adequate barrier methods of contraception to prevent pregnancy or agree to abstain from heterosexual activity throughout the study, starting with visit 1. Women of child-bearing potential must have a negative serum pregnancy test (β-hCG) within 7 days prior to receiving the first dose of ACY-1215. Men enrolled in the study must also agree to an adequate method of contraception for the duration of the study.

If a patient inadvertently becomes pregnant while on study, the patient will immediately be removed from the study and the drugs will be discontinued and the investigator must notify the Study Chair of the outcome within 5 days. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Investigators will follow the patient monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to appropriate parties within 24 hours if the outcome is a serious adverse event (i.e. death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study, the pregnancy will be reported to appropriate parties

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in utero exposure to the study drug should also be reported.

7.3 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs) for ACY-1215

7.3.1. Clinical Trials Experience

To date, 15 patients have been treated with ACY-1215 monotherapy, at doses of 40, 80, 160, 240, 360 mg (n = 3, 3, 4, 3, and 2, respectively).Eighteen patients have been treated with ACY-1215 in combination including 9 patient receiving ACY1215 in combination with bortezomib and 9 in combination with lenalidomide.

Of the 15 patients who received monotherapy with ACY1215, the median duration of therapy ranged from 1.7 weeks to 12.3 weeks with a maximum of 29.5 weeks. These patients all had a diagnosis of multiple myeloma and 93% had at least 1 AE that were reported as mild to moderate and unrelated to the study drug. The most common AE, regardless of the dose, were blood creatinine increase (33%), fatigue, hypercalcemia, and upper respiratory infections (27%), and anemia, cough diarrhea, and dizziness (20%). Diarrhea occurred only at doses >/= 160 mg.

7.3.2 Serious Adverse Reactions

AEs that were assessed by the investigator as Grade 3 or 4 and possibly related to study drug were seen at doses >/= 160 mg and were all hematologic abnormalities, including anemia (160 mg) and neutropenia (360 mg). None of these events were a dose limiting toxicity based on protocol definitions.

Two of the 15 patients (13%) experienced an SAE including Grade 5 (fatal) cardiac arrest at the dose level 40 mg and chronic obstructive pulmonary disease at 160 mg dose level. Neither event was considered by the investigator to be study drug related.

7.3.3 Discontinuations

No patients discontinued ACY1215 monotherapy because of an AE.

7.3.4 Dose Modifications

No DLTs were reported in any patient treated with ACY1215 monotherapy at doses up to 360 mg, and an MTD of ACY-1215 was not defined.

7.4 Adverse Event Characteristics and Reporting

7.4.1 Procedures for Evaluating AEs and SAEs

Each patient must be carefully monitored for the development of any adverse events. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All adverse events (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded in the CRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an adverse event and must be recorded in the CRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

7.4.2 AE and SAE Reporting

All SAEs that occur during the course of the study must be reported to the Sponsor Investigator – Jennifer Amengual at the contact information below. The Sponsor Investigator will notify INC Drug Safety (on behalf of Acetylon) within 1 working day, of all serious adverse events and expedited safety reports submitted to relevant regulatory authorities, as per the contact information below. All SAEs must be reported whether or not considered causally related to the study drug. SAE forms will be provided to each clinical study site. The information collected will include patient number, a narrative description of the event and an assessment by the Investigator as to the severity of the event and relatedness to study drug. A sample of the SAE form can be found in the study manual. Follow-up information on the SAE may be requested by CUMC and Acetylon.

Jennifer Amengual, MD
212-326-5720

INC Drug Safety on behalf of Acetylon - Drug Safety Reporting Contact Information

INC 24 Hour SAE Reporting
E-mail: incdrugsafety@incresearch.com
Fax: 1 (877) 464-7787

If there are serious, unexpected adverse drug reactions associated with the use of the study drug, the Sponsor will notify the appropriate regulatory agency(ies) and all participating Investigators

on an expedited basis. It is the responsibility of the Investigator to promptly notify the Institutional Review Board (IRB) of all unexpected serious adverse drug reactions involving risk to human patients. An unexpected event is one that is not reported in the Investigator's Brochure.

7.4.3 AE and SAE Definitions

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. A copy of the CTCAE version 4.0 can be found online (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.2 above) for expedited reporting purposes only.

