Official Title of Study:

A Phase 1B/2 Multi-Center, Open Label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of ACY-1215 (RICOLINOSTAT) in Combination With Pomalidomide and Low-Dose Dexamethasone in Patients With Relapsed and Refractory Multiple Myeloma

NCT Number: NCT01997840

Document Date (Date in which document was last revised): 12 July 2016

CLINICAL STUDY PROTOCOL

Protocol ACE-MM-102

EudraCT Number: 2014-002338-29

A PHASE 1B/2 MULTI-CENTER, OPEN LABEL, DOSE- ESCALATION STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE, SAFETY, AND EFFICACY OF ACY-1215 (RICOLINOSTAT) IN COMBINATION WITH POMALIDOMIDE AND LOW-DOSE DEXAMETHASONE IN PATIENTS WITH RELAPSED-AND-REFRACTORY MULTIPLE MYELOMA

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements

Study Sponsor:	Acetylon Pharmaceuticals, Inc. Seaport Center 70 Fargo Street, Suite 205 Boston, MA 02210-2138
Document Version (Date):	Original (15 August 2013) Amendment (7 April 2014) Amendment 2 (21 Aug 2014) Amendment 2.1 Greece (16 Jan 2015) Amendment 3 (09 February 2015) Amendment 4 (12 July 2016)

CONFIDENTIALITY NOTE:Acetylon

The information contained in this document is privileged and confidential. Any distribution, copying, or disclosure is strictly prohibited unless such disclosure is required by federal regulations or state law. Persons to whom the information is disclosed must know that it is confidential and that it may not be further disclosed by them.

STUDY PERSONNEL AND ADMINISTRATIVE STRUCTURE

Study Sponsor:

Acetylon Pharmaceuticals, Inc.
Seaport Center
70 Fargo Street, Suite 205
Boston, MA 02210-2138

Sponsor Contact:

[redacted]
Clinical Project Manager
Telephone: [redacted]
Fax: [redacted]
E-mail: [redacted]

Sponsor Medical Monitor:

[redacted]
Acetylon Pharmaceuticals, Inc.
Telephone (office): [redacted]
Telephone (mobile): [redacted]
E-mail: [redacted]

CRO Safety Monitor:

[redacted]
Medical Officer
INC Safety Monitor
Telephone: [redacted]
E-mail: [redacted]
Fax: [redacted]

SAE Reporting:

24-Hour SAE Reporting

E-mail: [redacted]
Fax: [redacted]

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by Acetylon Pharmaceuticals, Inc., or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board or Independent Ethics Committee (IRB/IEC). No changes will be made to the study protocol without the prior written approval of Acetylon Pharmaceuticals, Inc., and the IRB/IEC, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Name	Investigator Signature	Date

Investigational site or name of institution and location (printed)

CLINICAL STUDY SYNOPSIS

Protocol Title:	A Phase 1b/2 Multicenter, Open Label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of ACY-1215 (Ricolinostat) in Combination with Pomalidomide and Low-dose Dexamethasone in Patients with Relapsed-and-Refractory Multiple Myeloma
Protocol Number:	ACE-MM-102
EudraCT Number:	2014-002338-29
Study Phase:	1b/2
Lead Investigator:	[redacted] Telephone: [redacted] Fax: [redacted] E-mail: [redacted]
Number of Study Centers:	Approximately 19
Indication:	The treatment of multiple myeloma (MM) patients who have received at least 2 prior therapies, including a proteasome inhibitor and an immunomodulatory agent, and who are refractory to the most recent therapy.
Study Duration:	Patients are to receive study treatment until documented progressive disease (PD) or unacceptable toxicity.
Objectives:	
Primary:	**Phase 1b:** • To determine the maximum tolerated dose (MTD), or if not present, the recommended Phase 2 dose and schedule of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM. **Phase 2:** • To determine the efficacy of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone as treatment for patients with relapsed-and-refractory MM as assessed by overall response rate.
Secondary:	**Phase 1b and Phase 2**: • To evaluate the safety of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone as treatment for patients with relapsed-and-refractory MM. **Phase 1b**: • To assess the pharmacokinetics (PK) of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM.

- To assess the PK of pomalidomide administered in combination with ACY-1215 and low-dose dexamethasone in patients with relapsed-and-refractory MM.
- To assess the pharmacodynamics of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM.

Exploratory: **Phase 2:**

- To explore the relationship between response to treatment and any cytogenetic abnormalities.

Study Endpoints:

Primary: **Phase 1b:**

- MTD and schedule, or if not present, the recommended Phase 2 dose and schedule of ACY-1215 administered in combination with pomalidomide and dexamethasone.

Phase 2:

- Objective response to treatment as assessed by site Investigators using the International Myeloma Working Group (IMWG) Uniform Response criteria.

Secondary: **Efficacy:**

Phase 1b and Phase 2:

- Time to response (TTR).
- Duration of response (DOR).
- Time to progression (TTP).
- Progression-free survival (PFS).
- Objective response to treatment as blindly assessed by the Central Adjudication Committee using IMWG criteria and dates of PD.

Safety:

Phase 1b and Phase 2:

- Safety (type, frequency, and severity of adverse events [AEs] and relationship of AEs to study drug)

Pharmacokinetics: **Phase 1b:**

- Plasma levels of ACY-1215 to assess the single and multiple-dose PK of ACY-1215 in combination with pomalidomide and low-dose dexamethasone.
- Plasma levels of pomalidomide to assess the PK of pomalidomide in combination with ACY-1215 and low-dose dexamethasone.

Pharmacodynamics: **Phase 1b:**

- Exposure-response of ACY-1215 in combination with pomalidomide and low-dose dexamethasone, including biomarkers relating to intracellular protein acetylation.

Exploratory: **Phase 2:**

- Explore the relationship between response to treatment and any cytogenetic abnormalities.

Study Design:

This is a Phase 1b/2, multi-center, single-arm, open-label, dose-escalation study that will evaluate the safety and efficacy of oral (PO) ACY-1215 in combination with PO pomalidomide and low-dose PO dexamethasone in patients with relapsed-and-refractory MM. Eligible patients must have a documented diagnosis of MM and have relapsed-and-refractory disease. Patients must have relapsed after having achieved at least stable disease (SD) for at least one cycle of treatment to at least one prior regimen and then developed PD. Patients must also have documented evidence of PD during or within 60 days (measured from the end of the last cycle) of completing treatment with the last anti-myeloma drug regimen used just prior to study entry (refractory disease). Patients must also have undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of bortezomib (either in separate regimens or within the same regimen) and have measurable disease. This study will consist of a Phase 1b ACY-1215, pomalidomide and low dose dexamethasone dose-finding segment and a Phase 2 segment. The Phase 1b segment will determine the starting dose and schedule to be used in the Phase 2 segment of the study. All patients will receive ACY-1215 in combination with pomalidomide and dexamethasone administered orally in 28-day treatment cycles unless an alternative schedule is identified in Part 1b.

Potentially eligible patients will sign informed consent form (ICF) prior to undergoing any study-related procedures. Patients will undergo screening assessments for protocol eligibility within 28 days of study start (Cycle 1, Day 1 [C1D1]).

For all patients who enroll into either the Phase 1b or Phase 2 segment of this study, study visits and serial measurements of safety and efficacy will be performed as outlined in the Schedule of Assessments. In addition, all patients will be given aspirin 81 or 325 mg daily (commercial supply) as prophylactic anti-thrombotic treatment unless contraindicated. If aspirin is contraindicated, patients will receive another form of anti-thrombotic therapy according to hospital guidelines or physician preference. All patients will be monitored for signs and symptoms of venous thromboembolism (VTE) while on pomalidomide; diagnostic algorithms will be provided (Appendix 9.1).

Tumor response, including PD, will be assessed according to the consensus recommendations based on the IMWG[1] criteria, published by Rajkumar et al., in *Blood* in 2011, which includes the category of minimal response (MR) (as defined by the European Group for Blood and Marrow Transplantation [EBMT] criteria) for relapsed refractory MM. In order to assess response to treatment, M-protein component is to be measured in serum and urine, FreeLite™ testing is to be performed and, as applicable, bone marrow aspirate and biopsies, and appropriate imaging studies (e.g., computed tomography [CT], magnetic resonance imaging [MRI]) are to be performed.

[1]Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011. 117: 4691-4695.

Patients who are determined to have PD at any time are to be discontinued from the study.

The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.

Clinical laboratory tests are to be performed locally. In addition, a central laboratory will analyze duplicate samples of serum immunoglobulin levels, serum and urine protein electrophoresis of myeloma (M)-protein component (SPEP, UPEP), serum and urine immunofixation (IFE) studies, and serum free light chain (SFLC) analysis. A bone marrow aspirate will be centrally analyzed for fluorescence *in situ* hybridization (FISH)/cytogenetics.

In the Phase 1b segment, blood samples will be collected from all patients for the assessment of PK for ACY-1215. Blood samples will also be collected from patients at participating sites in the Phase 2 segment for sparse PK sampling. Pharmacodynamic evaluations will also be performed in the Phase 1b segment and will include the assessment of the exposure-response relationship of ACY-1215 in combination with pomalidomide and low-dose dexamethasone and potential biomarkers of response.

Exploratory assessments will include the evaluation of the relationship between response and cytogenetic abnormalities.

Patients who withdraw from the study are to be followed up either in person or by phone 30 days (± 3 days) after the last dose of study drug. Upon discontinuation from study treatment for PD or any other reason, patients will be assessed 3 times per year (e.g., April, August, and December), for up to 1 year, for survival, subsequent anti-myeloma therapies, and monitoring of second primary malignancies as outlined in Table 1. Patients who discontinue study treatment due to reasons other than PD will also be followed for efficacy assessments (assessment of response, extramedullary plasmacytoma assessment, quantitative serum immunoglobulin levels, SPEP and UPEP of M-protein levels, serum and urine IFE, and SFLC analysis) until PD, death, or initiation of an alternate MM therapy, whichever occurs first. Serious adverse events (SAEs) will be collected from C1D1 through the first 30 days of follow-up. Females of childbearing potential (FCBP) with regular or no menstruation will be required to have a final pregnancy test at study treatment discontinuation, and at Day 28 following study treatment discontinuation. Females with irregular menstruation must have a pregnancy test at study treatment discontinuation, and at Day 14 and Day 28 following study treatment discontinuation.

PHASE 1b SEGMENT

Identification of MTD and schedule

Patients who have completed all screening assessments and meet all eligibility criteria, may enter the Phase 1b segment of the study. The Phase 1b segment of the study will follow a standard 3 + 3 dose escalation design and will include assessment of the safety of treatment between each dose cohort by the Safety Review Committee (SRC). The SRC will be comprised of the Study Investigators, the Sponsor Medical Monitor, and the Safety Monitor. Safety assessments will be conducted in real-time by the

SRC after the first 3 patients have completed Cycle 1. Dose escalations or expansion of a dose cohort will occur only with full approval of the SRC.

The initial dose and schedule of ACY-1215 to be administered in this study is based on a dose and schedule similar to the ones explored in Study ACE-MM-101, which is evaluating ACY-1215 in combination with lenalidomide and dexamethasone: ACY-1215 160 mg once daily (QD) on Days 1 to 21 of a 28-day cycle. Pomalidomide will be administered based on the current approved dose and schedule: 4 mg PO QD on Days 1 to 21 of a 28-day cycle. The starting dose of dexamethasone will be 40 mg PO QD on Days 1, 8, 15, and 22 of a 28-day cycle for patients who are ≤ 75 years of age. For patients who are > 75 years of age, the starting dose of dexamethasone will be 20 mg PO QD on Days 1, 8, 15, and 22 of each 28-day cycle. Complete blood counts (CBCs) will be monitored every 7 days (weekly) for Cycle 1, every 14 days for Cycle 2, and on Day 1 of each cycle beginning with Cycle 3. A guideline for the reduction of the dose of ACY-1215 for dose-limiting toxicities (DLTs) is provided in Section 5.2.8.1.

Dose-Level Groups

Dose Level[a]	N	ACY-1215	Pomalidomide	Dexamethasone[b]
-2	3-6	160 mg QD on Days 1-5, and 8-12	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
-1	3-6	160 mg QD on Days 1-5, 8-12, and 15-19	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
1	3-6	160 mg QD on Days 1-21	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
2	3-6	240 mg QD on Days 1-21	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
3	3-6	160 mg BID on Days 1-21	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22

Key: BID = twice daily, QD = once daily.
Note: treatment cycle is 28 days.

[a] Patients will be initially enrolled at Dose Level 1. If 2 or more patients experience a DLT within the 28-day cycle, patients will be subsequently enrolled at Dose Level -1. If 2 or more patients experience a DLT at Dose Level -1 within the 28-day cycle, patients will subsequently be enrolled at Dose Level -2

[b] Patients ≤ 75 years of age will receive 40 mg of dexamethasone; patients > 75 years of age will receive 20 mg.

Based on emerging data from ongoing studies of ACY-1215, intermediate dose levels and schedules may be added, or dose levels eliminated, and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will be notified.

Definition of Dose Limiting Toxicity (DLT):

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. If a toxicity is not classified in the CTCAE, then it should be classified according to the criteria presented in Section 6.1.8.4.

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. For toxicities observed that may be attributable to pomalidomide (see Table 6) or dexamethasone (see Table 8), dose reductions should be attempted with these treatments prior to reducing the dose of ACY-1215.

The following AEs occurring during Cycle 1 that are considered by the Investigator to be ACY-1215-related will be considered to be DLTs:

Hematologic toxicity:

- Grade 4 neutropenia (absolute neutrophil count [ANC] < 500/μL) lasting > 5 days, *or*
- Febrile neutropenia (fever ≥ 38.5° C and ANC < 1,000/μL), *or*
- Grade 4 thrombocytopenia (platelet count < 25,000/μL), *or*

Grade 3 or 4 ACY-1215-related non-hematologic toxicity:

- All other Grade 3 or 4 non-hematologic toxicities with the exception of:
    - Grade 3 or 4 nausea, vomiting or diarrhea (Patients must have received optimal symptomatic treatment for Grade 3 or 4 nausea, vomiting, or diarrhea to be considered a DLT).
    - Grade 4 transaminitis (serum transaminase > 20 × upper limit of normal [ULN]) is a DLT, while Grade 3 transaminitis (serum transaminase >5 × ULN) must be present for ≥ 7 days to be considered a DLT.
    - Other asymptomatic Grade 3 and 4 laboratory investigations, excluding cardiac function tests, may be evaluated by the SRC to determine whether dose cohorts should be expanded.
- Delay of the start of Cycle 2 by > 7 days due to ACY-1215-related AE

No dose modifications for ACY-1215 are to be performed in Cycle 1. After Cycle 1, patients who are unable to tolerate ACY-1215 treatment may have the dose reduction steps presented below until a tolerable dose is achieved.

ACY-1215 Dose Modifications

Dose level	Starting dose of ACY-1215	1st dose reduction	2nd dose reduction
-2	160 mg QD on Days 1-5, and 8-12	80 mg QD on Days 1-5, and 8-12	NA
-1	160 mg QD on Days 1-5, 8-12, and 15-19	80 mg QD on Days 1-5, 8-12, and 15-19	NA
1	160 mg QD on Days 1-21	80 mg QD on Days 1-21	NA
2	240 mg QD on Days 1-21	160 mg QD on Days 1-21	80 mg QD on Days 1-21
3	160 mg BID on Days 1-21	160 mg QD on Days 1-21	80 mg QD on Days 1-21

Determination of MTD: Dose escalation rules

Study drug doses will be escalated sequentially after the SRC reviews safety data collected during Cycle 1 from patients at the current dose level to confirm any DLTs that were experienced and to make a determination regarding enrollment in the next dose cohort.

The following dose escalation rules will be used:

- If none of the 3 patients experiences a DLT within the first 28-day cycle, and pending SRC review as described above, then an additional 3 patients will be enrolled into the next higher dose level.
- If one of the 3 initial patients in a Dose-Level Group experiences a DLT within the first 28-day cycle, then an additional 3 patients will be enrolled into that Dose-Level Group.
- If 2 or more patients within the expanded dose cohort experience a DLT within the first 28-day cycle, then the MTD has been exceeded and no further dose escalations will occur.
- If no more than one of the 6 patients experiences a DLT within the first 28-day cycle, then the next dose cohort of 3 patients will be enrolled at the next higher dose level.

The MTD will be defined as the highest dose level at which no more than 1 of 6 patients experiences a DLT within the first 28-day cycle. If no more than 1 of these 6 patients experiences a DLT within the first 28-day cycle, then the last dose level enrolled to meet these criteria may be identified as the recommended dose for the Phase 2 segment of the study.

Teleconferences or email communication between the Sponsor or designee and the clinical study sites will occur weekly to monitor for DLTs and to communicate enrollment to the next dose level.

Patients who discontinue from the study for reasons other than DLT (e.g., non-compliance, patient request) before completing Cycle 1 will be replaced.

The use of hematopoietic growth factors will not be permitted during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segments of the study; however, they will be permitted in Cycle 2 and subsequent cycles.

Patients may not be enrolled in more than 1 dose cohort. Patients enrolled into the Phase 1b segment of the study cannot be enrolled into the Phase 2 segment upon discontinuation from Phase 1b.

Confirmation of the Safety of the MTD

Following the identification of the MTD or identification of the recommended Phase 2 dose, up to 6 additional patients may be enrolled at this dose. When all 6 patients have completed the 28-day cycle at the MTD, the SRC will review all Phase 1b safety data to determine the recommended dose of ACY-1215 to be used in the Phase 2 segment of the study. For all patients enrolled in the Phase 1b MTD segment, following the completion of Cycle 1, efficacy assessments will be conducted every cycle for the duration of the treatment period.

PHASE 2 SEGMENT

When the SRC has determined a recommended Phase 2 dose of ACY-1215, the Phase 2 segment will be initiated. Treatment will continue until PD or toxicity requiring removal from study.

Study Day 1 is defined as the first day the patient receives study drug.

Based on findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose and schedule to be administered in the Phase 2 segment will be 160 mg PO QD on Days 1 to 21 of a 28-day cycle. Pomalidomide will be administered based on the current approved dose and schedule: 4 mg PO QD on Days 1 to 21 of a 28-day cycle. The starting dose of dexamethasone will be 40 mg QD on Days 1, 8, 15 and 22 of each 28-day cycle for patients who are ≤ 75 years of age. For patients who are > 75 years of age, the starting dose of dexamethasone is 20 mg QD on Days 1, 8, 15, and 22 of each 28-day cycle. CBC will be conducted every 7 days for Cycle 1, every 14 days for Cycle 2, and on Day 1 of each cycle beginning with Cycle 3.

The use of bisphosphonates is permitted. The use of hematopoietic growth factors will not be permitted during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study; however, they will be permitted in Cycle 2 and subsequent cycles. Treatment with myeloid growth factors is encouraged when ANC < 1,000/μL.

Dose Interruption and Modification:

Dose interruption and reduction for ACY-1215, pomalidomide, and dexamethasone due to DLTs can be found in Section 5.2.8.

Central Response Adjudication Committee:	An Independent Central Adjudication Committee will be performing a blind review of the myeloma response data (i.e., laboratory data and radiographic data) to determine response to treatment and dates of PD for each study patient. Their assessments of response and dates of PD will be evaluated as a secondary endpoint.
Number of Patients Planned:	Up to 30 patients are planned to be enrolled in the Phase 1b segment and up to 95 patients are planned to be enrolled in the Phase 2 segment.
Diagnosis and Main Criteria for Inclusion:	Patients meeting the following criteria are to be enrolled in the study:

1. Must be able to understand and voluntarily sign an ICF.
2. Must be ≥ 18 years of age at the time of signing the ICF.
3. Must be able to adhere to the study visit schedule and other protocol requirements.
4. Must have a documented diagnosis of MM and have relapsed-and-refractory disease. Patients must have received at least 2 lines of prior therapies. Patients must have **relapsed** after having achieved at least SD for at least one cycle of treatment to at least one prior regimen and then developed PD. Patients must also have documented evidence of PD during or within 60 days (measured from the end of the last cycle) of completing treatment with the last anti-myeloma drug regimen used just prior to study entry (**refractory disease**).
5. Must have undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of a proteasome inhibitor (either in separate regimens or within the same regimen).
6. Must not be a candidate for autologous stem cell transplant (ASCT), has declined the option of ASCT, or has relapsed after prior ASCT.
7. Must have measurable levels of myeloma paraprotein in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g/24 hours). Nonsecretory myeloma and serum free light chain (SFLC)-only myeloma are excluded.
8. Must have Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
9. FCBP must have a negative serum or urine pregnancy test (must be serum for study participants in Canada), as described in Appendix 9.3 for the POMALYST REMS™ program (in the United States [US]) and Appendix 9.4 for the RevAid® program (in Canada). FCBP and males must either commit to continued abstinence from heterosexual intercourse or must abide by birth control requirements as described in Appendix 9.3 for the POMALYST REMS™ program (in US) and Appendix 9.4 for the RevAid® program (in Canada). The European Pomalidomide Pregnancy Prevention Risk Management Plans are described in Appendix 9.5.
10. Must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study.
11. Must agree not to share study medication with another person.
12. Must be able to take acetylsalicylic acid (ASA) (81 or 325 mg) daily as prophylactic anticoagulation. Patients intolerant to ASA may use low molecular weight heparin. Lovenox is recommended. Coumadin will be allowed provided the patient is fully anticoagulated, with an international normalized ratio (INR) of 2 to 3.
13. Must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program (or RevAid® for study participants in Canada).

Exclusion Criteria: Patients meeting any of the following criteria will be excluded from enrollment in the study:

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the ICF, including nonsecretory myeloma or SFLC-only myeloma.
2. Any serious concurrent medical conditions, laboratory abnormality, or psychiatric illness that might make the patient non-evaluable, put the patient's safety at risk, or prevent the patient from following the study requirements.
3. Pregnant or lactating females.
4. Prior therapy with histone deacetylase (HDAC) inhibitor or pomalidomide.
5. Any of the following laboratory abnormalities:
   - ANC < 1,000/µL (hematopoietic growth factors will not be permitted during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study) in either segment of the study.
   - Platelet count < 75,000/µL for patients in whom < 50% of bone marrow nucleated cells are plasma cells, and < 50,000/µL for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells.
   - Hemoglobin < 8g/dL (< 4.9 mmol/L; prior red blood cell [RBC] transfusion is permitted).
   - Creatinine clearance < 45 mL/min according to Cockcroft-Gault formula. If creatinine clearance calculated from the 24-hour urine sample is ≥ 45 mL/min, patient will qualify for the study.
   - Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), or serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) > 3.0 × ULN.
   - Serum total bilirubin > 2.0 mg/dL
6. Prior history of malignancies, other than MM, unless the patient has been free of the disease for ≥ 3 years. Exceptions include the following:
   - Basal or squamous cell carcinoma of the skin
   - Carcinoma *in situ* of the cervix or breast
   - Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b)
7. Corrected QT interval using Fridericia's formula (QTcF) value > 480 msec at screening; family or personal history of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy at screening; previous history of drug-induced QTc prolongation or the need for treatment with medications known or suspected of producing prolonged QTc intervals on electrocardiogram (ECG).
8. Positive human immunodeficiency virus (HIV), hepatitis B virus (HBV) and known or suspected active hepatitis C virus (HCV) infection.
9. Hypersensitivity to thalidomide, lenalidomide, or dexamethasone (such as Steven Johnson Syndrome). Hypersensitivity, such as rash, that can be medically managed is allowable.

10. Peripheral neuropathy ≥ Grade 2 despite supportive therapy.
11. Radiotherapy or systemic therapy (standard or an investigational or biologic anticancer agent) within 14 days of initiation of study drug treatment.
12. Current enrollment in another clinical study involving treatment and/or is receiving an investigational agent for any reason
13. Inability or unwillingness to comply with birth control requirements or any of the POMALYST REMS™ or RevAid® (region-specific), per Appendix 9.3 and Appendix 9.4, respectively, or to the European Pomalidomide Pregnancy Prevention Risk Management Plans, per Appendix 9.5.

Test Products, Doses, and Mode of Administration:

All patients will receive ACY-1215 in combination with pomalidomide and dexamethasone in 28-day treatment cycles.

Acetylon will supply liquid ACY-1215 in appropriately sized vials for PO administration to investigational pharmacies. Pomalidomide will be provided at 4, 3, 2, and 1 mg for PO administration. Sites in the US and Canada will utilize commercial supply of PO dexamethasone. Acetylon will supply dexamethasone to sites in the European Union (EU). All sites will utilize commercial supply of aspirin or other anti-thrombotics or anti-coagulants.

All patients will receive ACY-1215 in combination with pomalidomide and dexamethasone. On ACY-1215 administration days, pomalidomide and dexamethasone are to be taken immediately after ACY-1215. If the patient is receiving ACY-1215 twice daily (BID), pomalidomide and dexamethasone are to be taken immediately after the first (a.m.) dose of ACY-1215 only.

Phase 1b (MTD) Segment:

The starting dose of ACY-1215 (Dose Level 1) will be 160 mg QD, administered on Days 1-21 of a 28-day cycle in combination with the labeled dose of pomalidomide and dexamethasone. If that dose is tolerated per SRC safety review, 240 mg QD on the same days will be explored (Dose Level 2). If Dose level 2 is well tolerated, Dose Level 3 of 160 mg BID will be explored. If Dose Level 1 is not tolerated, the schedule will be modified (Dose Level -1) to 160 mg ACY-1215 QD on Days 1-5, 8-12, and 15-19. If Dose Level -1 is not tolerated, the schedule will be modified (Dose Level -2) to 160 mg ACY-1215 QD on Days 1-5, and 8-12.

Phase 2 Segment:

The ACY-1215 dose and schedule to be administered in the Phase 2 segment will be 160 mg PO QD on Days 1 to 21 of a 28- day cycle, as recommended by the SRC.

Phase 1b and Phase 2 Segments:

All patients will receive pomalidomide 4 mg PO QD on Days 1 to 21 of a 28 day cycle in combination with dexamethasone (40 mg PO for patients ≤ 75 years of age or 20 mg for patients > 75 years of age) on Days 1, 8, 15, and 22 of a 28-day cycle. Patients should take pomalidomide at the same time each day, immediately following ACY-1215 dosing when applicable. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal. Doses of ACY-1215 will be administered at least 1 hour after ingestion of food and followed by 4 ounces of water. Patients will be instructed not to ingest food or other oral medication, other than pomalidomide and dexamethasone, for at least 2 hours after each dose of ACY-1215.

Assessments:

Efficacy:

- Myeloma paraprotein (serum-M and urine M-protein; quantified by SPEP and UPEP, respectively)
- Serum and urine immunoglobulins (IFE)
- SFLCs
- Bone marrow aspiration/biopsy
- Skeletal survey and other imaging studies
- Extramedullary plasmacytoma assessments
- Disease response assessment (per IMWG criteria)

Safety:

- Vital signs
- Physical examinations
- ECOG performance status
- Clinical laboratory evaluations
- Pregnancy testing/counseling
- 12-Lead ECG
- VTE monitoring
- Concomitant medications and procedures
- AEs
- Secondary primary malignancies

Exploratory:

- Cytogenetic abnormalities
- Blood samples for the assessment of the PK of ACY-1215 and potential biomarkers in patients with relapsed-and-refractory MM

Statistical Methods:

Justification of Sample Size:

Phase 1b (MTD): Using a 3+3 design, the total number of patients required for the MTD phase will range from 9 to 30.

Phase 2: The reference response rate is assumed to be 0.29. For a study with a sample size of 66, a one-sided 0.05 level test with power of 80% would be adequate to detect the response rate of 0.29 against 0.44. Assuming a 10% drop out rate, a study of 75 patients would be sufficient. In order to have a robust study, a single interim analysis will be conducted when there are 30 evaluable patients. The SRC will use the totality of information from the interim analysis to recommend whether the study should proceed as planned, be terminated for superiority or futility, or extended to allow for 86 evaluable patients. Assuming a 10% dropout rate, a study with n=95 would be sufficient.

Statistical analysis:

Interim analysis:

The interim analysis with the first 30 evaluable patients will be conducted using a one-sided 95% CI estimate for the response rate. If the lower bound of the 95% CI estimate with the 30 patients is ≥ 29%, the SRC may recommend either terminating the study at the interim based on treatment superiority, or continuing the study as planned. If the lower bound is < 29%, various predicted lower bounds of one-sided 95% CIs for the response rate will be constructed to further guide the SRC's recommendation. For example, assuming a true response rate of 44% for the remaining 36 patients, the expected lower bound of one-sided 95% CI with 66 evaluable patients will be calculated. If the expected lower bound is ≥ 29%, the SRC may recommend continuing the study as planned. If the expected lower bound with 66 evaluable patients is < 29%, another simulation will be run with 86 evaluable patients. If the resulting lower bound is acceptable (e.g., close to or ≥ 29%), the SRC may recommend expanding the sample size by 20 patients. If the resulting lower bound is not acceptable (e.g., < 29%), the SRC may recommend terminating the study for futility. In addition, the expected lower bound of the one-sided 95% CI when the true response rate is equal to the observed value at the interim analysis will be calculated. The resulting scenario will be similar to the previous one: if the expected lower bound is ≥ 29%, the SRC may recommend continuing the study as planned, if the lower bound is < 29%, the SRC may recommend expanding the sample size by 20 patients. Additional simulations with other possible response rates (for example, assuming a 40% response rate), with or without adaptation, will also be conducted; the SRC will review all simulation results to make a recommendation at the interim. Furthermore, with the potential adaptations at the interim, we find via an extensive simulation study the final CI estimate would have the accurate coverage level. Therefore, no statistical penalty or adjustment will be needed for the final inferential statistical procedure for the response rate.

Demographic, Disposition, Study Medication:

The baseline (C1D1) characteristics of patients enrolled in each dose cohort, the Phase 1b MTD segment and the Phase 2 segment, will be summarized.

An accounting will be made of the study course for all patients who received study drug for each dose cohort and, in particular, the number of patients who died or withdrew during treatment will be specified and reasons for withdrawal categorized. Study drug administration will be summarized for each dose cohort. Information on dose reductions will be summarized.

Safety Analysis:

Safety data for the Phase 1b MTD segment will be summarized when all patients have completed the first 28-day cycle (Cycle 1).

Safety data for the Phase 2 segment, as well as for patients from the Phase 1b segment who continued treatment following the completion of the first cycle, will be analyzed when all patients have completed 48 weeks of the study or have discontinued the study.

All patients who received at least one dose of study medication will be included in the safety analyses. SAEs, treatment-emergent AEs, frequency of DLTs, vital sign measurements, clinical laboratory information, and concomitant medications will be tabulated and summarized for each dose cohort when appropriate. Patient incidence rates of all AEs (including serious, Grade 3/4, treatment-related, and events requiring the discontinuation of investigational product), will be tabulated by system organ class (SOC), preferred term, and severity using Medical Dictionary for Regulatory Activities (MedDRA) terms and NCI CTCAE Version 4.0 severity grades.

Death, SAEs, and AEs resulting in study discontinuation will also be summarized. AEs leading to dose reduction or interruption will also be tabulated.

All other measurements will be summarized using means, standard deviations, medians, minimum, and maximum. Graphical displays will be provided where useful in the interpretation of results.

Efficacy Analysis:

Efficacy analysis will be performed on both the Intent-to-Treat (ITT) Population and Efficacy Evaluable (EE) Population. The ITT Population will include all treated patients, and the EE Population will include all patients who meet eligibility criteria, receive at least 14 doses of study drug (i.e., ACY-1215, pomalidomide and low-dose dexamethasone), and have at least 1 post-baseline efficacy assessment. The primary analysis will be based on the EE population, and will use the Investigator-assessed response data evaluated according to consensus recommendations based on the IMWG criteria. Response rate will be percent of patients who achieve at least partial response (PR) at the recommended Phase 2 dose. Percent of patients achieving MR or better will also be collected as clinical benefit response. PFS will be defined as the time from first dose of study treatment to the first documentation of PD or death from any cause during study. OS will be defined as the time from first dose of study treatment to death from any cause. For responders, TTR and response duration will be analyzed. TTR will be defined as the time from first dose of study treatment to the first documentation of response (either PR or complete response [CR]). DOR

will be defined as the time from the first PR or CR to the first documentation of PD or death, whichever occurs earlier.

For data obtained from patients treated at doses of ACY-1215 not selected as the MTD, a case-by-case description of myeloma response (per IMWG criteria) will be provided. For the 12 patients who initiate ACY-1215 at the recommended Phase 2 dose level, response rates together with CIs will be provided. Kaplan-Meier curves will be used to characterize the time-to-event curves (PFS, OS, response duration) when there is censoring; univariate summary statistics will be provided for TTR.

For the Phase 2 segment, a 0.95 CI for the response rate will be constructed for evaluating the efficacy of ACY-1215. Kaplan-Meier curves will be constructed to characterize PFS, OS, and DOR. One sample standard inferences for PFS, OS, and DOR will be made accordingly.

Pharmacokinetic Analysis

Study drug serum concentrations of ACY-1215 and pomalidomide will be determined at all pre- and post-dose time points specified in the Schedule of Assessments. Parameters to be calculated based on a non-compartmental model approach will include maximum serum concentration (C_{max}), time to C_{max} (T_{max}), area under the concentration-time curve from time zero to the last quantifiable value ($AUC_{0\text{-}last}$), AUC from time zero to infinity ($AUC_{0\text{-}\infty}$), and serum half-life ($t_{1/2}$). ACY-1215 and pomalidomide serum levels and non-compartmental PK parameters will be tabulated by dose cohort using descriptive statistics. Tabulated single- and multiple-PK dose results will be presented.

Pharmacodynamic Analysis

The fold change between pre- and post-dose time points in the levels of acetylated histones and acetylated tubulin will be determined in peripheral blood mononuclear cells (PBMCs). The resulting data may be used to generate a PK/pharmacodynamic model(s) of the relationship of changes in acetylated histones and/or tubulin with the plasma levels of ACY-1215 over time. A summary report will be generated of the pharmacodynamic analysis and results from PK/pharmacodynamic modeling.

Schedule of Assessments

The Schedule of Assessments is presented in Table 1.

Table 1: Schedule of Assessments

Procedure	**Screening**		**Treatment/Follow Up**					
	Screening (Within 28 Days of Cycle 1, Day 1)	**Cycle 1 Day 1/ Baseline**	**Cycle 1 Day 2/**	**Cycle 1 Days 8, 15, 22**	**Cycles 2 and on, Day 1**	**Disease Progression/ Treatment Discontinuation[1]**	**30 Days After Study Treatment Discontinuation[2]**	**3 Times per Year[3]**
Visit Window				**± 2 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 7 Days**
Informed Consent	X	--	--	--	--	--	--	--
Inclusion/Exclusion Criteria	X	--	--	--	--	--	--	--
Confirmation of Diagnosis	X	--	--	--	--	--	--	--
Prior Anti-myeloma Therapies	X	--	--	--	--	--	--	--
Demographics	X	--	--	--	--	--	--	--
Medical and Surgical History (including MM history)	X	--	--	--	--	--	--	--
Review Concomitant Medications	X	X	X	X	X	X	--	--
Measurement of Vital Signs[4]	X	X	--	--	X	X	--	--
Physical Examination	X	--	--	--	--	X	--	--
ECOG Performance Score	X	X		--	X	X	--	--
Bone Marrow Aspiration and/Biopsy[5] (diagnosis and cytogenetics)	X	--	--	--	--	--	--	--
Serum Chemistry[6]	X	X	--	--	X	X	--	--
Haematology[7]	X	X	X	X	X Cycle 2 Day 15	X	--	--
Quantitative Serum Immunoglobulin Levels[8]	X	X	--	--	X	X	--	--

Procedure	**Screening**		**Treatment/Follow Up**					
	Screening (Within 28 Days of Cycle 1, Day 1)	**Cycle 1 Day 1/ Baseline**	**Cycle 1 Day 2/**	**Cycle 1 Days 8, 15, 22**	**Cycles 2 and on, Day 1**	**Disease Progression/ Treatment Discontinuation[1]**	**30 Days After Study Treatment Discontinuation[2]**	**3 Times per Year[3]**
Visit Window				**± 2 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 7 Days**
Protein Electrophoresis (serum and 24-hour urine)[9]	X	X	--	--	X	X	--	--
SFLC Analysis (serum)[10]	X	X	--	--	X	X	--	--
Immunofixation Studies (serum and 24-hour urine)[11]	X	X	--	--	X	--	--	--
Urinalysis[12]	X	X	--	--	X	X	--	--
Pregnancy Test for FCBP[13]	X	X	--	X	X	X	X	--
Pregnancy Counseling[14]	X	X	--	--	X	X	X	--
Skeletal Survey[15]	X	--	--	--	--	X	--	--
Extramedullary Plasmacytoma Assessment[16]	X	X	--	--	X	X	--	--
12-Lead Electrocardiogram[17]	X	X	--	Day 8	X	X	--	--
Serology (HIV, HBsAg, HCV)	X	--	--	--	--	--	--	--
Assessment of Response[18]	--	--	--	--	X	X	--	--
VTE Monitoring[19]	--	X	X	X	X	X	--	--
Adverse Events[20]	--	X	X	X	X	X	X	--
Assessment of Second Primary Malignancy[21]	--	X	--	--	X	X	X	X
Study Drug (ACY-1215) Administration[22]	--	X	--	--	X	--	--	--

Procedure	**Screening**		**Treatment/Follow Up**					
	Screening (Within 28 Days of Cycle 1, Day 1)	**Cycle 1 Day 1/ Baseline**	**Cycle 1 Day 2/**	**Cycle 1 Days 8, 15, 22**	**Cycles 2 and on, Day 1**	**Disease Progression/ Treatment Discontinuation[1]**	**30 Days After Study Treatment Discontinuation[2]**	**3 Times per Year[3]**
Visit Window				**± 2 Days**	**± 3 Days**	**± 3 Days**	**± 3 Days**	**± 7 Days**
Pomalidomide[23]	--	X	--	--	X	--	--	--
Dexamethasone[24]	--	X	--	X	X	--	--	--
Survival	--	--	--	--	--	--	--	X
Subsequent Anti-myeloma Therapies	--	--	--	--	--	--	X	X
PK/Pharmacodynamic Blood Sampling[25, 26]	--	X	X	Day 8	--	--	--	--

1 Patients who discontinue from study treatment for reasons other than PD will continue to be followed for efficacy measurements (assessment of response, extramedullary plasmacytoma assessment, quantitative serum immunoglobulin levels, serum and urine protein electrophoresis of M-protein component, and serum free light chain [SFLC] analysis) until PD, death, or initiation of an alternate MM therapy, whichever occurs first.

2 Pregnancy tests may be conducted locally for patients who are unable to attend the 30 day follow-up visit at the study center; all other assessments may be conducted via phone.

3 Patients will be followed 3 times per year, for up to 1 year, for survival, subsequent anti-myeloma therapies, and monitoring of second primary malignancy. Subsequent therapies should be collected until death or the end of the 1year follow-up period. Survival follow-up may be done via phone.

4 Vital signs will include weight, height (screening only), blood pressure (BP), temperature, and heart rate.

5 A bone marrow aspirate is to be performed at screening and a sample sent for central cytogenetic and fluorescence *in situ* hybridization (FISH) analysis (a bone marrow biopsy is needed only if the marrow is unable to be aspirated). A bone marrow biopsy/aspirate may be done as clinically indicated, at the discretion of the treating physician for assessment of disease.

6 Serum chemistry (glucose, calcium, albumin, total protein, sodium, potassium, magnesium, phosphorus, chloride, blood urea nitrogen, uric acid, alkaline phosphatase [ALP], creatinine, carbon dioxide, total bilirubin, lactate dehydrogenase [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and gamma-glutamyl transpeptidase [GGT]) will be performed at screening, on Day 1 of every cycle beginning with Cycle 1 Day1, PD, and at study treatment discontinuation.

7 Hematology will include hematocrit, hemoglobin, red blood cell (RBC) count, international normalized ratio (INR), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), white blood cell (WBC) count with differential, platelet count, reticulocyte count, and mean corpuscular volume. Complete blood count (CBC) will be conducted every 7 days for Cycle 1, every 14 days for Cycle 2 (Cycle 2, Day 15), and on Cycle Day 1 of every cycle beginning with Cycle 3. INR will be measured at screening and on Day 1 of every cycle for patients on coumadin.

8 Quantitative serum immunoglobulin levels will be obtained at screening, at Day 1 of each treatment cycle, PD, and at study treatment discontinuation.

9 Serum and 24-hour urine samples for M-protein analysis (see Section 6.2.1) will be collected from all patients at screening, on Day 1 of every cycle, at PD, and at study treatment discontinuation.

10 Serum samples for SFLC analysis (see Section 6.2.2) will be collected from all patients at screening, on Day 1 of every cycle, PD, and at study treatment discontinuation.

11 IFE studies will be performed at screening, Day 1 of each treatment cycle, and to confirm CR (undetectable M-protein by protein electrophoresis in urine and serum will trigger the central laboratory to perform IFE studies in urine and serum).

12 Urinalysis will include specific gravity, pH, glucose, bilirubin, protein, ketones, and microscopic analysis (casts, RBCs, and WBCs).

13 Pregnancy tests (serum or urine test with a sensitivity of at least 25 mIU/mL) must occur 10 - 14 days and again within 24 hours prior to initiation of study drug for study participants in the US (see Appendix 9.3 for the POMALYST REMS™ program, or 7 – 14 days and again within 24 hours prior to initiation of study drug for study participants in Canada (see Appendix 9.4 for the RevAid® program). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 4 weeks while on therapy (including breaks in therapy); at study treatment discontinuation, and at Day 28 following study treatment discontinuation. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14 days while on therapy (including breaks in therapy), at study treatment discontinuation, and at Day 14 and Day 28 following study treatment discontinuation. For additional information, including acceptable forms of

birth control, see Appendix 9.3 for the POMALYST REMS™ program, Appendix 9.4 for the RevAid® program, and Appendix 9.5 for the European Pomalidomide Pregnancy Prevention Risk Management Plans.

14 Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted on Day 1 of every cycle (or at a minimum of every 28 days), and at study treatment discontinuation. Additional pregnancy counseling may be performed; see Appendix 9.3 and Appendix 9.4 for requirements of the POMALYST REMS™ and RevAid® programs, respectively. See Appendix 9.5for the European Pomalidomide Pregnancy Prevention Risk Management Plans.

15 Skeletal survey to be performed at screening (or within 60 days of Study Day 1), and later, when clinically indicated.

16 Assessment/measurement required only if present or if clinically indicated. Plasmacytomas that can be assessed clinically are to be assessed everycycle. Plasmacytomas that are assessed by radiography will be assessed at screening, Day 1 of every treatment cycle, at study treatment discontinuation, and to assess best response.

17 Single 12-lead ECGs will be performed at screening, pre-dose on Day 1 of every treatment cycle, pre-dose Day 8 (Cycle 1, only for Phase 1b), at the Investigator's discretion, and at study treatment discontinuation. Corrected QT interval at screening (QTcF) must be < 480 msec at screening. Additional ECGs may be taken at any time point at the Investigator's discretion.

18 Response will be assessed every cycle while on study drug treatment, and at study treatment discontinuation. Screening labs do not need to be repeated at C1D1 if they have been completed within 14 days. Assessment of response will include measurement of serum M-protein by electrophoresis, SFLC analysis, and IFE studies (see footnotes 10-12).

19 VTE assessment will be performed at each visit during study treatment and at study treatment discontinuation.

20 AEs will be assessed starting at baseline (C1D1). AEs that lead to study treatment discontinuation should be followed until resolution or stabilization. Serious adverse events (SAEs) will be assessed until 30 days after study treatment discontinuation.

21 Second primary malignancies will be monitored as events of interest and must be reported as SAEs regardless of the dose cohort the patient is in. This includes any second primary malignancy, regardless of causal relationship to study drug (ACY-1215, pomalidomide, dexamethasone), occurring at any time for the duration of the study, from the time of signing the informed consent up to the time all patients have been followed for at least 1 year post the 30 day discontinuation visit or have died. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the case report form (CRF) and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans, etc.).

22 ACY-1215 will be administered on Day 1 of each 28-day cycle. For patients enrolled in Dose Level 1, the starting dose of ACY-1215 will be 160 mg QD on Days 1-21 of a 28-day cycle. Patients enrolled in Dose Level 2 will receive 240 mg QD on Days 1-21 of each 28-day cycle. Patients enrolled in Dose Level 3 will receive 160 mg BID on Days 1-21 of each 28-day cycle. In the Phase 2 segment, the ACY-1215 dose and schedule is 160 mg PO QD on Days 1 to 21 of a 28-day cycle.

23 Pomalidomide will be administered 4 mg PO on Days 1-21 of each 28-day cycle.

24 Dexamethasone will be administered once weekly on Days 1, 8, 15, and 22 of each 28-day cycle. Patients who are ≤ 75 years of age will receive 40 mg QD, and patients who are > 75 years, will receive 20 mg QD.

25 Serial blood samples for PK assessments are to be collected from all US and Canada patients during Cycle 1 of the Phase 1b segment and at participating sites in the Phase 2 segment at the following time points:

- Phase 1b, C1D1: pre-dose, 0.5, 1, 2, 4, and 6 hours post dose
- Phase 1b, C1D2: 24 hours post dose
- Phase 1b, C1D8: pre-dose, 0.5, 1, 2, 4, and 6 hours post dose
- Phase 2, C1D1: pre-dose, 0.5 and 1hour post dose
- Phase 2, C1D22: 24 hours post morning dose of Day 21
- Phase 2, Day 1 of C2-6: at least 1 hour post dose

26 Pharmacodynamic blood samples from all patients during Cycle 1 of the Phase 1b segment will be collected on Day 1 at the following time points:

- Phase 1b, C1D1: pre-dose, 0.5, 1, 2, 4, and 6 hours post dose
- Phase 1b, C1D2: 24 hours post dose.

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADLs	Activities of daily living
AE	Adverse event
ALC	Absolute lymphocyte count
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASA	Acetylsalicylic acid
ASCO	American Society of Clinical Oncology
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration time curve
$AUC_{0\text{-last}}$	AUC from time zero to the last quantifiable value
$AUC_{0\text{-}\infty}$	AUC from time zero to infinity
β2M	Serum beta-2 microglobulin
BID	Twice daily
BP	Blood pressure
BUN	Blood urea nitrogen
C	Cycle
C1D1	Baseline (Cycle 1 Day 1)
CBC	Complete blood count
CHO	Chinese hamster ovary
C_{max}	Maximum serum concentration
CR	Complete response
CRF	Case report form
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
DLT	Dose-limiting toxicity
DOR	Duration of response
DST	Dexamethasone suppression test
DVT	Deep venous thrombosis
EBMT	European Group for Bone and Marrow Transplant
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EE	Efficacy Evaluable
EU	European Union
FCBP	Female of childbearing potential
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* hybridization
GCP	Good Clinical Practice
GCSF	Granulocyte colony-stimulating factor
GGT	Gamma-glutamyl transpeptidase
HBsAg	Hepatitis B surface antigen

Abbreviation	Definition
HCV	Hepatitis C virus
HDAC	Histone deacetylase
hERG	human Ether-à-go-go Related Gene
HIV	Human immunodeficiency virus
HR	Hazard ratio
IC_{50}	50% Inhibitory Concentration
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFE	Immunofixation
IgA	Immunoglobulin A
IgD	Immunoglobulin D
IgE	Immunoglobulin E
IGF-1	Insulin-like growth factor 1
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL-6	Interleukin-6
IMiD	Immunomodulatory inhibitors
IMWG	International Myeloma Working Group
INR	International normalized ratio
IRAC	Independent Response Assessment Committee
IRB	Institutional Review Board
ISS	International Staging System
ITT	Intent-to-Treat
IUD	Intrauterine device
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minimal response
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NK	Natural killer
NOAEL	No observed adverse effect level
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PFS	Progression-free survival
P-gp	P-glycoprotein
PK	Pharmacokinetic
PO	Orally/Oral administration
PR	Partial response
QD	Once daily
RBC	Red blood cell
RSS	Radiographic skeletal survey
SAE	Serious adverse event
SD	Stable disease
SFLC	Serum free light chain
SGOT	Serum glutamic oxaloacetic transaminase

Abbreviation	Definition
SGPT	Serum glutamic pyruvic transaminase
SOC	System organ class
SPEP	Serum protein electrophoresis
SRC	Safety Review Committee
$t_{1/2}$	Serum half-life
T_{max}	Time to maximum serum concentration
TNF-α	Tumor necrosis factor alpha
TTP	Time to progression
TTR	Time to response
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
US	United States
VGPR	Very good partial response
VTE	Venous thromboembolism
WBC	White blood cell
WHO	World Health Organization

TABLE OF CONTENTS

LIST OF TABLES IN THE TEXT

LIST OF FIGURES IN THE TEXT

1. INTRODUCTION

Multiple myeloma (MM), a plasma cell dyscrasia, is the most common primary malignancy of the bone marrow.[1,2] The etiology of myeloma is largely unknown, although genetic predisposition and environmental factors have been speculated. MM arises from malignant plasma cells that clonally expand and accumulate in the bone marrow.[3] These clonal antibody-producing plasma cells produce high levels of monoclonal immunoglobulins, most commonly immunoglobulin G (IgG) (50-60%) and immunoglobulin A (IgA) (20-25%), and less frequently immunoglobulin M (IgM), immunoglobulin D (IgD), and immunoglobulin E (IgE).[4]

MM accounted for an estimated 20,180 (1.3%) new cancer cases in the United States (US) in the year 2010, including 11,170 cases in men (1.4%) and 9,010 (1.2%) cases in women.[5] Patients afflicted with MM are likely to suffer from bone pain and skeletal fragility.[6] Plasmacytomas are osteolytic in nature and are most often confined to the central skeleton, skull, and femur, and rarely involve distal bones and soft-tissues.[7] Production and secretion of cytokines such as interleukin-6 (IL-6) are thought to play a role in the stimulation of the plasma cells, increase in osteoclast activity, and possibly suppression of osteoblast activity resulting in retarded bone regeneration.[3,6] Lesions caused by osteoclastic bone destruction are replaced by the expanding malignant cell mass. The pattern of bone destruction is most often focal but may also be generalized in approximately 15% of patients.[7] Common methods of imaging include radiographic skeletal survey (RSS) for skull, rib, femur, and humerus, and magnetic resonance imaging (MRI) for spinal and pelvic bone lesions.[8,9] To protect patients from developing skeletal-related problems, most myeloma patients receive intravenous bisphosphonates either alone or with their other anti-myeloma therapies.[6,10,11]

Since 1975, the Durie-Salmon classification system has been widely used for disease diagnosis and staging. Stages I, II, and III are defined by criteria for bone lesion status, hemoglobin, serum calcium, and monoclonal protein (M-protein) levels and subcategorized as A or B depending on renal function. A clear correlation between disease stage and survival duration has been demonstrated.[12] The criteria for diagnosis, staging, risk stratification, and response assessment of MM, as described by Kyle and Rajkumar, has been widely used as well.[13] A variety of other prognostic markers and indicators have been studied, including plasma cell labeling index, serum beta-2 microglobulin (β2M), C-reactive protein (CRP), plasmablast morphology, cytogenetics, and bone marrow angiogenesis.[14,15] More recently, an International Staging System (ISS) was established based on the combination of levels of serum β2M and albumin among MM patients at diagnosis [16], which has been validated as an effective predictor of overall survival (OS) for MM patients.

Although MM is currently not curable, it is considered treatable.[17] The death rate due to the disease has declined by ~10% from 1990 to 2006, with an improvement in the 5-year survival rate from 29% in 1984 to 1986 to 37% in 1999 to 2005.[5] These improvements in survival have resulted in large part from major increases over the past several years in response rates to treatment with lenalidomide, a thalidomide analogue, and bortezomib, a reversible proteasome inhibitor, each of which are also often used in combination with the generic drug dexamethasone.[18] However, the rate of complete responses (CR) in relapsed disease, and particularly in refractory relapsed disease, remains relatively low, with substantial room for improvement.

1.1. ACY-1215

Histone deacetylases (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), 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 also dependent on the cofactor nicotinamide adenine dinucleotide.[19] The function of HDACs has until recently been associated with gene transcription through modification of histone tail acetylation and regulation of chromatin dynamics. However it has become apparent that HDACs play a critical role in the regulation and function of lysine acetylation of nonhistone proteins in most, if not all, major cellular functions.[20] The breadth of posttranslational regulation in many proteins of diverse functional roles is on par with that achieved through phosphorylation/dephosphorylation of hydroxyl groups by kinases/phosphatases.[21,22] Additionally, several HDACs, including HDAC6, are localized to the cytoplasm of cells while others can "shuttle" between the nucleus and cytoplasm. HDACs are thus substantially more diverse in their intracellular mechanisms of action than is implied by the "histone" in their name.[19]

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, vorinostat and romidepsin, with several other drug candidates also in clinical studies because of their potential for the treatment of various cancers.[23] The approved agents and development candidates that are structurally categorized as hydroxamates were previously considered to be nonselective across Class I and Class II, while the ortho aminoanilide inhibitors (e.g., entinostat [SNDX-275], Syndax Pharmaceuticals) are semi-selective for Class I. Recently it has been demonstrated that the hydroxamate-based inhibitors are selective for Class I and the Class IIb enzyme HDAC6, but they do not significantly inhibit Class IIa HDAC enzymes.[24]

HDAC6 has been shown to be crucial in the autophagic degradation of poly-ubiquitinated protein aggregates and misfolded proteins which is an alternative to the proteasome degradation pathway.[25,26,27] Autophagy requires the formation of autophagasomes containing aggregated protein that fuse with lysosomes to digest the protein. Failure by a cell to remove accumulated misfolded protein aggregates leads to apoptosis. HDAC6 mechanistically has two direct roles in aggresome formation. First, the deacetylase activity of HDAC6 is required, and the likely substrate is α-tubulin. Tubulin is a key component of microtubules, along which protein complexes are transported to the microtubule organizing center where aggresomes form. Second, HDAC6 acts as an adaptor protein binding poly-ubiquitinated proteins and dynein, a component of the motor complex that transports protein along the microtubules.