- **Attribution** of the AE:
- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4.4 Report of Adverse Events to the Institutional Review Board

Reportable information should always be reported by the PI directly to the IRB within 5 working days from when the PI learns of the event or new information.

7.4.5 Investigator Reporting to the FDA

The investigator is responsible for reporting any SAEs to the FDA. Serious adverse events (SAEs) that are unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone (1-800-332-1088), fax (1-800-FDA-0178). Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

7.4.6 Adverse event updates/IND safety reports

Acetylon shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Acetylon and the IRB/EC, on file (see Section 14.8 for records retention information).

7.4.7 Expedited Reporting Guidelines

Note: All deaths on study require expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "1 business day; 5 calendar days" – The investigator must initially report the AE within 1 business day of learning of the event followed by a complete report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported if the event occurs following treatment.

7.4.8 Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting. The following AEs must be reported through the routine reporting mechanism (Section 7):

Table 3: CTCAE AE Reporting Exclusions

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution
Blood/Bone Marrow	Neutropenia <7 days without fever	4	No	Yes
Blood/ Bone Marrow	Thrombocyotopenia <7 days without bleeding	4	No	Yes

7.4.9 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions.

For 30 days subsequent to study completion or withdrawal, new onset adverse events will be captured. Follow up of these events will follow the same procedure as described above for AEs observed during the study period.

8. Correlative Studies

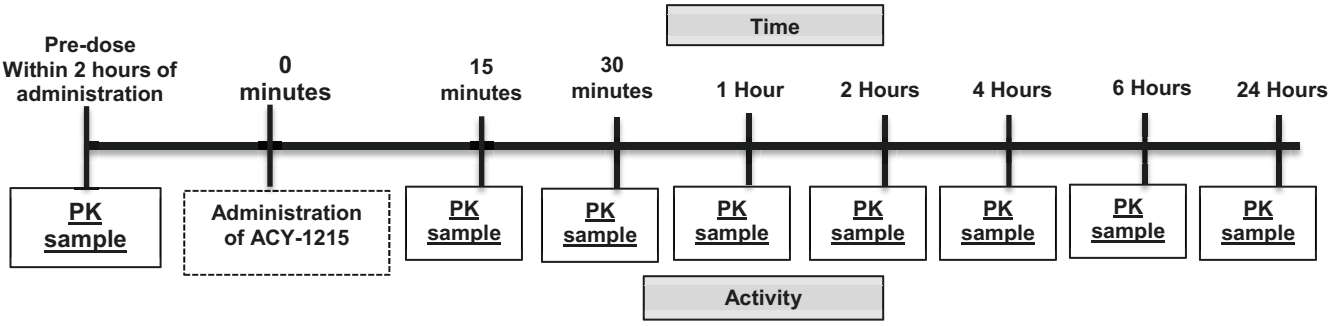
The single- and multiple-dose pharmacokinetics of ACY-1215 will be used to determine exposure response relationships (pharmacodynamics) including biomarkers relating to intracellular protein acetylation, changes in the unfolded response, STAT3, apoototic markers, and serum cytokine levels of IL6 and IL10. MR Spectroscopy will be used to determine early signals of response and prediction of overall response. No information gathered will be used to alter the course of therapy for the patients on trial.

8.1 Pharmacokinetic Studies (Discontinued in Phase II)

Blood samples will be collected and stored on ice until centrifuged. After centrifuge, plasma will be stored in polypropylene screw top tube at -80ºC until evaluation by liquid chromatography.

During cycle 1 day 1, 3 mL of blood will be collected in EDTA tubes pre-treatment and at the following time points:

Figure 4: Drug Administration and Pharmacokinetic Sampling Schedule



* All PKs should be drawn within 15 minutes of specified time.

8.2 Pharmacodynamics Studies (Discontinued in Phase II)

8.2.1 Biopsies

An effort will be made to obtain all patients' paraffin embedded blocks from all tissue samples obtained prior to administration of study drug for research purposes to define baseline levels of mediators of the unfolded protein response by immunohistochemical staining. For patients who have not had a biopsy within a year of study drug, efforts will be made to repeat a biopsy prior to initiation of ACY-1215.

A second effort will be made to obtain at least 5 paired patient biopsies for research purposes to interrogate the UPR. All patients will have the option of checking off boxes within the main consent form for this study to indicate consent or denial for the following optional studies.