Additionally, HDAC6 regulates function through modulating the acetylation state of a number of other important proteins, one of which is Hsp90, a molecular chaperone required for stability and function of numerous proteins.[28] Increased acetylation of Hsp90 decreases the functional activity of the chaperone and results in increased levels of poly-ubiquitinated protein complexes. Development of Hsp90 inhibitors has been an active area to discover new antitumor agents (e.g., geldanamycin) and analogs thereof.[29] HDAC6 appears to have a similar role in modulating the acetylation state of Hsp70 and other members of the heat shock protein family.

MM, a blood plasma cell malignancy is characterized by excessive production of immunoglobulins. The proteasome inhibitor bortezomib has been shown *in vitro* to trigger apoptosis in MM cells through protein accumulation.[30,31] Patients with MM relapse or become refractory to bortezomib treatment potentially due in part to the alternative aggresome

pathway being utilized for protein degradation.[32] Immunomodulatory inhibitors (IMiD) have well established clinical activity in myeloma and are considered standard therapy for patients with relapsed disease. One such agent is pomalidomide, a derivative of thalidomide, with higher potency and reduced toxicity. Pomalidomide is generated through modification of the thalidomide structure consisting of an amino group addition at the 4 position of the phthaloyl ring. The result is the generation of a thalidomide analog that is up to 50,000 times more potent at inhibiting tumor necrosis factor alpha (TNF-α) *in vitro* than its predecessor.

Clinical experience with pomalidomide includes Study CC-4047-MM-003, a Phase 3, randomized, multicenter, open-label study of pomalidomide plus low-dose dexamethasone therapy versus high-dose dexamethasone alone in previously treated adult patients with relapsed and refractory multiple myeloma.[33] Enrolled patients had received at least 2 prior treatment regimens, including both lenalidomide and bortezomib, and demonstrated disease progression on the last therapy. A total of 455 patients were randomized to treatment in a 2:1 ratio. The primary endpoint of the study, progression-free survival (PFS), was met as PFS was significantly longer with the pomalidomide plus low-dose dexamethasone arm compared with the high-dose dexamethasone alone, exceeding the pre-specified difference (observed hazard ratio [HR] 0.45 versus planned 0.67). The difference in overall survival (OS) between the 2 treatment arms was also statistically significant (HR 0.53 [95% CI: 0.37, 0.74], $p < 0.001$) exceeding the pre-specified OS difference (observed HR 0.53 versus planned 0.67).

Study CC-4047-MM-002 was a Phase 1b/2, multicenter, randomized, open-label, dose-escalation study to determine the maximum tolerated dose (MTD) and evaluate safety and efficacy of pomalidomide alone and in combination with low-dose dexamethasone.[34] Enrolled patients included those with relapsed/refractory MM who had received prior treatment that included lenalidomide and bortezomib and were refractory to their last treatment. A total of 221 patients were randomized in a 1:1 ratio. Median PFS was 10.7 weeks (95% CI: 8.3, 16.1) for patients in the pomalidomide group and 16.6 weeks (95% CI: 14.1, 21.1) for patients in the pomalidomide plus dexamethasone group. Median OS was 59.3 weeks (95% CI: 41.6, NE) for patients in the pomalidomide group and 62.6 weeks (95% CI: 53.6, NE) for patients in the pomalidomide plus dexamethasone group.

Study IFM 2009-02 was a Phase 2, multicenter, randomized, open-label study to evaluate the safety and efficacy of 2 regimens of oral pomalidomide in combination with low-dose dexamethasone.[35] Patients with relapsed/refractory MM who had received prior treatment with lenalidomide and bortezomib and had been non-responsive or refractory to the last course of treatment with both drugs were enrolled. Patients were randomized to treatment in a 1:1 ratio to Arm A or Arm B. Median PFS was 25.1 weeks (95% CI: 16.3, 41.7) for Arm A and 25.1 weeks (95% CI: 13.3, 36.0) for Arm B. Median OS was 58.4 weeks (95% CI: 38.7, 60.6) for Arm A and 66.4 weeks (95% CI: 39.9, NE) for Arm B.

Preclinical studies and clinical studies in patients with refractory/relapsed MM, have been conducted to evaluate the potential synergistic effect of Class I HDAC + HDAC6 inhibitors, vorinostat and panobinostat, in combination with bortezomib and/or with lenalidomide and dexamethasone.[36,37,38,39,40] However, nonselective Class I HDAC inhibitors as well as the ortho amino anilide inhibitors, such as entinostat (Syndax Pharmaceuticals), that are semi-selective for Class I HDACs (i.e., excluding HDAC6) exhibit similar side-effect profiles regardless of their ability to inhibit HDAC6.[41,42,43,44,45] Taken together, 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 [46] whereas Class I -/- animals are nonviable [19], 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 Hsp90 and thus potential anticancer effectiveness.

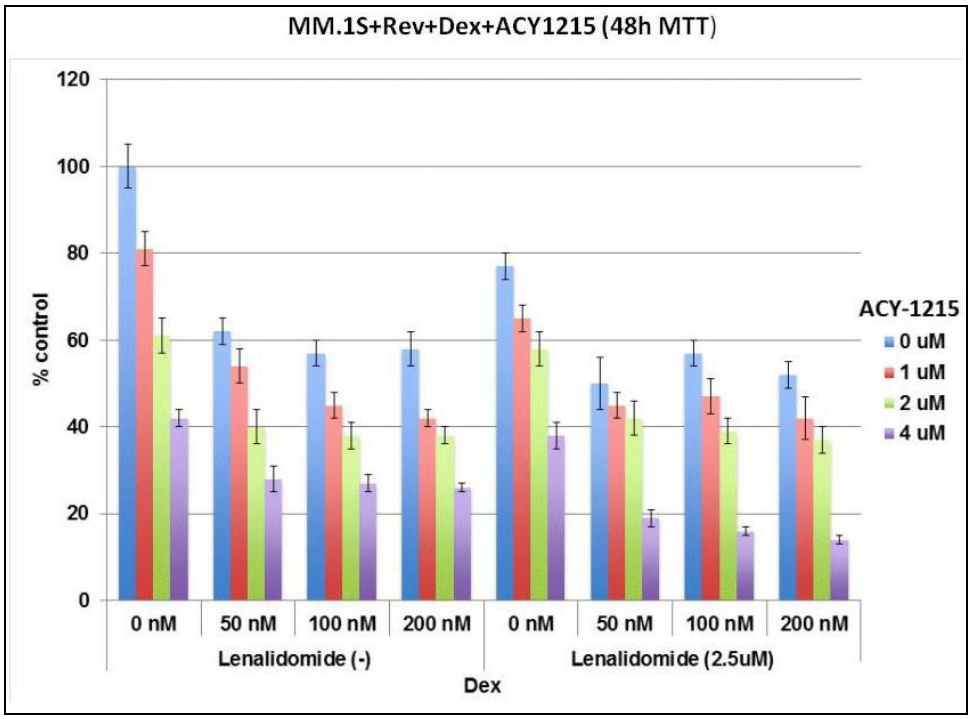
Based on this work, ACY-1215 (Ricolinostat), an HDAC6-selective, orally active small-molecule enzyme inhibitor, will be investigated for treatment of MM. In the current study, ACY-1215 will be evaluated in combination with the commercially-available thalidomide analog pomalidomide plus dexamethasone.

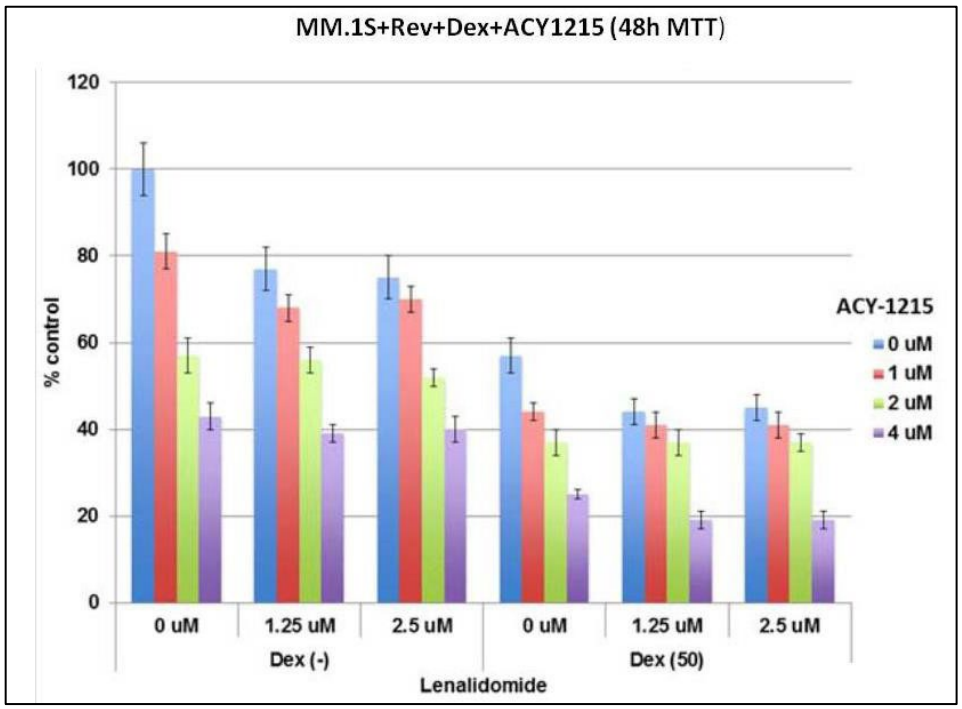
1.1.1. Pharmacology

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 2 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 MM cells. ACY-1215 can also increase the level of acetylated α-tubulin in human peripheral mononuclear cells (PBMCs) in a dose-dependent and time-dependent manner.

ACY-1215 can inhibit the growth of MM cell lines (MM.1S, OPM1, RPMI 8226, MM.1R, LR5, OPM2, INA6 and U266), including drug resistant cell lines and primary cells from MM patients in the 1-6 μM concentration range. The antiproliferative activity of ACY-1215 can overcome the growth supportive activity of growth factors such as IL-6 and insulin-like growth factor 1 (IGF-1) and bone marrow stroma from MM patients, while having minimal impact on normal cells such activated PBMCs. *In vitro* data with cultured MM1.S cells demonstrated that the presence of ACY-1215 enhances the activity of lenalidomide in a dose-dependent manner both with and without dexamethasone (50 nM) (see Figure 1).

Figure 1 ***In Vitro*** **Activity of ACY-1215 in Combination with Lenalidomide ±Dexamethasone in MM1.S Cells**





1.1.1.1. Safety Pharmacology

There were no significant interactions (inhibition > 50% at 10 µM) against an extensive panel of enzymes, including kinases, receptors and ion channels 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 the dog at ACY-1215 dose levels of 10, 30, and 60 mg/kg, a moderate and transient rise in heart rate (19 – 24 bpm) and decrease in systolic pressure (5 - 15 mmHg) was observed at 0.5 - 11 hours post-dose for all 3 dose levels. One dog in the high dose group (60 mg/kg) with the highest exposure and maximum serum 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 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.

1.1.2. Nonclinical Pharmacokinetics

ACY-1215 is rapidly absorbed (time to maximum serum concentration [T_{max}] ≤1 hour) following oral administration (PO) to 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 pharmacokinetics (PKs) of ACY-1215 in humans will be similar to that 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 PBMCs. ACY-1215 is classified as moderately permeable and is stable in human liver microsomes (serum half-life [$t_{1/2}$] > 45 minutes).

Two major inactive 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.

ACY-1215 was detected in feces and urine mainly in the 0-8 hour period following oral administration of a single dose (30 mg/kg) in rat. The 2 major metabolites (ACY-161-344 and ACY-161-349) were found predominately in feces at 4-24 hour post-dose of ACY-1215. Preliminary results following a single dose of radiolabeled (^{14}C) ACY-1215 in rat confirmed the observation that ACY-1215 and metabolites were predominately excreted in the feces (87%) compared to urine (9.1%) by 72 hours post-dose. In addition, 85% and 98% of radiolabeled material (feces, urine and cage wash) was excreted by 24 hours post-dose versus 98% by 72 hours post-dose, respectively.

1.1.3. 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 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 decrease in body weight and minimal to mild decrease in red blood cell (RBC) mass was observed at all 3 dose levels of 30, 60, and 120 mg/kg, and decreases in white blood cells (WBCs), lymphocytes, and monocytes were observed in males. The decreased RBC mass may reflect decreased hematopoiesis and/or increased turnover of RBCs suggested by minimal to slight pigment deposition in the liver of some dogs. Marginal, non-adverse, yet statistically significant from the control group, serum chemistry changes were noted in both sexes in all dose groups, including a decrease in hepatic enzyme activities (alanine aminotransferase [ALT], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]) and increases in triglyceride (males), total bilirubin (high dose male), albumin and total protein. Administration of 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 mutagenic ability in *in vitro* assays including the Ames test and the 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. In addition, ACY-1215 did not exhibit mutagenic potential in the GLP *in vivo* micronucleus and comet assay in rats.

Detailed descriptions of findings from nonclinical studies of ACY-1215 are summarized in the Investigator's Brochure.[47]

1.1.4. Clinical Data

To date, clinical data are available from 61 patients with MM, of whom 15 were treated with ACY-1215 monotherapy at doses up to 360 mg and 46 were treated with ACY-1215 in combination with other anti-neoplastic agents in 2 ongoing clinical studies. Of the 46 patients receiving combination therapy, 25 received ACY-1215 in combination with bortezomib and dexamethasone and 21 received ACY-1215 in combination with lenalidomide and dexamethasone.

1.1.4.1. Safety

Review of safety data from patients treated with ACY-1215 monotherapy or in combination with bortezomib/dexamethasone or lenalidomide/dexamethasone has shown ACY-1215 to be generally well tolerated and to have a manageable safety profile.

ACY-1215 monotherapy at doses up to 360 mg was well tolerated, no deaths or other serious adverse events (SAEs) were considered by the Investigator to be related to ACY-1215, and no adverse events (AEs) reported were considered to represent dose-limiting toxicities (DLTs). Across all dose levels, common treatment-emergent adverse events reported among 46 patients

treated with ACY-1215 monotherapy included elevated blood creatinine (33%), fatigue, hypercalcemia, and upper respiratory infection (27% each); and anemia, cough, diarrhea, and dizziness (20% each). Of these events, diarrhea occurred at doses ≥ 160 mg, and no dose relationship was apparent with regard to the occurrence of the other AEs. Most AEs reported were Grade 1 and 2 in intensity and unrelated to ACY-1215. Grade 3 AEs that were considered to be at least possibly related to ACY-1215 were hematologic in nature and included anemia, leukopenia, and neutropenia.

Safety data from patients treated with ACY-1215 on a Day 1-5 and Day 8-12 schedule, in combination with bortezomib, have shown ACY-1215 to be generally well tolerated.[48] The most common AEs seen to date with ACY-1215 in combination with bortezomib/dexamethasone included thrombocytopenia (40%); anemia, blood creatinine increased, diarrhea, and fatigue (36% each); hypokalemia (28%); decreased appetite (24%); ALT increased, amylase increased, cough, hypophosphatemia, and peripheral neuropathy (20% each). Most AEs were Grade 1 or 2 in intensity and unrelated to ACY-1215. Grade 3 or 4 AEs considered related to ACY-1215 among patients receiving ACY-1215 plus bortezomib/dexamethasone included elevated amylase, elevated lipase, hypophosphatemia, hyponatremia, anemia, worsening anemia, thrombocytopenia, worsening thrombocytopenia, decreased platelets, neutropenia, decreased WBC, fatigue, diarrhea and stomach pain/cramps. One DLT (amylase increased) was observed during a patient's first cycle. In this study, one death (due to pulmonary embolism) was reported, for a [redacted] patient with chronic atrial fibrillation and bilateral ankle edema who was receiving ACY-1215 160 mg in combination with bortezomib 1.3 mg/m^2/dexamethasone 20 mg; the Investigator considered the event possibly related to ACY-1215.

In a second clinical study (ACE-MM-101), 21 patients were treated with escalating doses of ACY-1215 in combination with lenalidomide/dexamethasone on two different schedules. The most common AEs reported to date include fatigue (57%); upper respiratory tract infection (38%); diarrhea, anemia, and thrombocytopenia (29% each); and neutropenia, headache, and hypophosphatemia (24% each). Most AEs were Grade 1 or 2 and assessed by the Investigator as unrelated to ACY-1215. Of all Grade 3 and 4 AEs, 2 events of neutropenia were considered by the Investigator to be possibly related to ACY-1215 and probably related to lenalidomide (1 was also deemed possibly related to dexamethasone); all other Grade 3 and 4 events were considered unrelated to ACY-1215. To date, one SAE of hypercalcemia and one event of interest, a secondary malignancy, have been reported, and both were assessed as unrelated to ACY-1215. No deaths or other SAEs have been reported among patients receiving ACY-1215 in combination with lenalidomide/dexamethasone; however, 1 DLT of syncope has been identified to date.

1.1.4.2. Efficacy

Anti-tumor activity of ACY-1215 may be preliminarily demonstrated in patients treated with ACY-1215 monotherapy at doses of 40, 160, or 240 mg in that 6 of 15 patients experienced stable disease. ACY-1215 in combination with bortezomib/dexamethasone yielded an overall response rate (i.e., ≥ PR) in 47% of 17 evaluable patients and 32% of 25 patients in the Intent-to-Treat (ITT) Population. ACY-1215 in combination with lenalidomide/dexamethasone yielded an overall response rate (≥ PR) of 65% and a clinical benefit (stable disease or better) of 100% has been seen in 20 evaluable patients. Some patients in both combination studies have had responses even if previously refractory to the combination agent.

1.1.4.3. Pharmacokinetics

Preliminary PK analysis of ACY-1215 monotherapy revealed measurable levels of ACY-1215 in all patients, with C_{max} levels ranging from 85±39 ng/mL to 503±195 ng/mL (0.2 to 1.2 μM) and area under the plasma concentration curve from time 0 to the last time point of quantifiable drug concentration (4 hours post-dose) (AUC_{0-4}) values ranged from 170±61 ng•h/mL to 1093±357 ng•h/mL at dose levels of 40 to 360 mg.[49] Maximal plasma (C_{max}) and exposure (AUC) levels observed in patients treated at 160 mg (C_{max} 626±150 ng/mL, and AUC_{0-4} 1074±439 ng•h/mL) and 240 mg (C_{max} 719±329 ng/mL, and AUC_{0-4} 1231±430 ng•h/mL) were similar, suggesting an exposure plateau was reached at dose levels ≥ 160 mg.[49] The drug was rapidly absorbed (T_{max} ~1 hour) from the gastrointestinal tract. The apparent elimination half-life was ~3 hours, and by 24 hours post-dose, drug levels ranged from ~1 ng/mL to below the lower limit of quantification (0.5 ng/mL). No accumulation was observed over multiple days of administration, and drug exposures at ≥ 160 mg were similar.[49] Since drug is rapidly cleared, twice daily dosing is being explored in ongoing studies.

A comparison of preliminary PK data of ACY-1215 alone and coadministered in combination with bortezomib 1.0 and 1.3 mg/m^2 on Days 1 and 11 of Cycle 1 and in combination with lenalidomide 15 and 25 mg on Days 1 and 8 in Cycle 1 suggest that the PK profile of ACY-1215 was not substantially altered by coadministration of bortezomib or lenalidomide.

1.1.4.4. Pharmacodynamics

Pharmacodynamic analyses in PBMCs revealed at least a 2-fold increase in acetylated tubulin, the pharmacological marker of HDAC6 inhibition, in all patients at ACY-1215 monotherapy doses of ≥ 160 mg. Additionally, a modest increase in acetylated histones was seen at an ACY-1215 monotherapy dose of 240 mg; at lower dose levels of 40 and 80 mg, 1 and 2 patients, respectively, had a measurable increase in acetylated tubulin in PBMCs.[49]

The data show that exposures observed at ACY-1215 doses ≥ 160 mg are likely to achieve the target change in pharmacodynamic markers and attain drug levels in the range where efficacy was observed in nonclinical studies (see Investigator's Brochure, [47]).

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

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives

2.1.1. Primary Objectives

The primary objectives of this study are the following:

Phase 1b:

- To determine the MTD dose, or if not present, the recommended Phase 2 dose and schedule of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM.

Phase 2:

- To determine the efficacy of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone as treatment for patients with relapsed-and-refractory MM as assessed by overall response rate.

2.1.2. Secondary Objectives

The secondary objectives of this study are the following:

Phase 1b and Phase 2:

- To evaluate the safety of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone as treatment for patients with relapsed-and-refractory MM.

Phase 1b:

- To assess the PK of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM.
- To assess the PK of pomalidomide administered in combination with ACY-1215 and low-dose dexamethasone in patients with relapsed-and-refractory MM.
- To assess the pharmacodynamics of ACY-1215 administered in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory MM.

2.1.3. Exploratory Objective

The exploratory objective of this study is the following:

Phase2:

- To explore the relationship between response to treatment and any cytogenetic abnormalities.

2.2. Study Endpoints

2.2.1. Primary Endpoints

The primary endpoints include the following:

Phase 1b:

- MTD dose and schedule, or if not present, the recommended Phase 2 dose and schedule of ACY-1215 administered in combination with pomalidomide and dexamethasone.

Phase 2:

- Objective response to treatment as assessed by site Investigators using International Myeloma Working Group (IMWG) Uniform Response criteria.

2.2.2. Secondary Endpoints

The secondary endpoints include the following:

Efficacy

Phase 1b and Phase 2:

- Time to response (TTR).
- Duration of response (DOR).
- Time to progression (TTP).
- Progression-free survival (PFS).

- Objective response to treatment as blindly assessed by the Central Adjudication Committee using IMWG criteria and dates of progressive disease (PD).

Safety

Phase 1b and Phase 2:

- Safety (type, frequency, and severity of AEs and relationship of AEs to study drug)

Pharmacokinetics

Phase 1b:

- Plasma levels of ACY-1215 to assess the single and multiple-dose PK of ACY-1215 in combination with pomalidomide and low-dose dexamethasone.
- Plasma levels of pomalidomide to assess the PK of pomalidomide in combination with ACY-1215 and low-dose dexamethasone.

Pharmacodynamics

Phase 1b:

- Exposure-response of ACY-1215 in combination with pomalidomide and low-dose dexamethasone, including biomarkers relating to intracellular protein acetylation.

2.2.3. Exploratory Endpoint

The exploratory endpoint is the following:

Phase 2:

- To explore the relationship between response to treatment and any cytogenetic abnormalities.

3. INVESTIGATIONAL PLAN

3.1. Overall Design and Plan of the Study

This is a Phase 1b/2, multi-center, single-arm, open-label, dose-escalation study that will evaluate the safety and efficacy of PO ACY-1215 in combination with pomalidomide and low-dose PO dexamethasone in patients with relapsed-and-refractory MM. Eligible patients must have a documented diagnosis of MM and have relapsed-and-refractory disease. Patients must have relapsed after having achieved at least stable disease (SD) for at least one cycle of treatment to at least one prior regimen and then developed PD. Patients must also have documented evidence of PD during or within 60 days (measured from the end of the last cycle) of completing treatment with the last anti-myeloma drug regimen used just prior to study entry (refractory disease). Patients must also have undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of bortezomib (either in separate regiments or within the same regimen) and have measurable disease.

This study will consist of a Phase 1b ACY-1215, pomalidomide and low dose dexamethasone dose-finding segment and a Phase 2 segment. The Phase 1b segment will determine the starting dose and schedule to be used in the Phase 2 segment of the study. All patients will receive ACY-1215 in combination with pomalidomide and dexamethasone administered orally in 28-day treatment cycles unless an alternative schedule is identified in Part 1b.

The study will employ a sequential group dose-escalation design to determine the DLT and MTD of ACY-1215 in combination with pomalidomide and dexamethasone, all administered

PO. The safety, tolerability, single- and multiple-dose PK, pharmacodynamics, and anti-tumor activity of ACY-1215 in combination with pomalidomide and dexamethasone also will be evaluated.

- ACY-1215:
  - Dose Level -2: ACY-1215 160 mg once daily (QD) on Days 1-5, and 8-12 of a 28-day cycle.
  - Dose Level -1: ACY-1215 160 mg QD on Days 1-5, 8-12, and 15-19 of a 28-day cycle.
  - Dose Level 1: ACY-1215 160 mg for 21 consecutive days of a 28-day cycle.
  - Dose Level 2: ACY-1215 240 mg QD for 21 consecutive days of a 28-day cycle.
  - Dose Level 3: ACY-1215 160 mg twice daily (BID) for 21 consecutive days of a 28-day cycle.
- Pomalidomide:
  - QD on Day 1 to 21 of a 28-day cycle. The starting dose of pomalidomide is 4 mg.
- Dexamethasone:
  - QD on Days 1, 8, 15, and 22 of a 28-day cycle. Patients ≤ 75 years of age will receive dexamethasone at a dose of 40 mg/day. Patients > 75 years of age will receive dexamethasone at a dose of 20 mg/day.

The planned dose escalation is presented in Table 2 in Section 5.2.4.

Initially, 3 patients will be enrolled into a Dose-Level Group as specified above. If none of the 3 patients experiences a DLT (as defined in 5.2.6) within the first 28-day cycle, the study will proceed with dose escalation to the next higher Dose-Level-Group following safety data review by the Safety Review Committee (SRC). Dose escalations or expansion of a dose cohort will occur only with full approval of the SRC. The SRC will be comprised of the Study Investigators, the Safety Monitor, and the Sponsor Safety Medical Monitor (Section 4.8). If one of the 3 initial patients in a Dose-Level Group experiences a DLT within the first 28-day cycle, then an additional 3 patients will be enrolled into that Dose-Level Group. If 2 or more patients within the expanded dose cohort experience a DLT within the first 28-day cycle, then the MTD has been exceeded and no further dose escalations will occur. If no more than 1 of the 6 patients experiences a DLT within the first 28-day cycle, then the next dose cohort of 3 patients will be enrolled at the next higher dose level. Following the identification of the MTD, or recommended Phase 2 dose, up to 6 additional patients may be enrolled at this dose.

The MTD will be defined as the highest dose level at which no more than 1 of 6 patients experiences a DLT within the first 28-day cycle. If no more than 1 of these 6 patients experiences a DLT within the first 28-day cycle, then the last dose level enrolled to meet these criteria may be identified as the recommended dose for the Phase 2 segment of the study.

After provision of written informed consent, patients are to be evaluated for study eligibility at screening within 28 days of study start, Cycle 1 Day 1 (C1D1). Patients who are determined to be eligible based on screening assessments, will be enrolled in the study on C1D1, which is the first day of study drug administration.

For all patients who enroll into either the Phase 1b or Phase 2 segment of this study, study visits and serial measurements of safety and efficacy will be performed as outlined in Table 1. In

addition, all patients will be given aspirin 81 or 325 mg daily (commercial supply) as prophylactic anti-thrombotic treatment unless contraindicated. If aspirin is contraindicated, patients will receive another form of anti-thrombotic therapy according to hospital guidelines or physician preference. All patients will be monitored for signs and symptoms of venous thromboembolism (VTE) while on pomalidomide; diagnostic algorithms are provided (Appendix 9.1). The study will conclude 30 days after the last enrolled patient discontinues from the study due to disease progression or treatment discontinuation.

Patients are to be evaluated for disease response after every cycle and at study treatment discontinuation, starting with Cycle 1. The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0 (Appendix 9.2). Patients who withdraw from the study are to be followed up either in person or by phone 30 days (±3 days) after the last dose of study drug. If patients are treated with an alternate MM therapy before the 30 day visit, assessments for the 30 day visit should be performed prior to initiation of the alternate therapy. Upon discontinuation from study treatment for PD or any other reason, patients will be assessed 3 times per year (e.g., April, August, and December), for up to 5 years, for survival, subsequent anti-myeloma therapies, and monitoring of second primary malignancies as outlined in Table 1. Patients who discontinue study treatment due to reasons other than PD will also be followed for efficacy assessments (assessment of response, extramedullary plasmacytoma assessment, quantitative serum immunoglobulin levels, serum and urine protein electrophoresis of myeloma [M]-protein levels [SPEP, UPEP], serum and urine immunofixation [IFE] studies, and serum free light chain [SFLC] analysis) until PD, death, or initiation of an alternate MM therapy, whichever occurs first. Subsequent therapies should be collected until death or end of 1 year follow up period. Survival follow up may be done via phone. Serious adverse events (SAEs) will be collected from C1D1 through the first 30 days of follow-up. Females of childbearing potential (FCBP) with regular or no menstruation will be required to have a final pregnancy test at study treatment discontinuation, and at Day 28 following study treatment discontinuation. Females with irregular menstruation must have a pregnancy test at study treatment discontinuation, and at Day 14 and Day 28 following study treatment discontinuation.

Safety is to be evaluated during the study by documentation of AEs, including SAEs, clinical laboratory tests (hematology, serum chemistry, and urinalysis), physical examinations, vital sign measurements, performance status, and 12-lead electrocardiograms (ECGs). All safety and efficacy laboratory tests will be analyzed by local laboratories. A central laboratory will analyze duplicate samples of serum immunoglobulin levels, SPEP and UPEP of M-protein levels, serum and urine IFE studies, and SFLC analysis. A bone marrow aspirate sample will be centrally analyzed for fluorescence *in situ* hybridization (FISH)/cytogenetics. Results from the central efficacy analysis will not be shared with sites.

Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators are to report any second primary malignancies as SAEs regardless of causal relationship to study drugs, occurring at any time for the duration of the study, from the time of signing the informed consent up to the time all patients have been followed for at least 1 year from randomization or have died.

The anti-tumor activity of ACY-1215 in combination with pomalidomide and dexamethasone will be determined by assessment of disease response using the consensus recommendations based on the IMWG criteria, published by Rajkumar et al., in Blood in 2011, which includes the category of minimal response (MR) (as defined by European Group for Blood and Marrow Transplantation [EBMT] criteria) for relapsed refractory MM (Appendix 9.5,

Appendix 9.7).[50,53] In order to assess response, M-protein component is to be measured in serum and urine, FreeLite™ testing is to be performed and, as applicable, bone marrow aspirate and biopsies, and appropriate imaging studies (e.g., computed tomography [CT], MRI) are to be performed. Patients who are determined to have PD at any time are to be discontinued from the study.

In the Phase 1b segment, blood samples will be collected from all patients for the assessment of PK for ACY-1215. Blood samples will also be collected from patients at participating sites in the Phase 2 segment for sparse PK sampling. Pharmacodynamic evaluations will also be performed in the Phase 1b segment and will include the assessment of the exposure-response relationship of ACY-1215 in combination with pomalidomide and low-dose dexamethasone and potential biomarkers of response. Exploratory assessments will include the evaluation of the relationship between response and cytogenetic abnormalities, including biomarkers relating to intracellular protein acetylation.

3.2. Rationale for the Study

Pomalidomide is approved for patients with MM who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.[51] Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. Apoptotic activity and inhibition of proliferation has been observed for pomalidomide in *in vitro* cellular assays using hematopoietic tumor cells. In addition, pomalidomide inhibited the proliferation of lenalidomide-sensitive MM cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the *in vitro* umbilical cord model.[51]

Combination treatment of MM cells with ricolinostat and pomalidomide resulted in synergistic decreases in cellular viability *in vitro*. Time course studies demonstrated accumulation of cell cycle arrest in cells after prolonged exposure to pomalidomide, as well as progressive induction of apoptosis in these cells. Notably, though, combination treatment with ricolinostat plus pomalidomide resulted in synergistic increases in the percentage of MM cells undergoing apoptosis. Furthermore, at the molecular level, MM cells are known to be dependent on expression of the MYC and IRF4 transcription factors. Both ricolinostat and pomalidomide as single agents reduced expression of the critical genes MYC and IRF4, which were reduced even further upon combination treatment.[52, 53]

In vitro data with cultured MM1.S cells demonstrated that the presence of ACY-1215 enhances the activity of lenalidomide in a dose-dependent manner both with and without dexamethasone. Safety data thus far in 15 patients treated with ACY-1215 monotherapy and 46 patients treated with ACY-1215 in combination with dexamethasone and either bortezomib or lenalidomide have shown ACY-1215 to be generally well tolerated and to have a manageable safety profile. Preliminary evidence of anti-tumor activity has been demonstrated in patients treated either with ACY-1215 monotherapy or combination therapy including SD in 6 patients treated with the former regimen. These data, and the potential for reduced side effects with a selective HDAC6 inhibitor with reduced activity against Class I epigenetic HDAC enzymes, support the rationale for clinical investigation of ACY-1215 in combination with pomalidomide/dexamethasone therapy in MM.

3.3. Rationale for the Dose and Schedule Selected

In this study, ACY-1215 will be administered PO for 21 consecutive days for 3 consecutive weeks (Days 1 through 21) with cycles repeating every 28 days in patients with relapsed and/or relapsed-refractory MM. As monotherapy, exposures achieved with 160 mg doses of ACY-1215 were sufficient to increase acetylated tubulin levels by 3-fold in PBMCs (a marker of HDAC6 inhibition) in 3 of 3 patients per dose cohort. Accordingly, a 160 mg dose is likely to be a biologically relevant dose. The initial dose and schedule of ACY-1215 to be administered in this study is based on a dose and schedule equivalent to that established in Study ACE-MM-101, which is evaluating ACY-1215 in combination with lenalidomide and dexamethasone. In the ACE-MM-101 study, ACY-1215 is well-tolerated in combination with lenalidomide with no DLTs or ACY-1215 related Grade 3 or 4 toxicities when administered at 160 mg for 5 out of 7 days for 2 weeks of a 28-day cycle. Dose escalation is ongoing in both magnitude and duration of dose administration.

Based on findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose and schedule to be administered in the Phase 2 segment will be 160 mg PO QD on Days 1 to 21 of a 28-day cycle.

3.4. Justification of the Study Design

Goals of Phase 1 studies include establishment of an MTD and determination of a recommended range of doses for evaluation in future clinical studies based on PK and pharmacodynamic effects [54,55,56]; the primary objectives of the current study are consistent with those typical of Phase 1 studies.

The Phase 1b segment of the study will employ a standard 3+3 dose escalation design, the most common dose escalation method for conducting Phase 1 oncology studies.[57] The minimum number of patients to be treated at each dose level is consistent with this standard dose escalation design. In order to ensure the safety of patients, an SRC consisting of Sponsor personnel including the Sponsor Medical Monitor, the Sponsor Safety Monitor, and Investigators will review safety data from all patients enrolled in each dose cohort to confirm any DLTs that were experienced and make a determination regarding enrollment in the next dose cohort.

Sparse PK sampling in Phase 2 will be analyzed to determine relationship of drug exposure to response and potential adverse events.

3.5. Study Termination

If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then study termination can occur only after appropriate consultation between the Sponsor and Investigators. Conditions that may warrant study termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.

Should the study be closed prematurely, all study materials must be returned to the Sponsor or designee.

4. STUDY POPULATION

4.1. Number of Patients

Based on the dose escalation scheme, a total of up to 125 patients are planned to be enrolled, including up to 30 patients in the Phase 1b segment and up to 95 patients in the Phase 2 segment.

4.2. Inclusion Criteria

Patients meeting all of the following criteria are to be enrolled in the study.

1. Must be able to understand and voluntarily sign an informed consent form (ICF).
2. Must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program (or RevAid® for study participants in Canada).
3. Must be ≥ 18 years of age at the time of signing the ICF.
4. Must be able to adhere to the study visit schedule and other protocol requirements.
5. Must have a documented diagnosis of MM and have relapsed-and-refractory disease. Patients must have received at least 2 lines of prior therapies. Patients must have **relapsed** after having achieved at least SD for at least one cycle of treatment to at least one prior regimen and then developed PD. Patients must also have documented evidence of PD during or within 60 days (measured from the end of the last cycle) of completing treatment with the last anti-myeloma drug regimen used just prior to study entry (**refractory disease**).
6. Must have undergone prior treatment with at least 2 cycles of lenalidomide and at least 2 cycles of a proteasome inhibitor (either in separate regimens or within the same regimen).
7. Must not be a candidate for autologous stem cell transplant (ASCT), has declined the option of ASCT, or has relapsed after prior ASCT.
8. Must have measurable levels of myeloma paraprotein in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g/24 hours). Nonsecretory myeloma and SFLC-only myeloma are excluded.
9. Must have Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
10. FCBP must have a negative serum or urine pregnancy test (must be serum for study participants in Canada), as described in Appendix 9.3 for the POMALYST REMS™ program (in the US) and Appendix 9.4 for the RevAid® program (in Canada) FCBP and males must either commit to continued abstinence from heterosexual intercourse or must abide by birth control requirements as described in Appendix 9.3 for the POMALYST REMS™ program (in US) and Appendix 9.4 for the RevAid® program (in Canada). The European Pomalidomide Pregnancy Prevention Risk Management Plans are described in Appendix 9.5.
11. Must agree to refrain from donating blood while on study drug and for 28 days after discontinuation from this study.
12. Must agree not to share study medication with another person.
13. Must be able to take acetylsalicylic acid (ASA) (81 or 325 mg) daily as prophylactic anticoagulation. Patients intolerant to ASA may use low molecular weight heparin.

Lovenox is recommended. Coumadin will be allowed provided the patient is fully anticoagulated, with an international normalized ratio (INR) of 2 to 3.

4.3. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from enrollment in the study:

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the ICF, including nonsecretory myeloma or SFLC-only myeloma.
2. Any serious concurrent medical conditions, laboratory abnormality, or psychiatric illness that might make the patient non-evaluable, put the patient's safety at risk, or prevent the patient from following the study requirements.
3. Pregnant or lactating females.
4. Prior therapy with HDAC inhibitor or pomalidomide.
5. Any of the following laboratory abnormalities:
   - ANC < 1,000/μL (hematopoietic growth factors will not be permitted during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study).
   - Platelet count < 75,000/μL for patients in whom < 50% of bone marrow nucleated cells are plasma cells, and < 50,000/μL for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells
   - Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion is permitted)
   - Creatinine clearance < 45 mL/min according to Cockcroft-Gault formula. If creatinine clearance calculated from the 24-hour urine sample is ≥ 45 mL/min, patient will qualify for the study.
   - Serum glutamic oxaloacetic transaminase (SGOT)/aspartate aminotransferase (AST), or serum glutamic pyruvic transaminase (SGPT)/ALT > 3.0 × upper limit of normal (ULN).
   - Serum total bilirubin > 2.0 mg/dL
6. Prior history of malignancies, other than MM, unless the patient has been free of the disease for ≥ 3 years. Exceptions include the following:
   - Basal or squamous cell carcinoma of the skin
   - Carcinoma *in situ* of the cervix or breast
   - Incidental histologic finding of prostate cancer (TNM stage of T1a or T1b)
7. Corrected QT interval using Fridericia's formula (QTcF) value > 480 msec at screening; family or personal history of long QTc syndrome or ventricular arrhythmias including ventricular bigeminy at screening; previous history of drug-induced QTc prolongation or the need for treatment with medications known or suspected of producing prolonged QTc intervals on ECG.

8. Positive human immunodeficiency virus (HIV), hepatitis B virus (HBV) and known or suspected active hepatitis C virus (HCV) infection.
9. Hypersensitivity to thalidomide, lenalidomide, or dexamethasone (such as Steven Johnson Syndrome). Hypersensitivity, such as rash, that can be medically managed is allowable.
10. Peripheral neuropathy ≥ Grade 2 despite supportive therapy.
11. Radiotherapy or systemic therapy (standard or an investigational or biologic anticancer agent) within 14 days of initiation of study drug treatment.
12. Current enrollment in another clinical study involving treatment and/or is receiving an investigational agent for any reason.
13. Inability or unwillingness to comply with birth control requirements or any of the POMALYST REMS™ or RevAid® requirements (region-specific), per Appendix 9.3 and Appendix 9.4, respectively, or to the European Pomalidomide Pregnancy Prevention Risk Management Plans, per Appendix 9.5.

4.4. Source of Patients

This will be a multi-center study. Each study center is required to obtain Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval to conduct the study before enrollment of patients may commence. Patients at the study center meeting the entrance criteria, or referred to the study center will be eligible for enrollment.

4.5. Patient Identification and Registration

To ensure accurate and timely monitoring of patient enrollment, the following procedures will be implemented:

- Patients who are candidates for enrollment into the study will be evaluated for eligibility by the Investigator to ensure that the entrance criteria (see Sections 4.2 and 4.3) have been satisfied and that the patient is eligible for participation in this clinical study.
- The patient will be assigned a sequential and unique patient number. Once a patient number has been assigned, it cannot be reused.
- The Investigator or the Investigator's research staff will provide eligibility information to Acetylon. As confirmation, Acetylon will provide the Investigator with written verification of each patient's registration. No patient may be enrolled or begin treatment prior to Acetylon registration.
- Patients who are registered but not treated will be replaced. Patients who discontinue from the study before completing Cycle 1 for reasons other than DLT also are to be replaced.
- Investigators will be notified by Acetylon when enrollment in a given dose cohort is closed and enrollment into the next dose cohort can begin.
- Investigators will be notified by Acetylon if the study is placed on administrative hold, when it is completed, closed to further patient enrollment, or unexpected AEs occur.

4.6. 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:

- Non-adherence to the POMALYST REMS™ or RevAid® Programs,
- Progressive Disease
    - Determination of PD requires two consecutive assessments of disease progression. There is no specific requirement for the timing of these two assessments,
- Occurrence of an unacceptable AE,
- Pregnancy,
- 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 (see Sections 4.2 and 4.3),
- Sponsor request.

At the time of withdrawal, all study procedures outlined in the Schedule of Assessments (Table 1) post-treatment follow-up visit (i.e., pregnancy test for FCBP, pregnancy counseling, AE evaluation, assessment of second primary malignancy, etc.) should be completed if possible. The primary reason for a patient's withdrawal from the study is to be recorded in the electronic case report form (eCRF).

Patients who discontinue from the study for reasons other than DLT (e.g., non-compliance, patient request) before completing Cycle 1 will be replaced.

4.7. Patient Management

This study will be conducted on an outpatient basis.

Patients will be evaluated for study eligibility at screening, within 28 days before the first study drug dose. All patients must provide written informed consent before any samples are collected or evaluations are performed in this study. If patients have had recent scans, bone marrow biopsy, or blood test for other purposes prior to enrollment, these tests may be used for determination of eligibility if they were performed within the 28-day period before Baseline (C1D1, before study drug administration). Patients who are determined to be eligible will be enrolled in the study at Baseline. Patients will be evaluated at the study center on Days 1, 2, 8, 15, and 22 of Cycle 1. During Cycle 2, patients will be evaluated at the study center on Days 1 and 15. For all subsequent cycles, patients will be evaluated at the study center on Day 1. Patients who withdraw from the study are to be followed up either in person or by phone 30 days (± 3 days) after the last dose of study drug. If patients are treated with an alternate MM therapy before the 30 day visit, assessments for the 30 day visit should be performed prior to initiation of the alternate therapy.

Patients are to receive study treatment until development of PD or an unacceptable toxicity that cannot be managed by dose reduction alone precludes further treatment. Upon discontinuation from the study for PD or any other reason, patients will be assessed 3 times per year (e.g., April, August, and December), for up to 1 years for survival, subsequent anti-myeloma therapies, and monitoring of second primary malignancies as outlined in Table 1. SAEs will be collected from C1D1 through the first 30 days of follow-up. Subsequent therapies should be collected until death or end of the 1 year follow-up period. Survival follow up may be done via phone, when relevant. Patients who discontinue study treatment due to reasons other than PD will also be followed for efficacy assessments (see Section 6.2) until PD, death, or initiation of an alternate MM therapy, whichever occurs first.

Patients who have been contacted at least 3 times without success (at least 1 month apart) should be sent a certified letter. If no contact is established, the patient will be deemed lost to follow up. A similar process will be followed for patients being followed up by phone. All attempted contact should be documented in the patient's medical chart.

4.8. Safety Review Committee

An SRC will be involved in the conduct of this study. The SRC will be comprised of the Study Investigators, the Sponsor Medical Monitor, and the Safety Monitor. The SRC has the responsibility for monitoring the clinical study's progress and the safety of the participating patients. The SRC will evaluate study conduct during the course of the clinical study based upon data defined in the SRC Charter for this clinical study. Safety assessments will be conducted in real-time by the SRC after the first 3 patients have completed Cycle 1. Dose escalations or expansion of a dose cohort will occur only with full approval of the SRC.

The SRC will review safety data from all patients enrolled in each dose cohort to confirm any DLTs that were experienced and make a determination regarding enrollment in the next dose cohort. Each of the first 3 patients in the dose cohort must have completed Cycle 1 (28-day cycle) to be eligible for SRC review and for a decision to be made regarding enrollment into the next dose level. If a DLT necessitates enrollment of additional patients into a dose cohort, the SRC will review all of the safety data for that dose cohort after those additional patients have completed Cycle 1 through Day 21. Based on evaluation of the data, the SRC may decide that enrollment at an alternate starting dose or an intermediate dose level not specified in this protocol may take place. If this occurs, the IRB/IEC will be informed of the intermediate dose level(s) or alternate dosing regimen.

The SRC will also review all Phase 1b safety data to determine the recommended dose of ACY-1215 to be used in the Phase 2 segment of the study. The SRC may decide that enrollment at an intermediate starting dose or alternate dosing regimen not specified in this protocol may take place. If this occurs, the IRB/IEC will be informed immediately of the intermediate dose level(s) or alternate dosing regimen.

4.9. Independent Response Assessment Committee

The Independent Response Assessment Committee (IRAC) will be composed of 3 hematologists with expertise and experience in the diagnosis and management of multiple myeloma and a biostatistician. The IRAC will review, at ad hoc and scheduled meetings, all efficacy data in a blinded manner (independent of investigator-reported response) and provide verifiable and objective assessment of each patient's disease response. Patient data will be displayed using a unique number for each patient.

IRAC meetings will be convened when sufficient data becomes available for 30 enrolled patients, as well as prior final analysis, and intermittently as appropriate. The IRAC will determine disease response according to the following categories as specified in the IMWG (Appendix 9.5) and EBMT (Appendix 9.7) criteria. The IRAC will also make a disease response determination at 28-day intervals (study visits) up to and including the discontinuation from treatment visit.

4.10. Investigator Compliance

Study centers that deviate significantly from the protocol without prior approval from the Sponsor and regulatory authorities may be discontinued from the study. The Investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study drug, and the conduct of clinical and laboratory evaluations as outlined in the protocol.

5. STUDY TREATMENTS

5.1. Study Drug Supply and Storage

All study drugs must be stored in a safe and locked place with no access by unauthorized personnel.

5.1.1. ACY-1215

ACY-1215 will be supplied by the Sponsor as a liquid (12 mg/ml) for PO administration in 20 mL glass vials. ACY-1215 will be stored in the pharmacy at -20ºC. Additional storage conditions and dose preparation instructions will be provided in detail within the Pharmacy Manual.

5.1.2. Pomalidomide and Dexamethasone

Pomalidomide will be provided at 4, 3, 2, and 1 mg for PO administration. Pomalidomide will be dispensed by pharmacists to patients for the duration of their participation in this study at no charge to them or their insurance providers, through the region-specific POMALYST REMS™ or RevAid®program. Patients will have to be registered in such a program and follow the required procedures to receive pomalidomide supply. Only enough pomalidomide for one cycle of therapy will be supplied to the patient every cycle. Pomalidomide capsules are to be stored, per the package insert [51,58].

For sites in the US and Canada, dexamethasone for PO administration will be supplied from commercially-available sources as 4 mg compressed tablets. (Dexamethasone tablets at strengths other than 4 mg may be used, as necessary.) Acetylon will supply dexamethasone to sites in the EU. Dexamethasone tablets are to be stored at room temperature between 68° to 77ºF (20° to 25ºC) away from light and moisture.

5.2. Study Drug Dose and Administration

All patients will receive ACY-1215 in combination with pomalidomide and dexamethasone. On ACY-1215 administration days, pomalidomide and dexamethasone are to be taken immediately after ACY-1215. If the patient is receiving ACY-1215 BID, pomalidomide and dexamethasone are to be taken immediately after the first (a.m.) dose of ACY-1215 only. Study Day 1 is defined as the first day the patient receives study drug.

5.2.1. ACY-1215

ACY-1215 will be administered orally QD or BID at least 1 hour after ingestion of food and followed by 4 ounces of water. Patients will be instructed not to ingest food or other PO medication, other than pomalidomide and dexamethasone, for at least 2 hours after each ACY-1215 dose. On study center visit days requiring PK/pharmacodynamic blood draws, ACY-1215 must be taken in the study center. On other study drug administration days that coincide with scheduled study center visits, ACY-1215 may be administered at the study center or at home. If ACY-1215 is being given BID, pomalidomide and dexamethasone are to be given with the first dose of ACY-1215. The ACY-1215 BID, doses should be taken approximately every twelve hours. A plus or minus 2 hour window is acceptable for BID dosing.

One cycle of therapy is comprised of either 21 doses every 28 days (QD), or 42 doses every 28 days (BID).

Phase 1b Segment:

Study Day 1 is defined as the first day the patient receives study drug. Patients in the Phase 1b segment of the study will receive single 160 mg QD doses of ACY-1215 for 21 consecutive days of a 28-day treatment cycle (Dose Level 1). Dose escalations will follow as outlined in Table 2. If that dose is tolerated per SRC safety review, 240 mg QD on the same days will be explored (Dose Level 2). If Dose level 2 is well tolerated, Dose Level 3 of 160 mg BID will be explored. If Dose Level 1 is not tolerated, the schedule will be modified (Dose Level -1) to 160 mg ACY-1215 QD on Days 1-5, 8-12, and 15-19. If Dose Level -1 is not tolerated, the schedule will be modified (Dose Level -2) to 160 mg ACY-1215 QD on Days 1-5, and 8-12.

Based on emerging data from ongoing studies of ACY-1215, intermediate dose levels and schedules may be added, or dose levels eliminated, and the IRB/IEC will be notified.

Investigators should consider providing prophylaxis for tumor lysis, including hydration, prior to administration of ACY-1215.

Phase 2 Segment:

Based on findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose and schedule to be administered in the Phase 2 segment will be be 160 mg PO QD on Days 1 to 21 of a 28- day cycle as recommended by the SRC. Treatment will continue until PD or toxicity requiring removal from study.

5.2.2. Pomalidomide

Pomalidomide (POMALYST®) will be provided to research patients for the duration of their participation in this study at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ or RevAid® program. Per the standard POMALYST REMS™ and RevAid®program requirements, all physicians who prescribe pomalidomide for research patients enrolled into this study, and all research patients enrolled into this study, must be registered in and must comply with all requirements of the POMALYST REMS™ and RevAid® program. Drug will be shipped to the patient's home or to the study site (in Canada only) for Investigational New Drug studies. Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ and RevAid®programs.

Pomalidomide (POMALYST®) will be administered based on the current approved dose and schedule: 4 mg PO QD on Days 1 to 21 of a 28-day cycle (see Table 2). Pomalidomide

capsules should be swallowed whole, and should not be broken, chewed or opened. Patients should take pomalidomide at the same time each day, immediately following ACY-1215 dosing when applicable. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal. If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up, rather it should be taken at the next scheduled time point. Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately. Pomalidomide will be sent to the patients' home or to the study site (in Canada only) via the POMALYST REMS™ and RevAid®programs (see Appendix 9.3 and Appendix 9.4, respectively).

5.2.3. Dexamethasone

All patients will receive dexamethasone, which will be taken PO QD on Days 1, 8, 15, and 22 of each 28-day cycle (see Table 2). For patients ≤ 75 years of age, the starting dose of dexamethasone will be 40 mg; for patients who are > 75 years of age, the starting dose of dexamethasone will be 20 mg.

5.2.4. Planned Study Drug Doses

The planned study drug doses for the combination regimen are shown in Table 2.

Table 2 Planned Dose Escalation

Phase 1b				
Dose Level[a]	**N**	**ACY-1215**	**Pomalidomide**	**Dexamethasone[b]**
-2	3-6	160 mg QD on Days 1-5, and 8-12	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
-1	3-6	160 mg QD on Days 1-5, 8-12, and 15-19	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
1	3-6	160 mg QD on Days 1-21	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
2	3-6	240 mg QD on Days 1-21	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22
3	3-6	160 mg BID on Days 1-21	4 mg QD Days 1-21	40 mg QD Days 1, 8, 15, 22

Key: BID = twice daily, QD = once daily.
Note: treatment cycle is 28 days.
[a] Patients will be initially enrolled at Dose Level 1. If 2 or more patients experience a DLT within the 28-day cycle, patients will subsequently be enrolled at Dose Level -1. If 2 or more patients experience a DLT at Dose Level -1 within the 28-day cycle, patients will subsequently be enrolled at Dose Level -2
[b] Patients ≤ 75 years of age will receive 40 mg of dexamethasone; patients > 75 years of age will receive 20 mg.

Based on the interim evaluation of the safety and tolerability data of the previous dose level, it may be decided to investigate an intermediate dose level not specified in Table 2 (as applicable) (see Section 5.2.5). If this occurs, the IRBs/IECs will be informed of the intermediate dose level(s).

The SRC will review safety data after the first 3 patients have completed Cycle 1 and make the determination to initiate enrollment of another 3 patients into the next dose level. Based on these evaluations the SRC may decide that enrollment at an alternate starting dose or an intermediate dose level not specified in this protocol may take place. If this occurs, the

IRB/IEC will be informed immediately of the alternate starting dose or intermediate dose level(s).

5.2.5. Dose Escalation Procedure

Study drug doses will be escalated sequentially after the SRC reviews safety data from all patients enrolled in each dose cohort to confirm any DLTs that were experienced and make a determination regarding enrollment in the next dose cohort. Each of the first 3 patients in the dose cohort must have completed Cycle 1 (28-day cycle) to be eligible for SRC review and for a decision to be made regarding enrollment into the next dose level (see Section 4.8). Based on the interim evaluation of the safety and tolerability data of the previous dose level, it may also be decided that escalation will take place at an intermediate dose level not specified in Table 2 (as applicable). If this occurs, the IRBs/IECs will be informed of the intermediate dose level(s). The SRC may be convened earlier at the discretion of the Sponsor if important safety issues arise requiring the attention of the committee.