An optional lymph node, core-needle biopsy or bone marrow biopsy will be performed prior to ACY-1215 administration on day 8 of cycle 1(+/- 1 Day). Biopsies will be performed as follows:

Tumor Tissue Biopsies: The biopsies will be performed by a surgeon if necessary, or by interventional radiology. A cytopathologist will evaluate the biopsy for tumor cells microscopically at the time of the biopsy. If multiple lymph nodes are available, the safest lymph node will be selected. The choice of core biopsy versus incisional or excisional biopsy will be made based on safety, accessibility, and likelihood of being pathologic. A biopsy confirming recurrent or refractory disease is mandatory for participation in study. The second biopsy is encouraged, but is not mandatory. Correlative studies will be performed on de-identified tissue samples. Tissue will be labeled only with the protocol-specific unique identifier. If the patient has a single target lesion, this lesion will not be eligible for correlative biopsy.

8.2.2 Handling of Specimens

All biopsies will be snap-frozen and sent to Surgical Pathology, flagged for use in the protocol. Paraffin blocks will be made to confirm histological diagnosis, and appropriate immunohistochemical staining will be performed. Remaining tissue will be used for the pharmacodynamic analysis.

Samples from collaborating institutions may be processed and stored with batched delivery at completion of accrual. All correlative studies will occur once all the samples have been received. Details regarding obtaining, processing, handling, and shipping samples will be outlined in the provided laboratory manual.

8.2.3 Serum collection

Serum will be collected to assess for changes in IL6 and IL10 secretion following administration of study drug. After centrifuge, serum will be stored in polypopylene screw to tube at -80oC until evaluation.

9. Study Calendar

Baseline evaluations are to be conducted as indicated in the table below, prior to start of protocol therapy. Scans must be done <4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Table 4. Study Calendar

Cycle		1				2 - onward			
	Screening	Day 1	Day 2	Day 8	Day 15	Day 1	End of Treatment[j]	End of Study (4 weeks after last dose) [k]	Follow-up
Eligibility & Safety Monitoring									
Informed Consent	X[e]								
Demographics	X[e]								
Medical History	X[e]								
Concurrent Medications	X[f]	X[h]				X	X	X	X
Physical exam	X[f]	X[h]				X	X	X	X
Vital Signs, weight	X[f]	X				X	X	X	X
Performance Status	X[f]	X				X	X	X	X
CBC w/ differential	X[f]	X[h]				X	X	X	X
Chemistries[a]	X[f]	X[h]				X	X	X	X
EKG	X[e]	X							
Toxicity Assessment			X	X	X	X	X	X	X
Serum β-hCG	X[f]	X				X	X		
Urinalysis	X[e]	X[h]				X			
Creatinine clearance	X	X				X			
Efficacy Measurements									
CT (PET/CT optional)	X[e]								
Bone Marrow Biopsy	X[c]								
Lymph Node Assessment	X[e]								

a) Chemistries include: Chem, Mg, K, Hepatic Function Panel, and LDH.
b) CT (PET optional) to occur within 7 days prior to starting cycle 3. The CT will be repeated per investigator discretion but at least every six months, PET/CT is optional.
c) Bone Marrow biopsy will be required after cycle 2 for patients with bone marrow involvement at baseline who have a complete response by imaging and physical exam
d) PK for ACY-1215: See section 8 for details.
e) To be done within 4 weeks of treatment start date
f) To be done within 1 week of treatment start date
g) To be performed at the discretion of the treating investigator
h) Not necessary if conducted within 72 hours of screening assessment
i) To be performed on C1D1 pre-dose
j) Follow-up visits will be every 3 months for 1 year, until the development of progressive disease or until the patient begins a new treatment for their disease. .
k) May be done +/- 7 days

ALL SCHEDULED EVENTS +/- 2 DAYS

10. Measurement of Effect

The following section describes the anti-tumor measurements that will be obtained during the study. Response will be evaluated with physical exam, computerized tomography (CT) and optional Positron emission tomography (PET) scans, and tissue biopsies as defined by the guidelines of the International Harmonization Project Group 2007 Revised Response Criteria [27].

10.1 Imaging Studies

CT, and optional PET scans are to be performed during Screening and within 7 days prior to starting Cycle 3. The CT, and optional PET scans will be done at Investigator's discretion thereafter, but not longer than every 6 months. Either CT or PET/CT scan may utilized, at the discretion of the investigator.