Determination of MTD: Dose escalation rules

Three patients are to be enrolled in each Dose-Level Group. After 3 patients have completed Cycle 1 (28-day cycle) and:

- If none of the 3 patients experiences a DLT within the first 28 day cycle, and pending SRC review as described above, then an additional 3 patients will be enrolled into the next higher dose level.
- If one of the 3 initial patients in a Dose-Level Group experiences a DLT within the first 28-day cycle, then an additional 3 patients will be enrolled into that Dose-Level Group.
- If 2 or more patients within the expanded dose cohort experience a DLT within the first 28-day cycle, then the MTD has been exceeded and no further dose escalations will occur.
- If no more than one of the 6 patients experiences a DLT within the first 28-day cycle, then the next dose cohort of 3 patients will be enrolled at the next higher dose level.

The MTD will be defined as the highest dose level at which no more than 1 of 6 patients experiences a DLT within the first 28-day cycle. If no more than 1 of these 6 patients experiences a DLT within the first 28-day cycle, then the last dose level enrolled to meet these criteria may be identified as the recommended dose for the Phase 2 segment of the study.

Teleconferences or email communication between the Sponsor or designee and the clinical study sites will occur weekly to monitor for DLTs and to communicate enrollment to the next dose level.

Patients who discontinue from the study for reasons other than DLT (e.g., non-compliance, patient request) before completing Cycle 1 will be replaced.

The use of hematopoietic growth factors will not be permitted during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study; however, they will be permitted in Cycle 2 and subsequent cycles. The use of bisphosphonates is permitted.

Patients may not be enrolled in more than 1 dose cohort. Patients enrolled into the Phase 1b segment of the study cannot be enrolled into the Phase 2 segment upon discontinuation from Phase 1b.

Complete blood counts will be monitored at least every 14 days during Cycle 2 and then at least at the first day of every cycle thereafter.

5.2.6. Dose-limiting Toxicity

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. If a toxicity is not classified in the CTCAE, then it should be classified according to the criteria presented in Section 6.1.8.4.

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. For toxicities observed that may be attributable to pomalidomide (see Table 6) or dexamethasone (see Table 8), dose reductions should be attempted with these treatments prior to reducing the dose of ACY-1215.

The following AEs occurring during Cycle 1 that are considered to be ACY-1215-related will be considered to be DLTs:

Hematologic toxicity:

- Grade 4 neutropenia (ANC < 500/μL), lasting > 5 days, *or*
- Febrile neutropenia (fever ≥ 38.5° C and ANC < 1,000/μL), *or*
- Grade 4 thrombocytopenia (platelet count < 25,000/μL), *or*

Grade 3 or 4 ACY-1215-related Non-hematologic toxicity:

- All other Grade 3 or Grade 4 non-hematologic toxicity with the exception of:
  - Grade 3 or 4 nausea, vomiting or diarrhea (Patients must have received optimal symptomatic treatment for Grade 3 or 4 nausea, vomiting, or diarrhea to be considered a DLT).
  - Grade 4 transaminitis (serum transaminase > 20 × upper limit of normal [ULN]) is a DLT, while Grade 3 transaminitis (serum transaminase > 5 × ULN) must be present for ≥ 7 days to be considered a DLT.
  - Other asymptomatic Grade 3 and 4 laboratory investigations, excluding cardiac function tests, may be evaluated by the SRC to determine whether dose cohorts should be expanded.
- Delay of the start of Cycle 2 by > 7 days due to ACY-1215-related AE.

Toxicity management procedures for ACY-1215 are presented in Table 4 and Table 5. No dose modifications for ACY-1215 are to be performed in Cycle 1.

5.2.7. Maximum Tolerated Dose

The DLT dose level is defined as the dose level of ACY-1215+pomalidomide+dexamethasone at which ≥ 2 of up to 6 patients experience a DLT. The MTD is defined as the dose level of ACY-1215+pomalidomide+dexamethasone immediately below the DLT dose level. Following the identification of the MTD, or recommended Phase2 dose, up to 6 additional patients may be enrolled at this dose. When all 6 patients have completed the 28-day cycle at the MTD, the

SRC will review all Phase 1b safety data to determine the recommended dose of ACY-1215 to be used in the Phase 2 segment of the study.

5.2.8. Dose Modifications

Before each scheduled study drug dose administered in the clinic, the patient will be evaluated for possible DLTs that may have occurred after the previous dose(s) as described in Section 5.2.6. 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 instructions outlined in Section 5.2.8.1, Section 5.2.8.2, and Section 5.2.8.3. Conversely, if the toxicity is considered unrelated to a particular drug(s), then no modification of that drug(s) is required.

No dose modifications for ACY-1215 are to be performed in Cycle 1. After Cycle 1, patients who are unable to tolerate ACY-1215 treatment may have the dose reduction steps presented below until a tolerable dose is achieved.

5.2.8.1. ACY-1215

Patients must remain on their assigned ACY-1215 dose in Cycle 1 during the dose escalation phase of the study, or be withdrawn from the study. If toxicity attributable to pomalidomide or dexamethasone is seen during Cycle 1, dose reductions may be made as described in Table 6 and Table 8. Patients should receive 80% of planned doses to be evaluable for SRC review.

For toxicities observed that may be attributable to pomalidomide (see Table 6) or dexamethasone (see Table 8), dose reductions should be attempted with these treatments prior to reducing the dose of ACY-1215.

After Cycle 1, patients who are unable to tolerate ACY-1215 treatment may have the dose reduction steps presented in Table 3 until a tolerable dose is achieved.

Table 3 ACY-1215 Dose Modifications

Dose level	Starting dose ofACY-1215	1st dose reduction	2nd dose reduction
-2	160 mg QD on Days 1-5, and 8-12	80 mg QD on Days 1-5, and 8-12	NA
-1	160 mg QD on Days 1-5, 8-12, and 15-19	80 mg QD on Days 1-5, 8-12, and 15-19	NA
1	160 mg QD on Days 1-21	80 mg QD on Days 1-21	NA
2	240 mg QD on Days 1-21	160 mg QD on Days 1-21	80 mg QD on Days 1-21
3	160 mg BID on Days 1-21	160 mg QD on Days 1-21	80 mg QD on Days 1-21

Table 4 Dose Modification Instructions for ACY-1215 for Hematologic Toxicities

Toxicity	Dose Modification
Neutropenia (1st occurrence): • ANC < 500/μL or febrile neutropenia (fever ≥ 38.5°C and ANC < 1,000/μL) • ANC return to ≥ 500/μL	Interrupt ACY-1215 treatment, follow CBC weekly. Resume ACY-1215 at one dose level lower than at the time of the first occurrence per Table 3. For the second occurrence of neutropenia (each subsequent drop of ANC <500, interrupt and follow as above and resume at one dose level below the current dose.
Thrombocytopenia (1st occurrence): • Platelets < 25,000/μL • Platelets return to ≥ 50,000/μL	Interrupt ACY-1215 treatment, follow CBC weekly. Resume ACY-1215 at one dose level lower than at the time of the first occurrence per Table 3. For the second occurrence of thrombocytopenia (each subsequent drop of platelets <25,000), interrupt and follow as above. When platelet count returns to 50,000, resume at one dose level below the current dose.

Table 5: Dose Modification Instructions for ACY-1215 for Non-hematologic Toxicities

Toxicity	Dose Modification
Grade 1 or Grade 2	Continue current ACY-1215 dose regimen at the discretion of the investigator.
Grade 3 Non-hematologic[1]	Hold ACY-1215 dose until value(s) return to ≤Grade 2; initiate therapy at one dose level lower than at the time of the first occurrence per Table 3.

5.2.8.2. Pomalidomide

Toxicities considered related to pomalidomide are to be managed as shown in Table 6 and Table 7.

Table 6 Dose Modification Instructions for Pomalidomide for Hematologic Toxicities

Toxicity	Dose Modification
Neutropenia Grade 4 neutropenia (ANC < 500/μL) or Febrile neutropenia (fever ≥38.5°C and ANC < 1,000/μL)	Hold the pomalidomide dose for remainder of cycle. If the patient was not receiving Granulocyte colony-stimulating factor (GCSF) therapy, initiate GCSF therapy at the discretion of the treating physician. On Day 1 of next cycle, continue GCSF as needed and maintain dose of pomalidomide if neutropenia was the only DLT (except during the first cycle for patients enrolled into the MTD segment of the study). Otherwise, decrease pomalidomide by one dose level at start of next cycle. (Note, ANC must be ≥ 500/μL in the US and Canada and ≥ 1,000/μL in the EU to restart dosing)
Grade 4 Thrombocytopenia (Platelets < 25,000/μL)	Hold the dose for remainder of cycle. Decrease pomalidomide by one dose level when dosing is resumed at next cycle. (Note, platelet count must recover to ≥ 50,000/μL to restart dosing)

Table 7 Dose Modification Instructions for Pomalidomide for Non-hematologic Toxicities

Toxicity	Dose Modification
Rash = Grade 3	Hold pomalidomide dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to ≤ Grade 1).
Rash = Grade 4 or Blistering	Discontinue pomalidomide dose and discontinue patient from study.
Constipation ≥ Grade 3	Hold pomalidomide dose for remainder of cycle. Initiate bowel regimen. Decrease pomalidomide by one dose level when dosing restarted at next cycle (constipation must resolve to ≤ Grade 2).
VTE ≥ Grade 3	Hold pomalidomide dose for remainder of cycle. Initiate anti-coagulation treatment. Maintain pomalidomide dose level when dosing restarted at next cycle at discretion of treating physician.
Hypo/hyperthyroidism ≥ Grade 2	Hold dose for remainder of cycle. Initiate appropriate medical therapy. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Peripheral Neuropathy = Grade 3	Hold pomalidomide dose for remainder of cycle. Decrease pomalidomide by one dose level when dosing restarted at next cycle (neuropathy must resolve to ≤ Grade 1).
Peripheral Neuropathy = Grade 4	Discontinue pomalidomide and discontinue patient from study.

For all other ≥ Grade 3 pomalidomide-related AEs, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to ≤ Grade 2 at the discretion of the Investigator.

Instructions for Initiating a New Pomalidomide Cycle

To initiate a new cycle of pomalidomide, ANC must be ≥ 500/µL in the US and Canada and ≥ 1,000/µL in the EU, the platelet count must be ≥ 50,000/µL, and non-hematologic AEs must have recovered as outlined in Table 7.

If recovery from toxicities is prolonged beyond 14 days, then the dose of pomalidomide or dexamethasone will be decreased by one dose level.

If the treatment has been interrupted and the next cycle is delayed beyond 29 days after Day 1 of the prior cycle, then Day 1 of the next cycle will be defined as the first day that the treatment is resumed.

5.2.8.3. Dexamethasone

Toxicities considered to be related to dexamethasone are to be managed as shown in Table 8.

Table 8 Dexamethasone Dose Modifications

Category	Toxicity	Grade	Dose Change
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, or gastritis	Grade 1-2 (requiring medical management)	Treat with H_2 blockers, sucralfate, omeprazole, or other comparable medications (i.e. proton pump inhibitors). If symptoms persist despite treatment, decrease the dexamethasone dose by 1 level.
		≥Grade 3 (requiring hospitalization or surgery)	Interrupt dexamethasone until symptoms are adequately controlled. Thereafter, resume dexamethasone reduced by one level with concomitant H_2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, permanently discontinue dexamethasone.
	Acute pancreatitis	≥Grade 3	Permanently discontinue dexamethasone.
Cardiovascular	Edema	≥ Grade 3 (limiting function and unresponsive to therapy or anasarca)	Treat with diuretics as needed and decrease dexamethasone by one level. If edema persists despite above measures, decrease by another level. If symptoms persist despite a second reduction, discontinue dexamethasone.
Neurology	Confusion or mood alteration	≥ Grade 2 (interfering with function ± interfering with activities of daily living [ADLs])	Interrupt dexamethasone for up to 2 weeks until symptoms resolve. If symptoms resolve, restart dexamethasone at dose decreased by one level. If symptoms persist despite above measures, then permanently discontinue dexamethasone.
Musculoskeletal	Muscle weakness	≥ Grade 2 (symptomatic and interfering with function ± interfering with ADLs)	Decrease dexamethasone dose by one level. If symptoms persist despite a dose reduction, decrease by another level. If symptoms persist despite above measures, permanently discontinue dexamethasone.
Metabolic	Hyperglycemia	≥ Grade 3	Administer insulin or oral hypoglycemics as needed. If hyperglycemia is not controlled despite treatment, decrease dexamethasone by one level until levels are satisfactory.

The dexamethasone dose reduction steps are summarized in Table 9 and Table 10.

Table 9 Dose Reduction Steps for Dexamethasone (≤ 75 years of age)

Dose Level	Dose (Days 1, 8, 15, and 22)
Starting Dose	40 mg
Dose Level -1	20 mg
Dose Level -2	10 mg

Note: Dexamethasone should be discontinued if patient is unable to tolerate 10 mg dose. Patients may continue on ACY-1215 and pomalidomide until PD.

Table 10 Dose Reduction Steps for Dexamethasone (> 75 years of age)

Dose Level	Dose (Days 1, 8, 15, and 22)
Starting Dose	20 mg
Dose Level -1	12 mg
Dose Level -2	8 mg

Note: Dexamethasone should be discontinued if patient is unable to tolerate 8 mg dose. Patients may continue on ACY-1215 and pomalidomide until PD.

5.3. Blinding, Packaging, and Labeling

5.3.1. Blinding and Breaking the Blind

This is single arm open label study; blinding methods are not applicable.

5.3.2. Packaging and Labeling

As stated previously, ACY-1215 will be supplied by the Sponsor as a liquid (12 mg/ml) for PO administration in 20 mL glass vials. Additional storage conditions and dose preparation instructions will be provided in detail within the Pharmacy Manual.

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 region-specific regulatory information.

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.

Pomalidomide will be provided at 4, 3, 2, and 1 mg for PO administration. Pomalidomide will be dispensed to patients for the duration of their participation in this study at no charge to them or their insurance providers, through the region-specific POMALYST REMS™ or RevAid®program (see Appendix 9.3 and Appendix 9.4, respectively). Pomalidomide capsules are to be stored, per the package insert [51, 58].

Dexamethasone will be packaged and labeled by the manufacturers according to their standard practices.

5.4. Assessment of Treatment Compliance

5.4.1. ACY-1215

Study center pharmacy personnel will prepare individual patient doses to be administered either during scheduled study center visits or by the patient at home.

On ACY-1215 administration days that coincide with study center visits, the ACY-1215 dose prepared by pharmacy personnel will be ingested by the patient at the study center. Prior to leaving the study center, the required number of doses of ACY-1215 prepared by pharmacy personnel will be dispensed to patients for ingestion at home on non-clinic dosing days.

Each time ACY-1215 is dispensed to a patient, study personnel will record the date dispensed, amount dispensed, and the recorder's initials. When the patient returns used and unused study drug containers, study personnel are to record the date returned, amount returned, the recorder's initials, and any comments. A diary will be provided to patients on C1D1 in order to document the date and time of each ACY-1215 dose for all treatment cycles. Following Cycle 1, the Investigator will confirm treatment compliance with the patient at each visit.

5.4.2. Pomalidomide

The date pomalidomide is administered and any changes in the dose will be documented in the eCRF. Date and time of all pomalidomide doses will be record in patient diaries.

5.4.3. Dexamethasone

The date dexamethasone is administered and any changes in dose will be documented in the eCRF. Date and time of all dexamethasone doses will be record in patient diaries.

5.5. Study Drug Accountability

Accountability for ACY-1215 (all centers), pomalidomide, and dexamethasone (EU only) 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 study 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 (or unless appropriately documented according to site procedure). 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 study drug will be treated and disposed of as hazardous waste in accordance with governing regulations.

5.6. Prior and Concomitant Treatment

All prescription and non-prescription medications, including pharmacologic doses of vitamins, herbal medicines, or other non-traditional medicines, taken within 28 days prior to the first dose of ACY-1215 through the final visit (30 days [±3 days] after the last dose of study drug) must be documented in the eCRF.

5.6.1. Permitted Medication

Supportive therapy for MM (e.g., erythropoietin) that is ongoing at Baseline will be permitted during the treatment phase of the study. The following medications and supportive therapies are examples of support therapies that may be used during the study:

- Antiemetics and Antidiarrheals: Antiemetic treatments may be used at the Investigator's discretion and in accordance with the American Society of Clinical Oncology (ASCO) guidelines after documented nausea or vomiting has occurred without medications having been used. While antiemetic choice is at the discretion of the Investigator, high dose steroids should be avoided if possible as an antiemetic therapy. Dolasetron mesylate (Anzemet) is no longer indicated for chemotherapy indications due to QT prolongation per guidance of the Food and Drug Administration (FDA). Other serotonin 5HT3 antagonists (which have been reported to prolong QT) may be used if required with caution and appropriate monitoring by the Investigator. If these agents are used

prophylactically on Cycle 1 Day 8 (when PK is performed) the time and dose must be noted on the eCRF. Antidiarrheals also may be used at the Investigator's discretion.

- Hematopoietic Growth Factors: The use of hematopoietic growth factors will not be permitted during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study. Hematopoietic growth factors may be used beginning with Cycle 2 of the Phase1b segment and during all additional cycles. The use of myeloid and erythroid growth factors are to be utilized as per the recommendations of the ASCO guidelines. Treatment with myeloid growth factors is encouraged when the ANC is less than 1,000/μL.
- Adequate hydration is recommended for the prevention of myeloma-related kidney disease. Generally, intravenous contrast is not used in CT scanning because of the risk to the kidney. Non-steroidal anti-inflammatory drugs should be avoided.
- Bisphosphonate may be used in patients with osteolytic or osteopenic myelomatous bone disease. Commercially available bisphosphonates are to be used, preferably according to the manufacturer's recommendations, as described in the prescribing information.
- Patients with advanced stage disease and/or high tumor burden should be closely monitored, appropriate precautions should be taken, and treatment should be instituted as appropriate.
- ASA (81 or 325 mg) is to be taken daily as prophylactic anticoagulation. Patients intolerant to ASA may use low molecular weight heparin. Lovenox is recommended. Coumadin will be allowed provided the patient is fully anticoagulate, with an INR of 2 to 3.

All patients will be monitored for signs and symptoms of VTE while on pomalidomide; diagnostic algorithms are provided in Appendix 9.1.

5.6.2. Excluded Medication and Substances

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

- Any anti-neoplastic treatment with activity against MM (with the exception of pomalidomide and dexamethasone).
- Radiotherapy or standard systemic therapy within 2 weeks of Baseline (C1D1). Investigational therapies or biologics within 3 weeks of Baseline. Any AEs from previous therapies must be resolved to Baseline.
- Because of the increased risk of VTE patients with MM taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective methods described in Appendix 9.2. The risk of VTE continues for 4 to 6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.
- Hematopoietic growth factors during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segments of the study.

The US pomalidomide package insert states that no formal drug interaction studies have been conducted; however pomalidomide is primarily metabolized by CYP1A2 and CYP3A and is also a substrate for P-glycoprotein (P-gp).[51]:

- Co-administration of pomalidomide with drugs that are strong inhibitors of CYP1A2, CYP3A (e.g. ketoconazole) or P-gp could increase exposure and should be avoided.
- Co-administration of pomalidomide with drugs that are strong inducers of CYP1A2, CYP3A (e.g. rifampin) or P-gp could decrease exposure and should be avoided.
- Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

The Canadian pomalidomide package insert states that no formal drug interaction studies have been conducted; however, pomalidomide is a substrate of P-glycoprotein (Pg-p) and is partly metabolized by CYP1A2 and CYP3A4.[58]:

- The use of pomalidomide with concomitant strong CYP1A2 inhibitors and strong CYP3A4 inhibitors together should be avoided.
- If strong inhibitors of CYP1A2 are coadministered with pomalidomide, patients should be closely monitored for the occurrence of AEs.
- The risk of thromboembolic events may be increased with the simultaneous use of pomalidomide with erythropoietic agents, hormone replacement therapy or hormonal contraceptives.
- Cigarette smoking may reduce the exposure to pomalidomide.
- Pomalidomide may possibly impair mental and/or physical abilities required for the performance of hazardous tasks, such as driving a car or operating other complex or dangerous machinery.
- Drugs that may interact with pomalidomide include:
    - fluvoxamine, Hormonal Replacement Therapy, and
    - Hormonal Contraception (estrogens and progestins).

The EU pomalidomide package insert states that no formal drug interaction studies have been evaluated; however, pomalidomide is a substrate of Pg-p and is partly metabolized by CYP1A2 and CYP3A4/5.[59]

- Co-administration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide.
- Co-administration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide in the presence of ketoconazole increased exposure to pomalidomide by 104% with a 90% CI [88%, 122%] compared to pomalidomide plus ketoconazole.
- If strong inhibitors of CYP1A2 (e.g. ciprofloxacin, enoxacin and fluvoxamine) are co-administered with pomalidomide, patients should be closely monitored for the occurrence of adverse reactions.

The dexamethasone prescribing information contains the following information regarding drug interactions [60]:

- Aminoglutethimide: Aminoglutethimide may diminish adrenal suppression by corticosteroids.
- Amphotericin B injection and potassium-depleting agents: When corticosteroids are administered concomitantly with potassium-depleting agents (e.g., amphotericin B,

diuretics), patients should be observed closely for development of hypokalemia. In addition, there have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure.

- Antibiotics: Macrolide antibiotics have been reported to cause a significant decrease in corticosteroid clearance.
- Anticholinesterases: Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.
- Anticoagulants, Oral: Co-administration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.
- Antidiabetics: Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
- Antitubercular Drugs: Serum concentrations of isoniazid may be decreased.
- Cholestyramine: Cholestyramine may increase the clearance of corticosteroids.
- Cyclosporine: Increased activity of both cyclosporine and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.
- Dexamethasone Suppression Test (DST): False-negative results in the DST in patients being treated with indomethacin have been reported. Thus, results of the DST should be interpreted with caution in these patients.
- Digitalis Glycosides: Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.
- Ephedrine: Ephedrine may enhance the metabolic clearance of corticosteroids, resulting in decreased blood levels, and lessened physiologic activity, thus requiring an increase in corticosteroid dosage.
- Estrogens, including Oral Contraceptives: Estrogens may decrease the hepatic metabolism of certain corticosteroids, thereby increasing their effect.
- Hepatic Enzyme Inducers, Inhibitors and Substrates: Drugs which induce cytochrome P450 3A4 (CYP 3A4) enzyme activity (e.g., barbiturates, phenytoin, carbamazepine, rifampin) may enhance the metabolism of corticosteroids and require that the dosage of the corticosteroid be increased. Drugs which inhibit CYP 3A4 (e.g., ketoconazole, macrolide antibiotics such as erythromycin) have the potential to result in increased plasma concentrations of corticosteroids.
- Dexamethasone is a moderate inducer of CYP 3A4. Co-administration with other drugs that are metabolized by CYP 3A4 (e.g., indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentration.
- Ketoconazole: Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60%, leading to increased risk of corticosteroid side effects. In addition, ketoconazole alone can inhibit adrenal corticosteroid synthesis and may cause adrenal insufficiency during corticosteroid withdrawal.

- Nonsteroidal Anti-Inflammatory Agents: Concomitant use of aspirin (or other nonsteroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids. ASA (81 or 325 mg) QD is permitted for deep venous thrombosis (DVT) prophylaxis.
- Phenytoin: In post-marketing experience, there have been reports of both increases and decreases in phenytoin levels with dexamethasone co-administration, leading to alterations in seizure control.
- Skin Tests: Corticosteroids may suppress reactions to skin tests.
- Thalidomide: Co-administration with thalidomide should be employed cautiously, as toxic epidermal necrolysis has been reported with concomitant use.
- Vaccines: Patients on corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines due to inhibition of antibody response. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. Routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued if possible.

6. STUDY ASSESSMENTS

6.1. Safety Measurements

6.1.1. Demographics and Medical History

A medical and surgical history will be obtained at screening for all patients. The medical history is to include demographic and background information, MM history, including date of and stage at diagnosis, and all previous treatment for MM, including radiation therapy, and response(s) to such treatment.

6.1.2. Physical Examination

A complete physical examination will be conducted for all patients at screening and at study treatment discontinuation.

6.1.3. Vital Signs

Vital signs, including weight, blood pressure (BP), heart rate, and temperature will be conducted for all patients at screening, on Day 1 of every treatment cycle, upon PD, and at study treatment discontinuation. Height will be collected at screening only.

6.1.4. Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG performance Status (Appendix 9.8) is to be documented for all patients at screening, on Day 1 of every treatment cycle, upon PD, and at study treatment discontinuation.

6.1.5. 12-Lead Electrocardiogram

Twelve-lead ECGs monitoring is to be performed at screening, pre-dose on Day 1 of every treatment cycle, Day 8 (Cycle 1 only for Phase 1B), and at study treatment discontinuation. Additional ECGs may be taken at any time point at the Investigator's discretion.

6.1.6. VTE Monitoring

Monitoring for VTE will be performed at each visit during study treatment and at study discontinuation.

6.1.7. Clinical Laboratory Tests

All serum hematology, serum chemistries, serum function tests, and urinalysis will be analyzed by local laboratories.

6.1.7.1. Hematology, Serum Chemistry and Urinalysis

Blood samples for hematology are to be collected for all patients at screening, on Days 1, 2, 8, 15, and 22 during Cycle 1, on Day 1 of every cycle beginning with Cycle 2, upon PD, and at study treatment discontinuation. In addition, complete blood count (CBC) will be conducted every 7 days for Cycle 1, every 14 days for Cycle 2, and on Day 1 of every cycle beginning with Cycle 3.

Blood samples for serum chemistry are to be collected for all patients at screening, on Day 1 of every treatment cycle, and at study treatment discontinuation. Hematology and serum chemistry results must be available and reviewed by the Investigator prior to study drug administration.

Urine for urinalysis is to be collected at screening, on Day 1of every treatment cycle, upon PD, and at study treatment discontinuation.

The following clinical laboratory parameters are to be measured:

Hematology

- Hematocrit
- Hemoglobin
- Red blood cell count (RBC)
- INR (for patients on coumadin)
- ANC
- Platelet count
- WBC with differential
- Reticulocyte count
- Mean corpuscular volume
- Absolute lymphocyte count (ALC)

Chemistry

- Glucose
- Calcium
- Albumin
- Total protein
- Sodium
- Potassium
- Magnesium
- Phosphorus
- Chloride
- Blood urea nitrogen (BUN)
- Uric acid
- ALP
- Creatinine
- Carbon dioxide
- Total bilirubin
- Lactate dehydrogenase (LDH)
- AST
- ALT
- Gamma-glutamyl transpeptidase (GGT)

Urinalysis

- Specific gravity
- pH
- Glucose
- Bilirubin
- Protein
- Ketones
- Microscopic examination [casts, RBCs, and WBCs]

INR will be measured at screening and on Day 1 of every treatment cycle for patients on coumadin. INR is to be between 2 to 3. If a patient's INR is outside this range, then the anticoagulant dose should be adjusted (see Section 5.6.1).

Clinical laboratory evaluations are to be repeated as necessary during treatment at a schedule determined by the Investigator, based on the patient's clinical status.