Other appropriate imaging studies (e.g., MRI, CT, X-ray) to document sites of disease are to be performed during Screening per standard of care, as determined by the Investigator. Appropriate imaging studies are to be repeated as necessary to confirm CR.

10.2 Bone Marrow Examination

Optional bone marrow aspiration and trephine biopsy are to be performed for patients during Screening. Bone marrow aspiration and biopsy are to be repeated during treatment as clinically indicated, at the Investigator's discretion, and in order to confirm CR.

10.3 Assessment of Disease Response

After discontinuation of therapy, patients are to have disease response assessed at the discretion of the treating physician, but not longer than every 6 months. Bone Marrow biopsy will be required after cycle 2 for patients with bone marrow involvement at baseline who have a complete response by imaging and physical exam

10.3.1 Definitions

Evaluable for objective response. Patients who have received at least one day of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered.

Measurable disease. Measurable lesions are defined as those that can be accurately measured in two dimension (longest diameter to be recorded) as $\geq$20 mm with conventional techniques (PET/CT, MRI, x-ray) or as $\geq$10 mm with spiral CT scan. All tumor measurements will be recorded in millimeters (or decimal fractions of centimeters). Tumor volume will be recorded as the sum of the product of the diameters (SPD) of the largest predominant target lesions.

FDG avidity is based on comparison with background tissues. There is no specific SUV value that is considered a cut-off.

Non-measurable disease (evaluable disease). All other lesions (or sites of disease), including

small lesions (<10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions. All measurable lesions up to a maximum of 6 lesions total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their SUV avidity (High SUV lesions will be prioritized, even if not the largest lesions) and size (lesions with the largest SPD diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). An SPD for all target lesions will be calculated and reported as the baseline sum SPD. The baseline sum SPD will be used as reference by which to characterize the objective tumor response based on CT criteria.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 6 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

10.3.2 Methods for Evaluation of Measurable Disease in Lymphoma

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions**:** Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

CT, PET/CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound (US): Will not be used for disease assessment

10.4 Response Criteria

10.4.1 Evaluation of Measurable Disease in Lymphoma

Table 5 outlines the response criteria used to evaluate disease response to therapy.

Table 5 : Response Criteria for NHL

Response	Definition	Nodal Masses	Spleen/Liver	Bone Marrow CR
CR	Disappearance of all evidence of disease	a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed or PD	Any new lesion or increase by 50% of previously involved sites from nadir	Appearance of a new lesion(s) 1.5 cm in any axis, 50% increase in SPD of more than one node, or 50% increase in longest diameter of a previously identified node 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
Abbreviations: CR, complete remission; FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.				

10.4.2 Response Definitions

Complete Response (CR): Disappearance of all non-target lesions by PET/CT

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

10.4.3 Evaluation of Best Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

10.4.4 Overall Response Rate

Overall Response Rate (OR) = CR + PR based on evaluation of best response in each patient.

11. Data Reporting / Regulatory Requirements

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1.1 Monitoring

The Institutional Review Board (IRB) at each respective institution will monitor this study.

11.1.2 Responsibility for Data Submission

The Study Coordinator is responsible for compiling data for all participants and for providing the data to the Study Chair for review.

11.2 Data Safety Monitoring Board

The Herbert Irving Comprehensive Cancer Center at Columbia University Medical Center's Data Safety Monitoring Board (DSMB) will oversee conduct of the study, patient safety and all interim analyses as specified in the data analysis plan. Detailed guidelines regarding the structure, function and decision-making mechanisms for the Data Safety Monitoring Board are provided in the DSMB charter.

11.3 Investigator Reporting Responsibilities and Compliance

The conduct of the study will comply with all FDA safety reporting requirements.

During the course of the study, the Sponsor may determine that certain safety reports are required to comply with regulations. The Sponsor is responsible for submission of such reports to their IND. The Investigator may receive a letter called an "IND Safety Report" from this study and/or other Acetylon sponsored studies (cross reports). These reports are required to be submitted to the IRB/EC.