Laboratory abnormalities that are considered by the Investigator to be clinically significant for a particular patient at screening, and before study drug administration on C1D1 are to be reported as part of the patient's medical history.

6.1.7.2. Screening Serology

A blood sample for serology, including Hepatitis B surface antigen (HBsAg), HCV, and HIV, is to be collected from all patients at screening.

6.1.7.3. Pregnancy Testing and Counseling

POMALYST REMS™ Program (United States)

A FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Pregnancy tests (serum or urine test with a sensitivity of at least 25 mIU/mL) must occur 10 to 14 days and again within 24 hours prior to initiation of study drug. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of study drug and at Day 28 following the last dose of study drug. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14 days while on therapy (including breaks in therapy), at discontinuation of study drug and at Day 14 and Day 28 following the last dose of study drug (see Appendix 9.3). FCBP must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, intrauterine device [IUD], hormonal birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap.

All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. For additional requirements of the POMALYST REMS™ Program regarding pregnancy testing, counseling, and acceptable methods of birth control, see Appendix 9.4.

RevAid® Program (Canada)

A FCBP is any female patient who: 1) is still menstruating; or 2) who is amenorrheic from previous chemotherapy treatments; 3) who is perimenopausal.

FCBP must have two medically supervised negative pregnancy tests prior to the first dispensed prescription of pomalidomide. Pregnancy tests must be performed in a licensed laboratory (serum test with a sensitivity of at least 25 mIU/mL) must occur 7 to 14 days and again within 24 hours prior to initiation of study drug. The dates and results of pregnancy tests must be documented. FCBP with regular or no menstruation must have a pregnancy test weekly for the first month of treatment, monthly thereafter during treatment (or every 2 weeks if menses are irregular) and for 4 weeks after discontinuation of treatment. FCBP must use at least 2 effective methods of contraception at the same time for at least 4 weeks before starting treatment, during interruptions of treatment, for at least 4 weeks after stopping treatment.

All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. For additional requirements of the RevAid® Program regarding pregnancy testing, counseling, and acceptable methods of birth control, see Appendix 9.4.

European Pomalidomide Pregnancy Prevention

For additional information on the European Pomalidomide Pregnancy Prevention Risk Management Plans, see Appendix 9.5.

6.1.8. Adverse Events

Monitoring of AEs will be conducted throughout the study. AEs, including SAEs, will be documented in the eCRFs from Baseline (i.e., C1D1) through 30 days after treatment discontinuation. Any SAE occurring more than 30 days after the last study drug dose that is considered by the Investigator to be study drug-related should also be reported. AEs that lead to study discontinuation should be followed until resolution or stabilization. SAEs will be assessed until 30 days after study treatment discontinuation.

6.1.8.1. Definitions, Documentation, and Reporting

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

Disease progression is not to be reported as an AE.

An SAE is any AE, occurring at any dose and regardless of causality that:

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

6.1.8.2. Pregnancy

Female Patients

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on Investigational Product (IP), or within at least 28 days of the patient's last dose of study drug, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the INC Safety Monitor immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female patient until completion of the pregnancy, and must notify the INC Safety Monitor immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to the INC Safety Monitor immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to the INC Safety Monitor immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Contact Information

INC 24 Hour SAE Reporting
E-mail: [redacted]
Fax: [redacted]

Male Patients

If a female partner of a male patient taking IP becomes pregnant, the male patient taking the IP should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately.

6.1.8.3. Second Primary Malignancies

Second primary malignancies will be monitored as events of interest and must be reported as SAEs. This includes any second primary malignancy, regardless of causal relationship to study drug (ACY-1215, pomalidomide, dexamethasone), occurring at any time for the duration of the study, from the time of signing the informed consent up to the time all patients have been followed for at least 1 year from discontinuation or have died. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

6.1.8.4. Procedures for AE and SAE Reporting

Each patient must be carefully monitored for the development of any AEs. 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 AEs (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 eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. All pomalidomide and dexamethasone AEs must be reported in accordance to the safety guidelines presented in the prescribing information.[51,58,59,60]

All SAEs that occur during the course of the study must be reported by the Investigator to the 24-hour Safety Reporting line (see below) and entered into electronic data capture (EDC) **within 1 working day** from the point in time when the Investigator becomes aware of the SAE.

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 IRB/IEC 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.

For both serious and non-serious AEs, the Investigator must determine both the intensity of the event and the relationship of the event to study drug administration.

Severity of AEs will be assessed by the Investigator according to the NCI CTCAE, Version 4.0 (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.). If the AE is not included in the CTCAE, Version 4.0, then the Investigator is to determine the intensity of the AE according to the following criteria:

Mild (Grade 1):	AE that disappears or is easily tolerated on continuation of study drug.
Moderate (Grade 2):	AE sufficiently discomforting to cause interference with usual work activities.
Severe (Grade 3):	AE that is incapacitating, with inability to work or perform daily activities.
Life-Threatening (Grade 4):	AE that is *potentially* life-threatening.[2]

If the severity (Grade) changes within a day, the maximum intensity (Grade) should be recorded. If the intensity (Grade) changes over a longer period of time, the changes should be recorded as separate events (having separate onset and stop dates for each grade).

[2] If a life-threatening (Grade 4) AE is *immediately* life-threatening, the event is, by definition, serious and is to be reported as described in Section 6.1.8.4.

Relationship to study drug administration will be determined by the Investigator according to the following criteria:

Unrelated:	There is little or no chance that the study drug caused the AE; other conditions, including concurrent illnesses, progression, or expression of the disease state, or a reaction to a concomitant medication best explain the event.
Possible:	The association of the AE with the study drug is unknown; however, the AE is not clearly due to another condition.
Probable:	A reasonable temporal association exists between the AE and treatment administration and, based on the Investigator's clinical experience, the association of the AE with the study treatment seems likely.

For the purpose of safety analyses, all AEs that are classified as possible or probable will be considered treatment-related events.

Reporting to the Sponsor

All SAEs must be reported to Acetylon whether or not considered causally related to the study drug. SAE event forms, created specifically by Acetylon, 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 Acetylon.

Contact Information

INC 24 Hour SAE Reporting
E-mail: [redacted]
Fax: [redacted]

6.1.8.5. Follow-Up of Adverse Events

The Investigator must continue to follow all SAEs and non-serious AEs considered to be at least possibly related to study drug either until resolution or the Investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

6.1.8.6. Reporting Safety Information

The Investigator must promptly report to his or her IRB/IEC all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs reasonably or possibly associated with the use of study drug.

6.1.8.7. Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. The Investigator or other physician in attendance in such an emergency must contact the Medical Monitor as soon as possible to discuss the circumstances of the emergency.

The Medical Monitor, in conjunction with the Investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be documented in the eCRF.

6.2. Efficacy Measurements

The following section describes the efficacy assessments that will be obtained during the study. All assessments collected on the same day as study drug administration must be collected before study drug is administered. In order to assess response to treatment, M-protein component is to be measured in serum and urine. FreeLite™ testing is to be performed and, as applicable, bone marrow aspirate and biopsies, and appropriate imaging studies (e.g., [CT], MRI) are to be performed.

Clinical laboratory tests of efficacy assessments are to be performed locally. In addition, a central laboratory will analyze duplicate samples of serum immunoglobulin levels, SPEP and UPEP of M-protein levels, serum and urine IFE studies, and FreeLite™ Testing. A bone marrow aspirate sample will centrally analyzed for FISH/cytogenetics. Results from the central efficacy analysis will not be shared with sites.

In the event of study treatment discontinuation for reasons other than PD, all patients will continue to be followed for efficacy assessments (assessment of response, extramedullary plasmacytoma assessment, quantitative serum immunoglobulin levels, SPEP and UPEP of M-protein levels, IFE, and SFLC) until the development of PD, or initiation of an alternate MM therapy.

6.2.1. Myeloma Protein Measurements and Serum Immunoglobulins

Serum-M protein levels (quantified from the SPEP test), urine M-protein levels (quantified from the UPEP test performed on 24-hour urine collection), and quantitative serum immunoglobulin levels will be obtained at screening, at Day 1 of each treatment cycle, PD, and at treatment discontinuation. Serum and urine IFE tests are to be performed at screening to identify the immunoglobulin subtype of MM and thereafter, will be performed by the central laboratory whenever M-protein is undetectable in both SPEP and UPEP studies to confirm CR. Response will be assessed using the IMWG criteria (see Appendix 9.5).

6.2.2. FreeLite™ Testing

Serum samples for FreeLite™ testing (serum FLCs) are to be collected from all patients at screening, on Day 1 of every treatment cycle, PD, and at treatment discontinuation.

6.2.3. Bone Marrow Examination

A bone marrow aspirate is to be performed at screening and when clinically indicated at the discretion of the treating physician. A biopsy is needed only if the marrow is unable to be aspirated. A bone marrow aspirate sample collected at screening will be sent for central cytogenetic and FISH analysis.

6.2.4. Skeletal Survey and Other Imaging Studies

Skeletal surveys (Appendix 9.9), are to be performed at screening (or within 60 days of Study Day 1), at treatment discontinuation, when clinically indicated, and to confirm CR.

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

6.2.5. Extramedullary Plasmacytoma Assessments

Assessment/measurement required only if present or if clinically indicated. Plasmacytomas that can be assessed clinically are to be assessed every cycle. Plasmacytomas that are assessed by radiography will be assessed at screening, every cycle, at study treatment discontinuation, and to assess best response.

6.2.6. Assessment of Disease Response

Assessment of response will include measurement of serum M-protein by SPEP and UPEP, SFLC analysis (see Section 6.2.2) and immunofixation studies. Objective response, as assessed by site Investigators using the recently revised IMWG criteria has been chosen as the primary endpoint for this study. The IMWG criteria were developed by the International Myeloma Working group in order to provide uniform reporting requirements for studies conducted in MM and to enable consistent comparison of results across studies. Based on the EBMT, IMWG criteria have been expanded, clarified, and updated to provide a new comprehensive evaluation system to assess not only response but also the magnitude of response, length of response, and OS, (Appendix 9.5). Use of the IMWG criteria, the international standard for the assessment of response for MM studies, will ensure that data across all centers is evaluated consistently. Response will be assessed every cycle throughout study drug treatment, and at treatment discontinuation in both the Phase 1b and Phase 2 segments of the study. In addition to the site Investigators, an Independent Central Adjudication Committee will review the myeloma response data (i.e., laboratory data and radiographic data) to determine response to treatment and dates of PD for each study patient. Determination of PD requires two consecutive assessments of disease progression. There is no specific requirement for the timing of these two assessments.

Additional secondary endpoints of disease response will include TTR, DOR, TTP, and PFS. In addition, central laboratory data will be employed to maintain consistency in evaluation of efficacy endpoints.

Overall response rates utilizing either or both criteria will be reported in the clinical study report. Response to treatment will also be blindly assessed by the Central Adjudication Committee using IMWG criteria and dates of PD.

6.2.7. Survival

All patients will be followed for survival for up to 1 year. Patients will be assessed 3 times per year (approximately every 4 months) to determine survival status. Cause of death is to be recorded in the CRF and the patient's medical record

6.3. Pharmacokinetic Measurements

Serial blood samples for PK assessments are to be collected from all patients during Cycle 1 of the Phase 1b and from patients at participating sites in the Phase 2 segment at the following time points:

- Phase 1b, C1D1: pre-dose, 0.5, 1, 2, 4, and 6 hours post dose
- Phase 1b, C1D2: 24 hours post dose
- Phase 1b, C1D8: pre-dose, 0.5, 1, 2, 4, and 6 hours post dose
- Phase 2, C1D1: pre-dose, 0.5 and 1 hour post dose
- Phase 2, C1D22: 24 hours post morning dose of Day 21,
- Phase 2, Day 1 of Cycles 2-6, at least 1 hour post dose

The date and time of the patient's most recent meal before the start of blood sample collection on each scheduled collection day and the date and time of each blood sample collection is to be documented in the eCRF on days that PK samples are drawn.

PK samples should be collected as close to the scheduled time as possible: ≤ 1 hour before drug administration, ±5 minutes through 6 hours post dose and ±1 hour at the 24 hour post dose. If deviations in timing occur, the timing of the sample collection should be clearly marked.

6.4. Pharmacodynamic Assessments

Blood samples for pharmacodynamic assessments are to be collected from all patients during Cycle 1 of the Phase 1b segment at the following time points:

- Phase 1b, C1D1: pre-dose, 0.5, 1, 2, 4, and 6 hours post dose
- Phase 1b, C1D2: 24 hours post dose

All details regarding handling and shipping of these samples will be provided in the Laboratory Procedures Manual.

7. STATISTICAL PROCEDURES

7.1. Sample Size Estimation

Phase 1b (MTD):

Using a 3+3 design, the total number of patients required for the MTD phase will range from 9 to 30.

Phase 2:

The reference response rate is assumed to be 0.29. For a study with a sample size of 66, a one-sided 0.05 level test with power of 80% would be adequate to detect the response rate of 0.29 against 0.44. Assuming a 10% drop out rate, a study of 75 patients would be sufficient. In order to have a robust study, a single interim analysis will be conducted when there are 30 evaluable patients. The SRC will use the totality of information from the interim analysis to recommend whether the study should proceed as planned, be terminated for superiority or futility, or extended to allow for 86 evaluable patients. Assuming a 10% dropout rate, a study with n=95 would be sufficient.

7.2. Probability of Dose Escalation

Table 11 displays the probabilities of dose escalation for any stage during the MTD determination, as a function of a given underlying DLT rate at the current dose level.

Table 11 Probabilities of Dose Escalation

Underlying DLT Rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Dose Escalation	91%	71%	49%	31%	17%	8%	3%	1%	0.1%

7.3. Populations for Analysis

For both Phase 1 (MTD) and Phase 2 (Open-label Treatment):

- Safety Population – all patients who receive at least 1 dose of study medication.
- Intent-to-Treat (ITT) Population – all patients.
- Efficacy Evaluable (EE) Population – all patients who meet eligibility criteria, receive at least 14 doses of study drug (i.e., ACY-1215, pomalidomide and low-dose dexamethasone) at the MTD, and have at least one post-baseline efficacy assessment. Safety analyses will be performed on the Safety Population, defined as all patients who receive at least 1 dose of study medication.

7.4. 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.

7.5. Analysis Schedule

7.5.1. Interim Analysis

The interim analysis with the first 30 evaluable patients will be conducted using a one-sided 95% CI estimate for the response rate. If the lower bound of the 95% CI estimate with the 30 patients is ≥ 29%, the SRC may recommend either terminating the study at the interim based on treatment superiority, or continuing the study as planned. If the lower bound is < 29%, various predicted lower bounds of one-sided 95% CIs for the response rate will be constructed to further guide the SRC's recommendation. For example, assuming a true response rate of 44% for the remaining 36 patients, the expected lower bound of one-sided 95% CI with 66 evaluable patients will be calculated. If the expected lower bound is ≥ 29%, the SRC may recommend continuing the study as planned. If the expected lower bound with 66 evaluable patients is < 29%, another simulation will be run with 86 evaluable patients. If the resulting lower bound is acceptable (e.g., close to or ≥ 29%), the SRC may recommend expanding the sample size by 20 patients. If the resulting lower bound is not acceptable (e.g., < 29%), the SRC may recommend terminating the study for futility. In addition, the expected lower bound of the one-sided 95% CI when the true response rate is equal to the observed value at the interim analysis will be calculated. The resulting scenario will be similar to the previous one: if the expected lower bound is ≥ 29%, the SRC may recommend continuing the study as planned, if the lower bound is < 29%, the SRC may recommend expanding the sample size by 20 patients. Additional simulations with other possible response rates (for example, assuming a 40% response rate), with or without adaptation, will also be conducted; the SRC will review all simulation results to make a recommendation at the interim. Furthermore, with the potential

adaptations at the interim, we find via an extensive simulation study the final CI estimate would have the accurate coverage level. Therefore, no statistical penalty or adjustment will be needed for the final inferential statistical procedure for the response rate.

7.5.2. Final Analysis

A final analysis is planned after all enrolled patients either complete 6 cycles of study treatment, at treatment discontinuation, or withdraw early from the study.

7.5.3. Addendum

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

7.6. Statistical Methods

7.6.1. General Methods

Statistical analyses will be primarily descriptive in nature, since the goal of the study is to determine the DLT, MTD, and recommended dose of ACY-1215 in combination with pomalidomide and dexamethasone for further investigation. This goal will be achieved by the results of a deterministic algorithm; thus, statistical hypothesis testing is neither intended nor appropriate within this context.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification. Graphical displays will be provided where useful in the interpretation of results.

7.6.2. 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 by dose cohort. Reasons for discontinuation that are the basis for DLT will be categorized in distinction from other reasons for discontinuation.

7.6.3. Demographics and Baseline Characteristics

The baseline (C1D1) characteristics of patients enrolled in each dose cohort, the Phase 1b MTD segment and the Phase 2 segment, will be summarized. An accounting will be made of the study course for all patients who received study drug for each dose cohort and, in particular, the number of patients who died or withdrew during treatment will be specified and reasons for withdrawal categorized. Study drug administration will be summarized for each dose cohort. Information on dose reductions will be summarized.

7.6.4. Extent of Exposure

Descriptive statistics for patients treated in and completing every treatment cycle, including the number of doses missed or held and dose reductions required, will be presented for every 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.

7.6.5. 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 tabulated in a data listing.

7.6.6. Safety Analysis

Safety data for the Phase 1b MTD segment will be summarized when all patients have completed the first 28-day cycle (Cycle 1). Safety data for the Phase 2 segment, as well as for patients from the Phase 1b segment who continued treatment following the completion of the first cycle, will be analyzed when all patients have completed 48 weeks of the study or have discontinued from the study.

Safety evaluations will be based on the incidence, intensity, and type of AEs, and changes in the patient's physical examination findings, vital signs, ECG findings, and clinical laboratory results. All patients who received at least one dose of study drug will be included in the safety analysis. Summarization will focus on occurrence rates of: any SAEs; treatment-emergent AEs by system organ class (SOC) and preferred term; discontinuation rates of study therapy due to AE or toxicity based on clinical laboratory assessment and rates of hematologic toxicity. The frequency of DLT by dose cohort also will be summarized.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All AEs occurring on study will be listed in by-patient data listings. Treatment-emergent events will be tabulated, where treatment-emergent is defined as any AE 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 AEs by maximum severity.

Deaths, SAEs and AEs resulting in study discontinuation will be tabulated. AEs leading to dose reduction or interruption will also 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, ANC, ALC, 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 BP, heart 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.

ECOG performance status will be summarized for changes from Baseline to treatment discontinuation; ECOG performance status on Day 1 of every 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.

7.6.7. Efficacy Analysis

Efficacy analysis will be performed on both the ITT Population and EE Population. The ITT Population will include all patients, and the EE Population will include all patients who meet eligibility criteria, receive at least 14 doses of study drug (i.e., ACY-1215, pomalidomide and low-dose dexamethasone), and have at least 1 post-baseline efficacy assessment. The primary analysis will be based on the EE population, and will use the Investigator-assessed response data evaluated according to consensus recommendations based on the IMWG criteria. Response rate will be percent of patients who achieve at least partial response (PR) at the recommended Phase 2 dose. Percent of patients achieving MR or better will also be collected as clinical benefit response. PFS will be defined as the time from first dose of study treatment to the first documentation of PD or death from any cause during study. Overall survival (OS) will be defined as the time from first dose of study treatment to death from any cause. For responders, TTR and response duration will be analyzed. TTR will be defined as the time from first dose of study treatment to the first documentation of response (either PR or CR). DOR will be defined as the time from the first PR or CR to the first documentation of PD or death, whichever occurs earlier.

For data obtained from patients treated at doses of ACY-1215 not selected as the MTD, a case-by-case description of myeloma response (per IMWG criteria) will be provided. For the 12 patients who initiate ACY-1215 at the recommended Phase 2 dose level, response rates together with confidence intervals will be provided. Kaplan-Meier curves will be used to characterize the time-to-event curves (PFS, OS, response duration) when there is censoring; univariate summary statistics will be provided for TTR.

For the Phase 2 segment, a 0.95 confidence interval for the response rate will be constructed for evaluating the efficacy of ACY-1215. Kaplan-Meier curves will be constructed to characterize PFS, OS, and DOR. One sample standard inferences for PFS, OS and DOR will be made accordingly.

7.6.8. Pharmacokinetic Analysis

Study drug serum concentrations of ACY-1215 and pomalidomide will be determined at all pre- and post-dose time-points as specified in the Schedule of Assessments (Table 1). Parameters to be calculated based on a non-compartmental model approach will include C_{max}, T_{max}, $AUC_{0\text{-}last}$, AUC from time zero to infinity ($AUC_{0\text{-}\infty}$), and $t_{1/2}$. ACY-1215 and pomalidomide serum levels and non-compartmental PK parameters will be tabulated by dose cohort using descriptive statistics. Tabulated single- and multiple-PK dose results will be presented.

7.6.9. Pharmacodynamic Analysis

The fold change between pre- and post-dose time points in the levels of acetylated histones and acetylated tubulin will be determined in PBMCs. The resulting data may be used to generate a PK/pharmacodynamic model(s) of the relationship of changes in acetylated histones and/or tubulin with the plasma levels of ACY-1215 over time. A summary report will be generated of the pharmacodynamic analysis and results from PK/pharmacodynamic modeling.

7.6.10. 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.

8. ADMINISTRATIVE REQUIREMENTS

8.1. 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.

8.2. Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (Appendix 9.10). The IRB/IEC 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/IEC 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/IEC by the Investigator.

8.3. 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).

8.4. Patient Confidentiality

In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient according to local or regulatory authority(ies). 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 documented in the eCRFs 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.

8.5. Protocol Compliance

The Investigator will conduct the study in compliance with the protocol provided by Acetylon, and given approval/favorable opinion by the IRB/IEC 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/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC 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/IEC. 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 Sponsor or designee, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the eCRF and source documentation.

8.6. Direct Access to Source Data

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

The study will be monitored by Acetylon or its designee. Monitoring will be done by personal visits from a representative of the Sponsor (site monitor) and will include on-site review of the eCRFs 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 (see Section 5.5).

Regulatory authorities, the IRB/IEC, and/or Acetylon's clinical quality assurance group may request access to all source documents, eCRFs, 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.

8.7. Case Report Form Completion

The Sponsor or designee will provide the study centers with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient dosed in the study. It is the Investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

The Sponsor or designee will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disk or other electronic media will be placed in the investigator's study file.

8.8. Record Retention

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). The Sponsor must be notified in writing if a custodial change occurs.

8.9. 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.

8.10. 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 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.

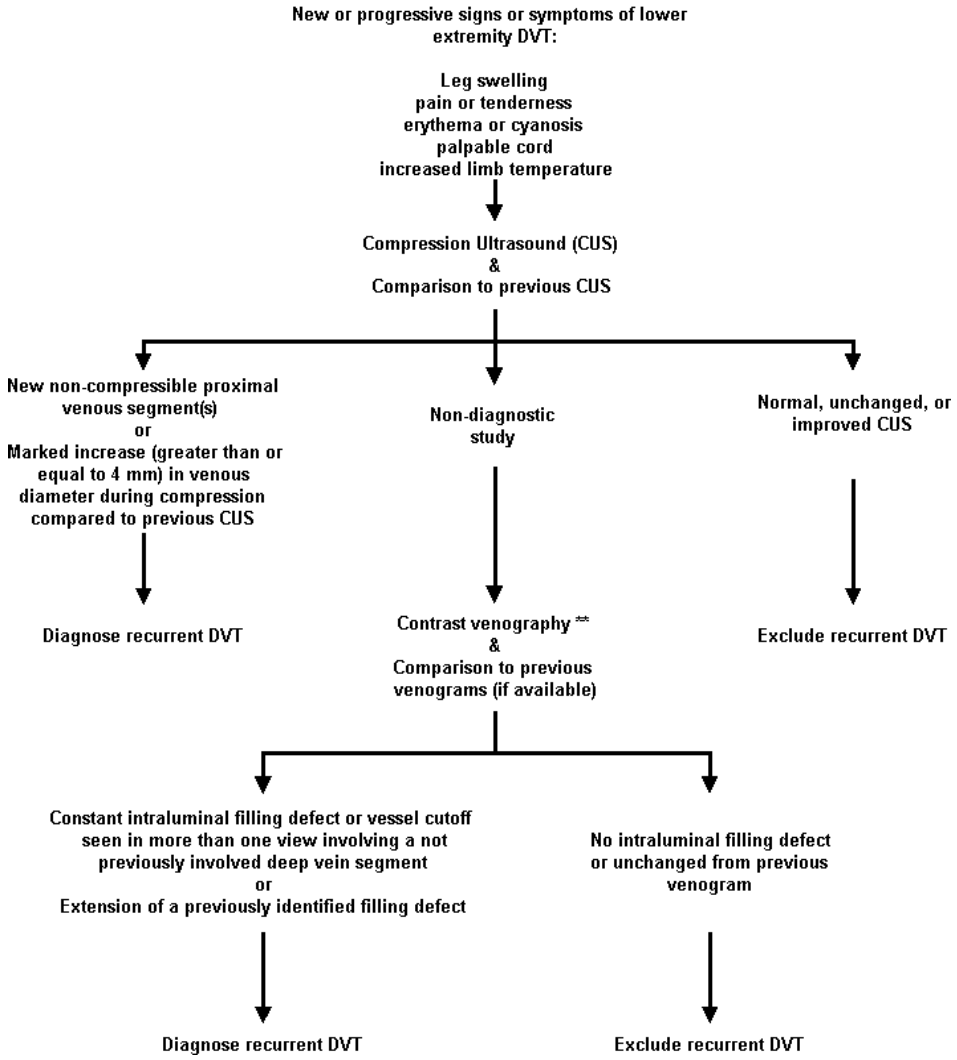
It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer reviewed scientific or medical journal. A Publications Committee, comprised of Investigators participating in the study and representatives from Acetylon, as appropriate, will be formed 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.

9. APPENDICES

9.1. VTE Algorithms

Diagnostic Algorithm for Patients with Clinically Suspected Recurrent Lower Extremity DVT



**** if significant renal insufficiency, contrast allergy, or patient refusal of invasive procedures precludes performance of contrast venography, then a positive finding on serial compression ultrasound of the leg can be accepted as diagnostic of recurrent DVT and PE**

9.2. 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.

9.3. POMALYST REMS™ Program (United States)

The full prescribing information, Pregnancy Testing Guideline and Pregnancy Risk Minimization Plan for FCBP and male patients in the US taking pomalidomide can be accessed using the following web link:

http://www.pomalystrems.com/

9.4. RevAid® Complete Guide for Health Care Practitioners (Canada)

The full prescribing information, Pregnancy Testing Guideline and Pregnancy Risk Minimization Plan for FCBP and male patients in Canada taking pomalidomide can be accessed using the following web link:

https://www.revaid.ca/revaid/

9.5. European Pomalidomide Pregnancy Prevention Risk Management Plans

9.5.1. Pregnancy Prevention Risk Management Plans

9.5.1.1. Pomalidomide (CC-4047) Pregnancy Prevention Risk Management Plan

9.5.1.1.1. Pomalidomide Pregnancy Risk Minimization Plan for Celgene Clinical Trials

Appendix 9.5 applies to all EU patients receiving pomalidomide therapy. The following Pregnancy Risk Minimization Plan documents are included in this Appendix:

1. Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods (Section 9.5.1.1.2);
2. Pomalidomide Education and Counselling Guidance Document (Section 9.5.1.1.3);
3. Pomalidomide Information Sheet (Section 9.5.1.1.4).