11.4 Study auditing

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by CUMC, Acetylon or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

11.5 Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by CUMC and Acetylon. Amendments should only be submitted to IRB/EC after consideration from CUMC and Acetylon review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

12. Statistical Considerations

12.1 Statistical Methods

12.1.1 Phase Ib:

The study will follow the similar principles of a standard 3+3 dose escalation study in which less than one third of patients enrolled to a particular Arm must not have a dose limiting toxicity to allow for expansion. Three patients will be sequentially enrolled in one of two cohorts: Arm A and then after a safety assessment has occurred, Arm B for a total of six patients (3 in each arm). If ≤33% of patients (N≤1) experiences a dose limiting toxicity (DLT) in a cohort, the cohort will be expanded to 6 patients. If there are ≤ 33% (N≤ 2 DLTs), the cohort will be further expanded to a total of 10 patients (3+3+4). The total number of patients for both Arms A and B with full expansions will total of 20. If more than 1/3 or 2/6 patients experience a DLT, there will be no expansion. Safety data obtained from this Phase Ib will be analyzed by the sponsor and collaborating investigators to recommend a Phase II dose.

12.1.2 Phase II:

The study will employ the minimax Simon 2-stage design. In Stage 1, 22 patients will be enrolled. If <2 patients experience an objective tumor response (defined as CR, or PR, as outlined by the 2007 International Harmonization Project criteria), the study will be discontinued. If 2 or more of the first 22 patients experiences CR, or PR, additional 18 patients will be enrolled in Stage 2. Enrollment into Stage 2 will begin only after least 2 objective response have been observed in Stage 1. (Enrollment into Stage 2 need not be delayed until the response status of all 22 Stage 1 patients is known.) The design parameters are as follows:

- 0.15: unacceptable response rate.

- 0.25: target response rate.
- α =0.05: the probability of declaring the drug effective when the true response probability is less or equal to 0.15.
- β=0.20: the probability of declaring the drug as not effective when its true response probability is as large or larger than the target response rate 0.30.

Once enrollment begins for stage 2 of the study, an additional 20 patients will be enrolled per lymphoma subtype, specifically Mantle Cell Lymphoma. Therefore the total number of patients estimated to be enrolled is 60.

12.2 Disposition of Patients

Patients who are screened for study entry and do not meet the eligibility criteria will be listed. Reasons for study discontinuation after the start of study treatment will be tabulated.

12.3 Analysis of Primary and Secondary Endpoints

12.3.1 Phase Ib

12.3.1.1 Primary Objective: Safety and tolerability of ACY-1215 monotherapy

Analysis of dose limiting toxicities will be assessed for Arm A and Arm B of the Phase Ib. If more than 1/3 or 2/6 patients experience a DLT, enrollment into the cohort will be stopped. Safety data obtained from this Phase Ib will be analyzed by the sponsor and collaborating investigators to recommend a Phase II dose.

12.3.2 Phase II

12.3.2.1 Primary Objective: Activity Analysis

Efficacy endpoints in this study include defining the proportion of patients with disease response (CR+PR).

CR, PR, and SD are to be determined according to the International Harmonization Project revised Criteria (2007), Patients who discontinue the study before response evaluation will be considered un-evaluable.

In the expansion cohort, analysis for activity in mantle cell lymphoma will be measured for proportion of patients with disease response (CR+PR) determined according to the International Harmonization Project revised Criteria (2007). Patients who discontinue the study before response evaluation will be considered un-evaluable.

For responding patients, the duration of response and time to progression will be reported on a per-patient basis.

Data that may further characterize the activity of ACY-1215 will be summarized and assessed for a potential dose-response relationship.

Overall response rates will be estimated upon completion of the study along with exact 95% confidence intervals.

12.3.2.2 Secondary Objectives

Pharmacokinetic Analysis

Study drug serum concentrations will be determined at all pre- and post-dose timepoints. Parameters to be calculated based on a non-compartmental model approach include:

- C_{max}.
- Minimum observed serum concentration (C_{min}).
- T_{max}.
- Area under the serum concentration time curve (AUC), for time 0 to the last observed value and to the last measurable value, and from time 0 extrapolated to infinity.
- Half-life ($t_{1/2}$).

ACY-1215 serum levels will be tabulated as single- and multiple-PK doses and results will be presented.

Pharmacodynamic Analysis

Details regarding the analysis of pharmacodynamic data will be included in the statistical analysis plan.