1. The Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods document (Section 9.5.1.1.2) provides the following information:
    - Potential risks to the fetus associated with pomalidomide exposure
    - Definition of Female of Childbearing Potential (FCBP)
    - Pregnancy testing requirements for patients receiving pomalidomide who are females of childbearing potential
    - Acceptable birth control methods for both female of childbearing potential and male patients receiving pomalidomide in the study
    - Requirements for counselling of all study patients receiving pomalidomide about pregnancy precautions and the potential risks of fetal exposure to pomalidomide
2. The Pomalidomide Education and Counselling Guidance Document (Section 9.5.1.1.3) must be completed and signed by either a trained counselor or the Investigator at the participating clinical center prior to each dispensing of pomalidomide study treatment. A copy of this document must be maintained in the patient records.
3. The Pomalidomide Information Sheet (Section 9.5.1.1.4) will be given to each patient receiving pomalidomide study therapy. The patient must read this document prior to starting pomalidomide study treatment and each time they receive a new supply of study drug.

9.5.1.1.2. Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-

threatening human birth defects. If Pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counselling

For a female of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol (Section 9.5.1.1.2)
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

- Comply with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male patients taking pomalidomide must meet the following conditions (ie, all males must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential

- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

Contraception

Females of childbearing potential (FCBP) enrolled in this protocol must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment discontinuation.

The two methods of reliable contraception must include one highly effective method and one additional effective (barrier) method. FCBP must be referred to a qualified provider of contraceptive methods if needed. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
- Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to another one of the effective methods listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the

start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counselling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counselling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

- Counselling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.

- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

9.5.1.1.3. Pomalidomide Education and Counselling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____DOB: _____/_____/_____(mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: ☐

If female, check one:

☐ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)

☐ NOT FCBP

Male: ☐

Do Not Dispense study drug if:

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counselled FCBP regarding the following:
   - Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception
   - Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:

- Highly effective methods:
  - Intrauterine device (IUD)
  - Hormonal (birth control pills, injections, implants)
  - Tubal ligation
  - Partner's vasectomy
- Additional effective methods:
  - Male condom
  - Diaphragm
  - Cervical Cap

- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counselled the female NOT of childbearing potential regarding the following:
   - Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules
   - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the patient.

MALE:

1. I counselled the Male patient regarding the following:
   - Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not donate semen or sperm while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____
(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____
(circle applicable)

Maintain a copy of the Education and Counselling Guidance Document in the patient records.

9.5.1.1.4. Pomalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits. **If you are a female who is able to become pregnant:**
    - **Do not take study drug if you are pregnant or plan to become pregnant**
    - **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
        - for 28 days before starting study drug
        - while taking study drug
        - during dose interruptions of study drug
        - for 28 days after stopping study drug
    - **You must have pregnancy testing done at the following times:**
        - within 10 – 14 days and again 24 hours prior to the first dose of study drug
        - weekly for the first 28 days
        - every 28 days after the first month or every 14 days if you have irregular menstrual periods
        - if you miss your period or have unusual menstrual bleeding
        - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
    - **Stop taking study drug if you become pregnant during treatment**
        - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.
    - **Do not breastfeed while taking study drug**
        - The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

1. Male patients (including those who have had a vasectomy) must either **not have any sexual relations with a pregnant female or a female who can become pregnant,** or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking study drug
    - During dose interruptions of study drug
    - For 28 days after you stop taking study drug
2. **Male patients should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
3. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
    1. **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
    2. **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
    3. **Do not break, chew, or open study drug capsules.**
    4. You will be supplied with no more than one cycle of study drug
    5. Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

9.6. International Myeloma Working Group Response Criteria

Response Category	Response Criteria[1]
SCR	CR as defined below, plus 1. Normal FLC ratio and 2. Absence of clonal plasma cells in bone marrow by immunohistochemistry or 2 to 4-color flow cytometry
CR[2]	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤ 5% bone marrow plasma cells[b]
VGPR	Serum and urine M-protein component detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg per 24 hours
PR	1. ≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours 2. If the serum and urine M-protein are unmeasurable, a decrease ≥ 50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria 3. If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein provided baseline bone marrow plasma cell percentage was ≥ 30% 4. In addition to the above, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD	Not meeting criteria for CR, VGPR, PR, or PD
PD[3]	**Requires only one of the following:** Increase of ≥ 25% from lowest response in: 1. Serum M-component (the absolute increase must be ≥ 0.5 g/dl) and/or 2. Urine M-component (the absolute increase must be ≥ 200 mg/24 hours) and/or 3. In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dl. 4. In patients without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%). 5. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. 6. Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) that can be attributed solely to the plasma cell proliferative disorder.
Clinical relapse (Not used for TTP or PFS)	**Clinical relapse requires one or more of:** 1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 11.5 mg/dl [2.875 mmol/L]) 4. Decrease in hemoglobin of ≥ 2 g/dl (1.25 mmol/L) 5. Rise in serum creatinine by 2 mg/dl or more (≥ 177 mmol/L) 6. Hyperviscosity

1 All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed.

VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-protein component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

2 Clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels

3 Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

Source: adapted from Rajkumar et al, 2011 [50]

9.7. European Group for Blood and Bone Marrow Transplantation: Definition of Minimal Response

Minimal Response (MR) requires all of the following:

1. 25–49% reduction in the level of the serum monoclonal paraprotein maintained for a minimum of 6 weeks.
2. 50–89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 h, maintained for a minimum of 6 weeks.
3. For patients with non-secretory myeloma only, 25–49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
4. 25–49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
5. No increase in the size or number of lytic bone lesions lesions (development of a compression fracture does not exclude response).

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements.

No Change (NC)

1. Not meeting the criteria of either MR or PD.

Plateau

1. Stable values (within 25% above or below value at the time response is assessed) maintained for at least 3 months.

Time point for assessing response

1. Response to the transplant procedure will be assessed by comparison with results immediately prior to conditioning.
2. If transplant is part of a treatment programme response to the whole treatment programme will be assessed by comparison with the results at the start of the programme.

Source: adapted from Bladé et al, 1998 [61]

9.8. Eastern Cooperative Oncology Group (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

Source: adapted from Oken et al, 1982 [62]

9.9. Skeletal (Bone) Survey Films

The following are the minimum plain radiological films required for the skeletal (bone) survey:

1. Lateral skull
2. AP and lateral cervical spine
3. AP and lateral thoracic spine
4. AP and lateral lumbar spine
5. PA chest
6. AP pelvis
7. AP upper extremities, shoulder to elbow
8. AP lower extremities, hip to knee

Other radiological films may be necessary to view symptomatic areas or known pre-existing lesions in skeletal regions not included in the films above.

9.10. Declaration of Helsinki

The Declaration of Helsinki can be found at:

http://www.wma.net/en/30publications/10policies/b3/

10. REFERENCES

1 Smith, ML, Newland AC. Treatment of myeloma. QJM 1999;92:11-14.

2 Morgan GJ. Advances in the biology and treatment of myeloma. Br J Haematology 1999;105(Suppl 1):4-6.

3 Kastrinakis N, Gorgoulis V, Foukas P, Dimopoulos M, Kittas C. Molecular aspects of multiple myeloma. Annals of Oncol 2000;11:1217-1228.

4 Mulligan, M. Myeloma and lymphoma. Semin Musculoskelet Radiol 2000;4:127-135.

5 Jemal A, Siegel R, Xu J, Ward E. CA Cancer J Clin 2010;60;277-300.

6 Musto P. The role of bisphosphonates for the treatment of bone disease in multiple myeloma. Leuk Lymphoma 1998;31:453-462.

7 Wang M, Dimopoulos MA, Chen C, Cibeira MT, Attal M, Spencer A, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med 2007;357:2123-32.

8 Lecouvet F, Malghem J, Michaux L, Maldague B, Ferrant A, Michaux J-L, et al. Skeletal survey in advanced multiple myeloma: radiographic versus MR imaging survey. Br J Haem 1999;106:35-39.

9 Van de Berg B, Lecouvet F, Michaux L, Ferrant A, Maldague B, Malghem J. Magnetic resonance imaging of the bone marrow in hematological malignancies. Eur Radiol 1998;8:1335-1344.

10 Berenson JR. New Advances in the biology and treatment of myeloma bone disease. Semin Hematol 2001;38(2, Suppl 3):15-20.

11 Kanis J, McCloskey E. Bisphosphonates in multiple myeloma. Cancer. 2000;88(12 Suppl):3022-32.

12 Durie, B. Staging and kinetics of multiple myeloma. Semin Oncol 1986;13:300-9.

13 Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia 2009;23(1):3-9.

14 Greipp P, Leong T, Bennett J, Gaillard J, Klein B, Stewart J, et al. Plasmablastic morphology-an independent prognostic factor with clinical and laboratory correlates: Eastern Cooperative Oncology Group (ECOG) myeloma trial E9486 report by the ECOG myeloma laboratory group. Blood 1998;7:2501-2507.

15 Rajkumar S, Greipp P. Prognostic factors in multiple myeloma. Hematol Oncol Clin North Am 1999;13: 1295-1314.

16 Greipp PR, San Miguel J, Durie BG, Crowley JJ, Barlogie B, Blade J, et al. International Staging System for Multiple Myeloma. J Clin Oncol 2005;23(15):3412-3420.

17 Cook R. Introduction: Multiple myeloma. J Manag Care Pharm 2008;14(7; Suppl):S4-S6.

18 Richardson PG, Weller E, Lonial S, Jakubowiak AJ, Jagannath S, Raje NS, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;5;116(5):679-86.

19 Haberland M, Montgomery RL, Olson EN. The many roles of histone deacetylases in development and physiology: implications for disease and therapy. Nat Rev Genet 2009;10(1):32-42.

20 Choudhary C, Kumar C, Gnad F, Nielsen ML, Rehman M, Walther TC, et al. Lysine acetylation targets protein complexes and co-regulates major cellular functions. Science 2009;325(5942):834-840.

21 Zhou Q, Chaerkady R, Shaw PG, Kensler TW, Pandey A, Davidson NE. Screening for therapeutic targets of vorinostat by SILAC-based proteomic analysis in human breast cancer cells. Proteomics 2010;10(5):1029-1039.

22 Mogk A, Bukau B. Cell biology: When the beginning marks the end. Science 2010;327(5968):966-967.

23 Tan J, Cang S, Ma Y, Petrillo RL, Liu D. Novel histone deacetylase inhibitors in clinical trials as anti-cancer agents. J Hematol Oncol 2010;3:5.

24 Bradner JE, West N, Grachan ML, Greenberg EF, Haggerty SJ, Warnow T, et al. Chemical phylogenetics of histone deacetylases. Nat Chem Biol 2010;6(3):238-243.

25 Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A, Yao TP. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. Cell 2003;115(6):727-738.

26 Lee JY, Koga H, Kawaguchi Y, Tang W, Wong E, Gao YS, et al. HDAC6 controls autophagosome maturation essential for ubiquitin-selective quality-control autophagy. EMBO J 2010;29(5):969-980.

27 Boyault C, Zhang Y, Fritah S, Caron C, Gilquin B, Kwon SH, et al. HDAC6 controls major cell response pathways to cytotoxic accumulation of protein aggregates. Genes Dev 2007;21(17):2172-2181.

28 Bali P, Pranpat M, Bradner J, Balasis M, Fiskus W, Guo F, et al. Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: a novel basis for antileukemia activity of histone deacetylase inhibitors. J Biol Chem 2005;280(29):26729-26734.

29 Gao Z, Garcia-Echeverria C, Jensen MR. Hsp90 inhibitors: clinical development and future opportunities in oncology therapy. Curr Opin Drug Discov Devel 2010;13(2):193-202.

30 Hideshima T, Richardson P, Chauhan D, Palombella VJ, Elliott PJ, Adams J, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res 2001;61(7):3071-3076.

31 LeBlanc R, Catley LP, Hideshima T, Lentzsch S, Mitsiades CS, Mitsiades N, et al. Proteasome inhibitor PS-341 inhibits human myeloma cell growth in vivo and prolongs survival in a murine model. Cancer Res 2002;62(17):4996-5000.

32 Hideshima T, Bradner JE, Chauhan D, Anderson KC. Intracellular protein degradation and its therapeutic implications. Clin Cancer Res 2005;11(24 Pt 1):8530-8533.

33 San Miguel J et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomized, open-label, phase 3 trial. Lancet Oncol 2013; 14: 1055-66.

34 Lacy MQ, Hayman SR, Gertz MA, Dispenzieri A, Buadi F, Kumar S, et al. Pomalidomide (CC 4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma. J Clin Oncol 2009;27(30):5008-5014.

35 Lacy MQ, Hayman SR, Gertz MA, Short KD, Dispenzieri A, Kumar S, et al. Pomalidomide (CC-4047) plus low dose dexamethasone (pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (mm). Leukemia 2010;24(11):1934-1939.

36 Mazumder A, Vesole DH, Jagannath S. Vorinostat plus bortezomib for the treatment of relapsed/refractory multiple myeloma: a case series illustrating utility in clinical practice. Clin Lymphoma Myeloma Leuk 2010;10(2):149-151.

37 Catley L, Weisberg E, Kiziltepe T, Tai YT, Hideshima T, Tassone P, et al. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. Blood 2006;108(10):3441-3449.

38 Ocio EM, Vilanova D, Atadja P, Maiso P, Crusoe E, Fernandez-Lazaro D, et al. *In vitro* and in vivo rationale for the triple combination of panobinostat (LBH589) and dexamethasone with either bortezomib or lenalidomide in multiple myeloma. Haematologica 2010;95(5):794-803.

39 Badros A, Burger AM, Philip S, Niesvizky R, Kolla SS, Goloubeva O, et al. Phase I study of vorinostat in combination with bortezomib for relapsed and refractory multiple myeloma. Clin Cancer Res 2009;15(16):5250-5257.

40 U.S. National Institutes of Health. ClinicalTrials.gov. Accessible at: http://clinicaltrials.gov/. Last accessed on November 30, 2011.

41 Gore L, Rothenberg ML, O'Bryant CL, Schultz MK, Sandley AB, Coffin D, et al. A phase I and pharmacokinetic study of the oral histone deacetylase inhibitor, MS-275, in patients with refractory solid tumors and lymphomas. Clin Cancer Res 2008;14(14):4517-4525.

42 Shah MH, Binkley P, Chan K, Xiao J, Arbogast D, Collamore M, et al. Cardiotoxicity of histone deacetylase inhibitor depsipeptide in patients with metastatic neuroendocrine tumors. Clin Cancer Res 2006;12(13):3997-4003.

43 Giles F, Fischer T, Cortes J, Garcia-Manero G, Beck J, Ravandi F, et al. A phase I study of intravenous LBH589, a novel cinnamic hydroxamic acid analogue histone deacetylase inhibitor, in patients with refractory hematologic malignancies. Clin Cancer Res 2006;12(15):4628-4635.

44 de Bono JS, Kristeleit R, Tolcher A, Fong P, Pacey S, Karavasilis V, et al. Phase I pharmacokinetic and pharmacodynamic study of LAQ824, a hydroxamate histone deacetylase inhibitor with a heat shock protein-90 inhibitory profile, in patients with advanced solid tumors. Clin Cancer Res 2008;14(20):6663-6673.

45 Duvic M, Olsen EA, Breneman D, Pacheco TR, Parker S, Vonderheid EC, et al. Evaluation of the long-term tolerability and clinical benefit of vorinostat in patients with advanced cutaneous T-cell lymphoma. Clin Lymphoma Myeloma 2009;9(6):412-416.

46 Zhang Y, Kwon S, Yamaguchi T, Cubizolles F, Rousseaux S, Kneissel M, et al. Mice lacking histone deacetylase 6 have hyperacetylated tubulin but are viable and develop normally. Mol Cell Biol 2008;28(5):1688-1701.

47 Acetylon Pharmaceuticals, Inc. Investigator's Brochure for ACY-1215, Version 2.0, 24 January 2012.

48 Raje N, Mahindra A, Vogl D, Voorhees P, Bensinger W, Hari P, et al. New Drug Partner for Combination Therapy in Multiple Myeloma (MM): Phase 1 Development of ACY-1215, a Selective Histone Deacetylase (HDAC6) 6 Inhibitor Alone and in Combination with Bortezomib or Lenalidomide. Haematologica June 1 2013; 98 (supplement 1): 765/p.320.

49 Raje N, Hari P, Vogl DT, Jagannath S, Orlowski RZ, Supko JG, et al. Rocilinostat (ACY-1215), a Selective HDAC6 Inhibitor, Alone and in Combination with Bortezomib in Multiple Myeloma:

50 Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011. 117: 4691-4695.

51 POMALYST® (pomalidomide) prescribing information (United States). Celegne Corporation, 2013.

52 Quayle SN, Tamang D, Yang M, Jones SS. ACY-1215, a selective inhibitor of HDAC6, synergizes with immunomodulatory drugs (IMiDs) to induce apoptosis of multiple myeloma (MM) cells. American Association for Cancer Research Annual Meeting, San Diego, CA, Apr 5-9, 2014.

53 Quayle SN, Jones SS. ACY-1215, a first-in-class selective inhibitor of HDAC6, demonstrates significant synergy with immunomodulatory drugs (IMiDs) in preclinical models of multiple myeloma (MM). American Society of Hematology Annual Meeting, New Orleans, LA, Dec 7-10, 2013.

54 Ahn C. An evaluation of phase I cancer clinical trial designs. Statistics in Medicine 1998;17(14):1537-1549.

55 Gatsonis C, Greenhouse JB. Bayesian methods for phase I clinical trials. Stat Med 1992;11(10):1377-1389.

56 Dillman RO, Koziol JA. Phase I cancer trials: limitations and implications. Mol Biother 1992;4(3):117-121.

57 Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in Phase 1 cancer trials. 2009;101(10):708-720.

58 PrPOMALYST™ (pomalidomide) prescribing information (Canada). Celegne Corporation, 2014.

59 Imnovid (pomalidomide) summary of product characteristics (EU). Celgene Europe Limited, 2013.

60 Dexamethasone Prescribing Information. Roxane Laboratories, Inc., September 2007.

61 Bladé J1, Samson D, Reece D, Apperley J, Björkstrand B, Gahrton G, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. Br J Haematol 1998;102(5):1115-23.

62 Oken, MM, Creech, RH, Tormey, DC, Horton, J, Davis, TE, McFadden, ET, Carbone, PP: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5(6):649-655.

SUMMARY OF PROTOCOL CHANGES

CLINICAL STUDY PROTOCOL
Protocol ACE-MM-102
EudraCT Number: 2014-002338-29

A phase 1b/2 multi-center, open label, dose- escalation study to determine the maximum tolerated dose, safety, and efficacy of ACY-1215 (ricolinostat) in combination with pomalidomide and low-dose dexamethasone in patients with relapsed-and-refractory multiple myeloma

Prior Protocol Version: Amendment 3: 09 February 2015

New Protocol Version: Amendment 4: 12 July 2016

I. SUMMARY OF SIGNIFICANT CHANGES

Changes included in Amendment 4, from Protocol Amendment 3 ACE-MM-102 (dated 09 February 2016), are itemized below and detailed in Section II:

- Protocol version.
- Clerical change in Study Personnel.
- Clarification for Duration of Survival Follow-up

II. DETAILED TABLE OF CHANGES

Protocol Item	Location of Changes	Description of Changes in Amendment 4, 20 July 2016	Rationale for Change
Protocol Version	• Cover Page • Page Header and Footer	(additions are shown in bold): The protocol version was updated from Amendment 3 (09 February 2015) to **Amendment 4 (12 July 2016)**.	Administrative Change.
Length of follow-up to monitor survival, subsequent anti-myeloma therapies, and incidence of second primary malignancy (SPM)	• Study Design (p.9) • 3.1 Overall Design and Plan of the Study (p. 47)	Upon discontinuation from study treatment for PD or any other reason, patients will be assessed 3 times per year (e.g., April, August, and December), for a period of ~~5~~1 year~~s~~, for survival, subsequent anti-myeloma therapies, and monitoring of second primary malignancies as outlined in Table 1: Schedule of Assessments. . Investigators are to report any second primary malignancies as SAEs regardless of causal relationship to study drugs, occurring at any time for the duration of the study, from the time of signing the informed consent up to the time all patients have been followed for at least 1~~5~~ year~~s~~ from randomization or have died.	An initial concern with the use of pomalidomide by Celgene was the possibility of secondary primary malignancies occurring in this population, mainly due to the structural similarities with lenalidomide. However, extensive research and tracking during commercial use of pomalidomide has shown no increased frequency of secondary primary malignancies with pomalidomide use over time. Therefore, we are reducing the follow-up period from 5 years to one year post-treatment discontinuation.
	• Table 1 . Schedule of Assessments (SOA) Footnote 3 (p.24)	Patients will be followed 3 times per year, for ~~up to~~ a period of ~~5~~ 1 year~~s~~, for survival, subsequent anti-myeloma therapies, and monitoring of second primary malignancy. Subsequent therapies should be collected until death or the end of the 1~~5~~ year~~s~~ follow-up period. Survival follow-up may be done via phone.	As above
	• Table 1 . Schedule of Assessments (SOA) Footnote 21 (p.25) • 6.1.8.3 SPMs (p. 76)	Second primary malignancies will be monitored as events of interest and must be reported as SAEs regardless of the dose cohort the patient is in. This includes any second primary malignancy, regardless of causal relationship to study drug (ACY-1215, pomalidomide, dexamethasone), occurring at any time for the duration of the study, from the time of signing the informed consent up to the time all patients have been followed for at least 1~~5~~ year~~s~~ post the 30 day discontinuation visit ~~from randomization~~ or have died. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no	As above

		other serious criteria apply; these events must also be documented in the appropriate page(s) of the case report form (CRF) and patient's source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as an SAE (e.g., any confirmatory histology or cytology results, X-rays, computed tomography [CT] scans, etc.).	
	• 6.2.7 Overall Survival (p. 80)	All patients will be followed for survival for up to ~~5~~ 1year~~s~~. Patients will be assessed 3 times per year (approximately every 4 months) to determine survival status. Cause of death is to be recorded in the CRF and the patient's medical record.	As above

Summary of Changes
Clinical Study Protocol ACE-MM-102
Amendment 3 (09 February 2015)

A Phase 1b/2 Multicenter, Open Label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of ACY-1215 (Ricolinostat) in Combination with Pomalidomide and Low-dose Dexamethasone in Patients with Relapsed-and-Refractory Multiple Myeloma

I. One substantive change was made to the protocol, as follows:

- Identification of the ACY-1215 dose regimen to be utilized in the Phase 2 segment of the study (i.e., 160 mg by mouth [PO] once daily [QD] on Days 1 to 21 of a 28-day cycle).

II. One key administrative change was made to the protocol, as follows:

- The Medical Monitor was changed and applicable contact information provided.

Additionally, administrative and editorial changes were made to update information and correct typographical errors; such changes are not itemized in the following table of changes.

TABLE OF CHANGES:

Location(s) of Changes	Description of Changes in Amendment 3, 09 February 2015 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Study Personnel and Administrative Structure	The Sponsor Medical Monitor was updated as follows: [redacted] ~~Clinical Development~~ ~~Telephone:~~ [redacted] ~~Mobile telephone:~~ [redacted] ~~E-mail:~~ [redacted] ~~Fax:~~ [redacted] [redacted] **Acetylon Pharmaceuticals, Inc.** **Telephone (office):** [redacted] **office** **Telephone (mobile):** [redacted] **cell** **E-mail:** [redacted]	Administrative change.
Synopsis, Study Design	The following text was updated: ~~ACY-1215 will be given QD or twice daily (BID) at the dose and schedule determined in the Phase 1b segment of the study.~~ **Based on findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose and schedule to be administered in the Phase 2 segment will be 160 mg PO QD on Days 1 to 21 of a 28-day cycle.**	As planned, based on the findings from the Phase 1 segment of the study and as recommended by the Safety Review Committee (SRC), the ACY-1215 dose to be utilized in the Phase 2 segment has been selected.
Synopsis, Test Products, Doses, and Mode of Administration	The following text was updated: The ACY-1215 dose and schedule to be administered in **the** Phase 2 **segment** will be ~~the dose~~**160 mg PO QD on Days 1 to 21 of a 28-day cycle, as** recommended by the SRC ~~following review of the safety data from the Phase 1b segment of the study~~.	As planned, based on the findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose to be utilized in the Phase 2 segment has been selected.

Location(s) of Changes	**Description of Changes in Amendment 3, 09 February 2015** (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	**Rationale for Change**
Table 1, Schedule of Assessments	The following text was added to Footnote 22: **In the Phase 2 segment, the ACY-1215 dose and schedule is 160 mg PO QD on Days 1 to 21 of a 28-day cycle.**	As planned, based on the findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose to be utilized in the Phase 2 segment has been selected.
3.3, Rationale for the Dose and Schedule Selected	The following text was added: **Based on findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose and schedule to be administered in the Phase 2 segment will be 160 mg PO QD on Days 1 to 21 of a 28-day cycle.**	As planned, based on the findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose to be utilized in the Phase 2 segment has been selected.
5.2.1, ACY-1215	The following text was updated: **Based on findings from the Phase 1 segment of the study and as recommended by the SRC,** the ACY-1215 dose and schedule to be administered in ~~Phase 2 will be the dose recommended by the SRC following review of the safety data from the Phase 1b segment of the study. Patients in~~ the Phase 2 segment ~~of the study will receive study drug ACY-1215 either~~**will be 160 mg PO** QD ~~or BID at the dose and schedule determined in the Phase 1b segment of the study~~**on Days 1 to 21 of a 28-day cycle**.	As planned, based on the findings from the Phase 1 segment of the study and as recommended by the SRC, the ACY-1215 dose to be utilized in the Phase 2 segment has been selected.

Summary of Changes
Clinical Study Protocol ACE-MM-102
Amendment 2 (21 Aug 2014)

A Phase 1b/2 Multicenter, Open Label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of ACY-1215 (Ricolinostat) in Combination with Pomalidomide and Low-dose Dexamethasone in Patients with Relapsed-and-Refractory Multiple Myeloma

I. Substantive changes to the protocol include the following:

- The addition of European Union (EU) study sites, requiring:
  - EU pomalidomide information, including The European Pomalidomide Pregnancy Prevention Risk Management Plans (new Appendix 9.5).
  - Updated patient privacy and record retention policies inclusive of US, Canadian, and EU regions.
- Updates to study drug supply and accountability.
- Updated timing and frequency of the following assessments: Immunofixation studies, assessment of response, skeletal surveys, and extramedullary plasmacytoma assessments.
- Removal of serum thyroid function tests (TSH, T4, and T3).
- Clarification to inclusion and exclusion criteria, including:
  - The exclusion of nonsecretory myeloma and serum free light chain-only myeloma.
  - Updates to the exclusion criteria of the following laboratory abnormalities: absolute neutrophil count (ANC), platelet count, and hemoglobin values.
- Updates to dose modification instructions for pomalidomide for hematologic toxicities.
- Updates to the use of hematopoietic growth factors.
- Clarification to the definition of progressive disease.
- Incorporation of the updated Investigator's Brochure (IB) Version 5.0, including the following:
  - Information pertaining to pharmacokinetic (PK) data was updated.
  - Information pertaining to ongoing clinical studies was updated.
  - Additional nonclinical data and clinical data for ACY-1215 alone and in combination with immunomodulatory inhibitors (IMiDs).