12.4 Demographics and Baseline Characteristics

Demographic and baseline disease characteristic data summarization will be performed in order to descriptively assess the outcomes related to lymphoma subtype. Data to be tabulated will include at least demographic features such as sex, age and race, height, and weight as well as disease-specific status and medical history.

12.5 Extent of Exposure

Descriptive statistics for patients treated in and completing each treatment cycle, including the number of doses missed or held and dose reductions required, will be presented for each treatment cycle. Furthermore, descriptive statistics for the number of doses received, percent of expected dose received, and actual dose received will be summarized by treatment cycle. A tabular summary and listing of drug administration and dose intensity by treatment cycle and a by-patient listing of the date and time of each study drug dose and the dose administered also will be presented.

12.6 Concomitant Medications

A tabulation of all concomitant medications will be produced, with concomitant medications coded using the World Health Organization (WHO) drug dictionary. All concomitant medications administered will be presented in a data listing.

12.7 Safety Analysis

Safety evaluations will be based on the incidence, intensity, and type of adverse events, and changes in the patient's physical examination findings, vital signs, ECG findings, and clinical laboratory results. Safety variables will be tabulated and presented for all patients who receive any amount of study drug and have follow-up safety data. Summarization will focus on occurrence rates of: any serious adverse events; treatment-emergent adverse events by system organ class (SOC) and preferred term; discontinuation rates of study therapy due to adverse event or toxicity based on clinical laboratory assessment and rates of hematologic toxicity. The

frequency of DLT by dose cohort also will be summarized.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All adverse events occurring on study will be listed in by-patient data listings. Treatment-emergent events will be tabulated, where treatment-emergent is defined as any adverse event that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at Baseline but worsens in intensity or is subsequently considered drug-related by the Investigator.

Events that are considered related to treatment (possibly or probably drug-related) will also be tabulated; it should be noted, however, that without a control the primary safety conclusions must be based on overall incidence rates, not those considered treatment-related.

A tabulation will also be provided that enumerates adverse events by maximum severity.

Deaths, serious adverse events, and events resulting in study discontinuation will be tabulated.

Change from Baseline in clinical laboratory parameters will be summarized across time on study, and the frequency of clinically significant abnormal laboratory values will be tabulated. Shift tables will be produced for selected laboratory parameters, to include at least hemoglobin, WBC count, ANC, absolute lymphocyte count, platelet count, AST, ALT, bilirubin, creatinine, ALP, and electrolytes. These tables will summarize by cycle the number of patients with each baseline CTCAE grade and changes to the maximum CTCAE grade in the cycle.

Changes in vital sign parameters (including systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) will be summarized over time in a similar fashion to laboratory parameters, and any abnormal values will be tabulated. Changes in ECG findings will be presented in data listing format.

Karnofsky/ECOG performance status will be summarized for changes from Baseline to the Final Study Visit; Karnofsky/ECOG performance status on D1 of each treatment cycle will be presented in data listing format.

Additional safety analyses may be determined at any time without prejudice, in order to most clearly enumerate rates of toxicities and to define further the safety profile of ACY-1215.

12.8 Populations for Analysis

Patients will be evaluable for response in the context of the Simon 2-stage methodology.

Safety analyses will be performed on the safety population, defined as all patients who receive any amount of study drug.

The evaluation of drug-specific toxicity will be based on data from patients who receive 1 dose of ACY-1215.

12.9 Analysis Schedule

12.9.1 Interim Analysis

12.9.1.1 Phase Ib

Upon enrollment of three patients into Arm A and then after a safety assessment has occurred,

Arm B, no additional patients will be accrued until completion of cycle one to adequately evaluate for dose limiting toxicities. Following determination of <1/3 of patients experiencing a DLT 3 additional patients will be enrolled for a total of 6 patients per Arm. If < 1/3 or < 2/6 patients experience a DLT, planned accrual will expand to a maximum of 10 patients in each arm. The Phase II study will not begin until all 10 patients have completed one full cycle of therapy.

12.9.1.2 Phase II

Interim analysis will be performed following accrual of the first 22 patients to ensure a response rate of at least 10% to proceed to stage 2 of accrual. An early stopping rule will be in effect if <10% of patients achieve a response. If >10% achieve a response, Stage 2 will proceed.

12.9.2 Final Analysis

A final analysis is planned after all enrolled patients either complete 6 cycles of study treatment, or their final study visit, or following early withdrawal from the study.

12.9.3 Addendum

An addendum to the final analysis will be prepared when all patients have withdrawn from the study.

12.10 Procedures for Handling Missing, Unused, and Spurious Data

All available safety, PK, pharmacodynamic, and activity data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

12.11 Procedures for Reporting Deviations to Original Statistical Analysis Plan

A formal statistical plan for the analysis and presentation of data from this study will be prepared before database lock. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

13. Accrual Rate

We estimate accrual of an average of 6 patients per month across the study centers, with a goal of completing accrual within 12-18 months.

14. Administrative Requirements

14.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The Investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

14.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of

Helsinki (see Appendix). The IRB will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the Investigator.

14.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.4 Patient Confidentiality

In order to maintain patient privacy, all CRFs, study drug accountability records, study reports, and communications will identify the patient by initials and the assigned patient number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

14.5 Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by Acetylon, and given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Modifications to the protocol should not be made without agreement of both the Investigator and Acetylon. Changes to the protocol will require written IRB approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. Acetylon will submit all protocol modifications to the regulatory authority(ies) in accordance with the governing regulations.

When immediate deviation from the protocol is required to eliminate an immediate hazard(s) to patients, the Investigator will contact the study coordinator at CUMC, the Sponsor or designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the CRF and source documentation.

14.6 Direct Access to Source Data

Monitoring and auditing procedures developed by CUMC, the Sponsor or designee will be followed, in order to comply with GCP guidelines.

The study will be monitored by CUMC, Acetylon or its designee. Monitoring will be done by personal visits from a representative of CUMC, the Sponsor (site monitor) and will include on-site review of the CRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

The site monitor will ensure that the investigation is conducted according to protocol design and regulatory requirements by frequent communications (letter, telephone, and facsimile).

All unused study drug and other study materials are to be returned to Acetylon after the clinical phase of the study has been completed.

Regulatory authorities, the IRB, and/or Acetylon's clinical quality assurance group may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Investigator, who must provide support at all times for these activities.

14.7 Case Report Form Completion

CUMC will provide the study centers with CRFs for each patient.

CRFs will be completed for each study patient. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the patient's CRF. Source documentation supporting the CRF data should indicate the patient's participation in the study and should document the dates and details of study procedures, adverse events, and patient status.

The Investigator, or designated representative, should complete the CRF pages as soon as possible after information is collected, preferably on the same day that a patient is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must sign and date the Investigator's Statement at the end of the CRF to endorse the recorded data.

CUMC will retain the originals of all CRFs. The Investigator will retain a copy of all completed CRF pages.

14.8 Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). Records will be retained for at least two years after the last marketing application approval or two years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

14.9 Liability and Insurance

Acetylon has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

14.10 Publication of Study Findings and Use of Information

All information regarding ACY-1215 supplied by the Sponsor to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Acetylon. It is understood that there is an obligation to provide CUMC and the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of ACY-1215 and may be disclosed to regulatory authority(ies), other Investigators, corporate

partners, or consultants as required.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of Investigators participating in the study and representatives from Acetylon, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor.

A pre-publication manuscript is to be provided to Acetylon at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company prepared manuscript to the Investigators for review at least 30 days prior to submission to a publisher.

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APPENDIX

Karnofsky Performance Status Scale

The following table presents the Karnofsky performance status scale:

Points	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self unable to carry on normal activity or to do active work
60	Required occasional assistance but is able to care for most of his/her needs
50	Required considerable assistance and frequent medical care
40	Disabled; required special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processed progressing rapidly
0	Dead

Source: Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. Cancer 1984;53:2002-2007.

ECOG PS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Creatinine Clearance Calculation

Calculate creatinine clearance for males and females as follows:

In males: $$\frac{\left[\left(140 - age\right) \times weight\left(kg\right)\right]}{\left[72 \times creatinine\left(mg / dL\right)\right]}$$

In females: $$\frac{\left[\left(140 - age\right) \times weight\left(kg\right)\right]}{\left[72 \times creatinine\left(mg / dL\right)\right]} \times 0.85$$

New York Heart Association Classification of Heart Failure

Class	Symptomatology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

Toxicity Grading Scale

The NCI CTCAE, Version 4.0, can be accessed using the following link:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Declaration of Helsinki

World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the Sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, Sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality

of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.