II. Key administrative changes to the protocol include the following:

- Addition of EudraCT Number (2014-002338-29).
- Incorporation of Independent Ethics Committees for regulatory approvals.
- Updates to the list of abbreviations and references.

Additionally, administrative and editorial changes were made to update information and correct typographical errors; most of these updates are not itemized in the following table of changes.

TABLE OF CHANGES:

Location(s) of Changes	Description of Changes in Amendment 2, 21 Aug 2014 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Title Page and Clinical Synopsis Cover Page	EudraCT number was added (2014-002338-29)	Administrative addition.
Study Personnel and Administrative Structure	Sponsor contact was updated to: [redacted] Clinical Project Manager Telephone: [redacted] Fax: [redacted] Email: [redacted]	Administrative change.
Clinical Study Synopsis, Number of Study Centers	Approximately ~~15~~ **19**	To increase the number of allowed study centers.
Clinical Study Synopsis, Study Design, Phase 1b Segment, *Identification of MTD and schedule* **Section 5.2.1,** ACY-1215, Phase 1b segment	~~Patients will be treated at Dose level 3 after the highest QD dose level has been determined.~~	Updated to provide clarification.
Clinical Study Synopsis, Study Design, Phase 1b Segment, *Determination of MTD: Dose escalation rules* **Clinical Study Synopsis,** Study Design, Phase 2 Segment **Section 5.2.5,** Dose Escalation Procedure	The use of hematopoietic growth factors will not be permitted during ~~Cycle 1~~ **screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study;** however...	Updated to clarify use of hematopoietic growth factors.
Clinical Study Synopsis, Study Design, Phase 1b Segment, *Confirmation of the Safety of the MTD*	For all patients enrolled in the Phase 1b MTD segment, following the completion of Cycle 1, efficacy assessments will be conducted every **cycle** ~~2 cycles~~ for the duration of the treatment period.	Update to efficacy assessment frequency.
Clinical Study Synopsis, Diagnosis and Main Criteria for Inclusion #7 **Section 4.2,** Inclusion Criteria #8	Must have measurable levels of myeloma paraprotein in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g/24 hours). ~~Patients who do not have myeloma paraprotein must have SFLC concentration of > 10 mg/dl provided SFLC ratio is abnormal.~~ Nonsecretory myeloma **and serum free light chain-only myeloma are** ~~is~~ excluded.	Update to acceptable levels of serum paraprotein.

Location(s) of Changes	Description of Changes in Amendment 2, 21 Aug 2014 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Clinical Study Synopsis, Diagnosis and Main Criteria for Inclusion #9 **Section 4.2,** Inclusion Criteria #10	...**The European Pomalidomide Pregnancy Prevention Risk Management Plans are described in Appendix 9.5.**	Addition of EU pomalidomide information.
Clinical Study Synopsis, Exclusion Criteria #1 **Section 4.2**, Exclusion Criteria #1	Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the patient from signing the ICF, **including nonsecretory myeloma or SFLC-only myeloma**.	Addition of exclusion of nonsecretory or SFLC-only myeloma.
Clinical Study Synopsis, Exclusion Criteria #5 **Section 4.3,** Exclusion Criteria #5	Any of the following laboratory abnormalities: • ANC < 1,000/µL **(hematopoietic growth factors will not be permitted during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study).** • Platelet count ~~< 50,000/µL~~ **< 75,000/µL** for patients in whom < 50% of bone marrow nucleated cells are plasma cells~~.~~ **and < 50,000/µL for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells.** • Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion ~~or recombinant human erythropoietin use~~ is permitted)	Updated to clarify laboratory (ANC, platelet count, and hemoglobin) abnormalities.
Clinical Study Synopsis, Exclusion Criteria #13 **Section 4.3,** Exclusion Criteria #13	...**or to the European Pomalidomide Pregnancy Prevention Risk Management Plans, per Appendix 9.5.**	Addition of European (EU) pomalidomide information.
Clinical Study Synopsis, Test Products, Doses, and Mode of Administration	Acetylon will supply liquid ACY-1215 in appropriately sized vials for PO administration to investigational pharmacies. ~~Celgene will supply pomalidomide~~ **Pomalidomide will be provided at** 4, 3, 2, and 1 mg for PO administration. Sites **in the US and Canada** will utilize commercial supply of PO dexamethasone ~~and~~. **Acetylon will supply dexamethasone to sites in the European Union (EU). All sites will utilize commercial supply of** aspirin or other anti-thrombotics or anti-coagulants.	Removal of Celgene's responsibility to provide pomalidomide. Dexamethasone will be considered as an investigational medicinal product (IMP) in EU and the sponsor is required to arrange cover for the cost and supply to the EU sites.

Location(s) of Changes	Description of Changes in Amendment 2, 21 Aug 2014 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Clinical Study Synopsis, Statistical Methods	~~Equivalently, the corresponding expected one-sided 95% confidence interval (CI) for the response rate will exclude 0.29 with 80% of chance.~~ **Assuming a 10% drop out rate, a study of 75 patients would be sufficient.** …The SRC will use the totality of information from the interim analysis to recommend whether the study should proceed as planned, be terminated for superiority or futility, or extended to allow for ~~95~~**86** evaluable patients.	Update to clarify sample size estimation.
Schedule of Assessments, Immunofixation studies (serum and 24-hour urine)	Assessments were added to the following timepoints: • Cycle 1 Day 1/Baseline • Cycles 2 and on, Day 1	Update to immunofixation study assessment frequency.
Schedule of Assessments, Footnote 11	IFE studies will be performed at screening, **Day 1 of each treatment cycle,** and to confirm CR (undetectable M-protein by protein electrophoresis in urine and serum will trigger the central laboratory to perform IFE studies in urine and serum).	Update to immunofixation study assessment frequency.
Schedule of Assessments, Footnote 13	For additional information, including acceptable forms of birth control, see Appendix 9.3 for the POMALYST REMS™ program, Appendix 9.4 for the RevAid® program, **and Appendix 9.5 for the European Pomalidomide Pregnancy Prevention Risk Management Plans.**	Addition of European (EU) pomalidomide information.
Schedule of Assessments, Footnote 14	**...See Appendix 9.5 for the European Pomalidomide Pregnancy Prevention Risk Management Plans.**	Addition of EU pomalidomide information.
Schedule of Assessments, Footnote 15	Skeletal survey to be performed at Screening (or within 60 days of Study Day 1)~~, study treatment discontinuation~~ **and later,** when clinically indicated~~, and to confirm CR~~.	Update to skeletal survey assessment frequency.
Schedule of Assessments, Footnote 16	Plasmacytomas that can be assessed clinically are to be assessed every **cycle** ~~2 cycles~~.	Update to plasmacytoma assessment frequency.
Schedule of Assessments, Footnote 18	Response will be assessed every **cycle** ~~2 cycles~~ while on study drug treatment, and at study treatment discontinuation. **Screening labs do not need to be repeated at C1D1 if they have been completed within 14 days.**	Update to assessment of response frequency.
Schedule of Assessments, Footnote 25	Serial blood samples for PK assessments are to be collected from all **US and Canada** patients during Cycle 1 of the Phase 1b segment and at participating sites in the Phase 2 segment at the following time points:	Update to clarify regions for PK assessment collection.
Section 1, Introduction	A clear correlation between disease stage and survival duration has been demonstrated.[12] **The criteria for diagnosis, staging, risk stratification, and response assessment of MM, as described by Kyle and Rajkumar, has been widely used as well.[13]**	Additional reference added regarding multiple myeloma assessment.
Section 1.1, ACY-1215	Clinical experience with pomalidomide was updated to include details of Phase 1b/2, Phase 2, and Phase 3 studies.	New Phase 1b/2, Phase 2, and Phase 3 data available.
Section 1.1.2, Nonclinical Pharmacokinetics	Nonclinical pharmacokinetics text was updated to include the detection of ACY-1215 in urine and feces.	New nonclinical pharmacokinetics data available.

Location(s) of Changes	Description of Changes in Amendment 2, 21 Aug 2014 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Section 1.1.3, Toxicology	The mutagenic potential for ACY 1215 appears to be low. ACY 1215 did not exhibit mutagenic ability in ~~either~~ ***in vitro*** **assays including** the Ames test ~~or~~ **and the** Chinese hamster ovary (CHO) micronucleus test...**In addition, ACY-1215 did not exhibit mutagenic potential in the GLP *in vivo* micronucleus and comet assay in rats.**	New toxicology data available.
Section 1.1.4, Clinical Data	To date, clinical data are available from ~~33~~ **61** patients with MM...and ~~18~~ **46** were treated with ACY-1215 in combination with other anti-neoplastic agents... Of the ~~18~~ **46** patients receiving combination therapy, ~~9~~ **25** received ACY-1215 in combination with bortezomib and dexamethasone and ~~9~~ **21** received ACY-1215 in combination....	Updates to the number of subjects for whom clinical data are available.
Section 1.1.4.1, Safety	Updated safety data available for ACY-1215.	New safety data available.
Section 1.1.4.2, Efficacy	**New section**	Section added to present available efficacy data for ACY-1215.
Section 1.1.4.3, Pharmacokinetics	Updated pharmacokinetics data available for ACY-1215.	New pharmacokinetics data available.
Section 3.1, Overall Design and Plan of the Study	...All patients will be monitored for signs and symptoms of venous thromboembolism (VTE) while on pomalidomide; diagnostic algorithms are provided (Appendix ~~Section~~ 9.1). **The study will conclude 30 days after the last enrolled patient discontinues from the study due to disease progression or treatment discontinuation.**	Clarification added to provide clear definition to the end of the study.
Section 3.1, Overall Design and Plan of the Study	Frequency of disease response was updated: • Patients are to be evaluated for disease response after **every cycle** and at study treatment discontinuation, starting with Cycle 1	Update to frequency of disease response assessment.
Section 3.2, Rationale for Study	Text was added regarding the effects of combination treatment with ricolinostat and pomalidomide on MM cells.	New data added to support study rationale.
Section 3.2, Rationale for Study	Safety data thus far in ~~33~~ **15** patients treated with ACY-1215 monotherapy and ~~18~~ **46** patients treated with ACY-1215 in combination with dexamethasone and either bortezomib or lenalidomide...	Updates to the number of subjects treatment with ACY-1215 in mono- and combination therapy.
Section 4.6, Withdrawal and Replacement of Patients, bullet #2	~~PD~~ **Progressive Disease** • **Determination of PD requires two consecutive assessments of disease progression. There is no specific requirement for the timing of these two assessments.**	Updated to clarify definition of progressive disease.
Section 4.9, Independent Response Assessment Committee	**New section**	Section add to describe role of the Independent Response Assessment Committee (IRAC).

Location(s) of Changes	Description of Changes in Amendment 2, 21 Aug 2014 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Section 5.1.2, Pomalidomide and Dexamethasone **Section 5.3.2,** Packaging and labeling	~~Celgene~~ **Pomalidomide** will ~~provide pomalidomide~~ **be provided at** 4, 3, 2, and 1 mg for PO administration.	Removal of Celgene's responsibility to provide pomalidomide.
Section 5.1.2, Pomalidomide and Dexamethasone	**For sites in the US and Canada,** ~~D~~**d**examethasone for PO administration will be supplied from commercially-available sources as 4 mg compressed tablets. (Dexamethasone tablets at strengths other than 4 mg may be used, as necessary.) **Acetylon will supply dexamethasone to sites in the EU**....	Dexamethasone is considered an IMP in EU and the sponsor is required to arrange cover for the cost and supply to the EU sites.
Section 5.2.2, Pomalidomide, Paragraphs #1 and #2	Drug will be shipped ~~on a per patient basis by the contract~~ **to the patient's home or to the** ~~clinic site pharmacy~~ **study site (in Canada only)** for Investigational New Drug studies. Pomalidomide will be sent to the patients' home **or to the study site (in Canada only)** via the POMALYST REMS™ and RevAid® programs (see Appendix 9.3 and Appendix 9.4, respectively).	Pomalidomide can be shipped to the patient's home or to the study site (Canada only).
Section 5.2.2, Pomalidomide, Paragraph #2	Pomalidomide (POMALYST®) will be administered based on the current approved dose and schedule: 4 mg PO QD on Days 1 to 21 of a 28-day **cycle** (see Table 2).	Updated to provide clarification.
Section 5.2.8.2, Pomalidomide, Table 6	(Note, ANC must be ≥ **500/µL in the US and Canada and ≥** 1,000/µL **in the EU** to restart dosing)	Updated to clarify ANC criteria in the US, Canada, and EU.
Section 5.2.8.2, Pomalidomide, *Instructions for Initiating a New Pomalidomide Cycle*	To initiate a new cycle of pomalidomide, ANC must be ≥ 500/µL **in the US and Canada and ≥ 1,000/µL in the EU**,	Clarified ANC criteria to initiate a new pomalidomide in the US, Canada, and EU.
Section 5.3.2, Packaging and Labeling	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:~~ **region-specific regulatory information.** • ~~Caution: New Drug - Limited by Federal (or US) law to investigational use.~~ • ~~Canada: Investigational Drug to be used by qualified investigators only.~~	Label information updated to reflect regulatory information for all regions.
Section 5.5, Study Drug Accountability	Accountability for ACY-1215 **(all centers)**, **pomalidomide, and dexamethasone (EU only)** at the study center is the responsibility of the Investigator...The Sponsor or its designee will review ~~ACY-1215~~ **study drug** accountability at the study center on an ongoing basis during monitoring visits. All material containing ~~ACY-1215~~ **study drug** will be treated and disposed of as hazardous waste in accordance with governing regulations.	Updated as pomalidomide and dexamethasone are considered IMPs.

Location(s) of Changes	Description of Changes in Amendment 2, 21 Aug 2014 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Section 5.6.1, Permitted Medication, Bullet #2	Hematopoietic Growth Factors: The use of hematopoietic growth factors will not be permitted during ~~Cycle 1~~ **screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segment of the study.**	Updated to clarify use of hematopoietic growth factors.
Section 5.6.2, Excluded Medication and Substances, Bullet #4	**(New bullet added)** • **Hematopoietic growth factors during screening in the Phase 1 or Phase 2 segments of the study or in Cycle 1 of the Phase 1b segments of the study.**	Added bullet to clarify use of hematopoietic growth factors.
Section 5.6.2, Excluded Medication and Substances	New text added to provide EU pomalidomide package insert information	Addition of European (EU) pomalidomide information.
Section 6.1.7.1, Hematology, Serum Chemistry and Urinalysis, Clinical laboratory parameter table	Removal of T4 (serum), TSH (serum), and T3 (serum).	Newly enrolled patients will not have thyroid function testing.
Section 6.1.7.3, Pregnancy Testing and Counseling, *RevAid® Program (Canada)* Criteria #3	3) who is ~~premenopausal~~ **perimenopausal**.	Update to clarify definition of female of child bearing potential (FCBP).
Section 6.1.7.3, *European Pomalidomide Pregnancy Prevention*	**New subheading added**	Addition of European (EU) pomalidomide information.
Section 6.1.8.4, Procedures for AE and SAE Reporting	When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. **All pomalidomide and dexamethasone AEs must be reported in accordance to the safety guidelines presented in the prescribing information.[51,58,59,60]**	Updated to provide safety reference document for pomalidomide and dexamethasone.
Section 6.2.5, Extramedullary Plasmacytoma Assessments	Plasmacytomas that can be assessed clinically are to be assessed every **cycle** ~~2 cycles~~. Plasmacytomas that are assessed by radiography will be assessed at screening, every **cycle** ~~2 cycles~~, at study treatment discontinuation, and to assess best response.	Updated to clarify assessment frequency.
Section 6.2.6, Assessment of Disease Response	Based on the EBMT, IMWG criteria have been expanded, clarified, and updated to provide a new comprehensive evaluation system to assess not only response but also the magnitude of response, length of response, **and** OS~~, and allow for the evaluation of patients with oligo-secretory disease~~ (Appendix 9.5). … Response will be assessed every ~~2 cycles~~ cycle throughout study drug treatment, and at treatment discontinuation in both the Phase 1b and Phase 2 segments of the study. **...Determination of PD requires two consecutive assessments of disease progression. There is no specific requirement for the timing of these two assessments.**	Updated to clarify disease response assessment.

Location(s) of Changes	Description of Changes in Amendment 2, 21 Aug 2014 (Deleted text are shown by ~~strikethrough~~; additional text added in **bold**, as appropriate)	Rationale for Change
Section 7.1, Sample Size Estimation, Phase 2	For a study with a sample size of 66, a one sided 0.05 level test with power of 80% would be adequate to detect the response rate of 0.29 against 0.44. **Assuming a 10% drop out rate, a study of 75 patients would be sufficient.** …The SRC will use the totality of information from the interim analysis to recommend whether the study should proceed as planned, be terminated for superiority or futility, or extended to allow for ~~95~~**86** evaluable patients.	Update to clarify sample size estimation.
Section 8.4, Patient Confidentiality	In order to maintain patient privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the patient **according to local or regulatory authority(ies)** ~~by initials and the assigned patient number~~.	Updated to allow for consideration of EU regulations.
Section 8.8, 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 2 years after the last marketing application approval or 2 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.	Updated to allow for consideration of region-specific regulations.
Appendix 9.5, European Pomalidomide Pregnancy Prevention Risk Management Plans	**(New Appendix)**	New Appendix added to provide EU pomalidomide pregnancy prevention risk management plans.

SUMMARY OF PROTOCOL CHANGES

Protocol ACE-MM-102: A Phase 1b/2 Multi-center, Open Label, Dose- escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of ACY-1215 in Combination with Pomalidomide and Low-dose Dexamethasone in Patients with Relapsed-and-Refractory Multiple Myeloma

Prior Protocol Version: Original; 15 August 2013

New Protocol Version: Amendment 1; 7 April 2014

I. SUMMARY OF SIGNIFICANT CHANGES

The primary changes made to the protocol by Amendment 1 include modification of eligibility criteria for increased patient safety and to be aligned with the current usage of pomalidomide, the addition of sparse blood sample collection time points for patients participating in Phase 2 of the study for pharmacokinetic (PK) assessment and the addition of text describing the pregnancy testing and counseling requirements of the RevAid® Program for study participants in Canada.

Additionally, the text describing the statistical methods for the interim analysis that will be conducted on the first 30 evaluable patients was expanded to clarify how the analyses will be performed and how the Safety Review Committee (SRC) will use these data to issue recommendations regarding the future of the study.

Other administrative and editorial changes incorporated into the Protocol by Amendment 1 are summarized in Section III. Minor editorial changes and abbreviation substitutions are not itemized.

II. RATIONALE

The protocol eligibility criteria were modified to better align the eligible patient population with the current standards for pomalidomide usage including the exclusion of patients with hemoglobin <8 g/dL, and creatinine clearance <45 mL/minute (per Cockcroft-Gault formula). An additional modification was made to the platelet count exclusion criterion in order to increase patient safety and in light of the definition of dose limiting toxicity (DLT) at platelet count < 25,000/μL. Eligibility was expanded to allow patients with non-secretory Multiple Myeloma. Eligibility criteria, study drug administration text, and labeling information were also updated to reflect the approval of pomalidomide in Canada and to incorporate the pregnancy testing, birth control, and pregnancy counseling requirements of the RevAid® Program. Additional PK blood sampling time points added during Phase 2 of the study.

Finally, the statistical methods for the interim analysis were expanded to clarify how the totality of these data will be used by the SRC to make decisions regarding the future of the study (i.e. continue as planned, terminate for futility, or expand patient population).

III. DETAILED TABLE OF CHANGES

Deleted text is indicated by ~~strikthrough~~ while new text is indicated by **bold** font.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Title	Title Page, Synopsis	The title was edited as follows: *Old text:* A Phase 1B/2, Open-label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of ACY-1215 in Combination with Pomalidomide and Low-dose Dexamethasone in Patients with Relapsed-and-Refractory Multiple Myeloma *New text:* A Phase 1B/2, Open-label, Dose-Escalation Study to Determine the Maximum Tolerated Dose, Safety, and Efficacy of ACY-1215 **(ricolinostat)** in Combination with Pomalidomide and Low-dose Dexamethasone in Patients with Relapsed-and-Refractory Multiple Myeloma	Administrative change.
Protocol Version	Cover Page	Version was updated from "*Original (15 August 2013)"* to "***Amendment 1 (7 April 2014)"***	Administrative change.
Sponsor Contact Information	Study Personnel and Administrative Structure	Changed the contact information for the Sponsor Contact: *Old text:* [redacted] ~~Clinical Operations~~ ~~Telephone:~~ [redacted] ~~Mobile telephone:~~ [redacted] ~~Fax:~~ [redacted] *New text:* [redacted] **linical Project Manager** **Telephone:** [redacted] **Fax:** [redacted] **Email:** [redacted]	Administrative change.
SAE Reporting	Study Personnel and Administrative Structure, Section 6.1.7.2, Section 6.1.7.4	Changed the contact information for SAE Reporting: *Old text:* 24-Hour SAE Reporting ~~Telephone:~~ [redacted] ~~Fax:~~ [redacted] *New text:* 24-Hour SAE Reporting	Administrative change.

3URWRFRO ,WHP	/RFDWLRQ RI &KDQJHV	'HVFULSWLRQ RI &KDQJHV LQ $PHQGPHQW 1, 7 $SULO 2014	5DWLRQDOH IRU &KDQJH
		(PDLO: [redacted] **)D[: [redacted]**	
3ULPDU\ 2EMHFWLYH: 3KDVH 1E	6\QRSVLV (3ULPDU\ 2EMHFWLYH IRU 3KDVH 1E), 6HFWLRQ 2.1.1	$GGHG WKH IROORZLQJ QHZ WH[W: • 7R GHWHUPLQH WKH PD[LPXP WROHUDWHG GRVH (0**7' RU LI QRW SUHVHQW, WKH UHFRPPHQGHG 3KDVH 2 GRVH** DQG VFKHGXOH RI $&<-1215 DGPLQLVWHUHG LQ FRPELQDWLRQ ZLWK SRPDOLGRPLGH DQG ORZ-GRVH GH[DPHWKDVRQH LQ SDWLHQWV ZLWK UHODSVHG-DQG-UHIUDFWRU\ 00.	7R HQDEOH D GRVH VHOHFWLRQ LQ DEVHQFH RI DQ **07'.** $Q **07'** KDV QRW EHHQ LGHQWLILHG LQ RWKHU WULDOV RI ULFROQRVWDW GXH WR D SKDUPDFRORJLF SODWHDX DW GRVHV !160-240 PJ.
6**7**XG\ **(**QGSRLQ**7**: 3ULPDU\, 3KDVH 1E	6\QRSVLV (3ULPDU\ 6WXG\ (QGSRLQW IRU 3KDVH 1E), 6HFWLRQ 2.2.1	0RGLILHG WH[W DV IROORZV: 07' DQG VFKHGXOH, **RU LI QRW SUHVHQW, WKH UHFRPPHQGHG 3KDVH 2 GRVH DQG VFKHGXOH RI $&<-1215 DGPLQLVWHUHG LQ FRPELQDWLRQ ZLWK SRPDOLGRPLGH DQG GH[DPHWKDVRQH.**	7R HQDEOH D GRVH VHOHFWLRQ LQ DEVHQFH RI DQ **07'**. $Q **07'** KDV QRW EHHQ LGHQWLILHG LQ RWKHU WULDOV RI ULFROQRVWDW GXH WR D SKDUPDFRORJLF SODWHDX DW GRVHV !160-240 PJ.

3URWRFRO ,WHP	/RFDWLRQ RI &KDQJHV	'HVFULSWLRQ RI &KDQJHV LQ $PHQGPHQW 1, 7 $SULO 2014	5DWLRQDOH IRU &KDQJH
6WXG\ ❨QGSRLQW: 3KDUPDFRG\QDPLFV, 3KDVH 1E	6\QRSVLV (3KDUPDFRG\QDPLF 6WXG\ ❨QGSRLQW IRU 3KDVH 1E), 6HFWLRQ 2.2.2, 6HFWLRQ 3.1	'HOHWHG WKH IROORZLQJ WH[W: • ([SRVXUH-UHVSRQVH RI $&<-1215 LQ FRPELQDWLRQ ZLWK SRPDOLGRPLGH DQG ORZ-GRVH GH[DPHWKDVRQH, LQFOXGLQJ ELRPDUNHUV UHODWLQJ WR LQWUDFHOOXODU SURWHLQ DFHW\ODWLRQ, ~~OHYHOV RI SURWHLQV, PHVVHQJHU ULERQXFOHLF DFLG (P51$) DQG PLFUR51$ H[SUHVVLRQ SURILOHV ZLOO EH DQDO\]HG IRU SRWHQWLDO UHODWLRQVKLSV.~~	&ODULILFDWLRQ RI WKH SKDUPDFRG\QDPLF HQGSRLQWV.
6WXG\ ❢HVLJQ	6\QRSVLV (6WXG\ ❢❒Q)	'HOHWHG WKH IROORZLQJ WH[W: • ~~,Q DGGLWLRQ, SDWLHQWV ZKR DUH GLVFRQWLQXHG IURP IXUWKHU VWXG\ WUHDWPHQW ZLOO EH DVVHVVHG 3 WLPHV SHU \HDU IRU XS WR 5 \HDUV IRU RYHUDOO VXUYLYDO (26), VXEVHTXHQW 00 WUHDWPHQW UHJLPHQV, DQG VHFRQG SULPDU\ PDOLJQDQFLHV DV RXWOLQHG LQ WKH 6FKHGXOH RI $VVHVVPHQWV.~~	7H[W ZDV UHGXQGDQW DV LW DOUHDG\ DSSHDUHG RQ WKH IROORZLQJ SDJH.
6WXG\ ❢HVLJQ	6\QRSVLV (6WXG\ ❢❒Q), 6HFWLRQ 6.2	$GGHG WKH IROORZLQJ QHZ WH[W: **&OLQLFDO ODERUDWRU\ WHVWV DUH WR EH SHUIRUPHG IRFDO\. ,Q DGGLWLRQ, D FHQWUDO ODERUDWRU\ ZLOO DQD\]H GXSOLFDWH VDPSOHV RI VHUXP LPPXQRJORERXOLQ OHYHOV, VHUXP DQG XULQH SURWHLQ HOHFWURSKRUHVLV RI P\HORPD (0)-SURWHLQ FRPSRQHQW (63(3, 83(3), VHUXP DQG XULQH LPPXQRIL[DWLRQ (,)() VWXGLHV, DQG VHUXP IUHH OLJKW FKDLQ (6)/&) DQDO\VLV. $ ERQH PDUURZ DVSLUDWH ZLOO EH FHQWUDOO\ DQDO\]HG IRU IOXRUHVFHQFH *LQ VLWX* K\EULG]DWLRQ),6+)/F\WRJHQHWLFV.**	&ODULI\ FROOHFWLRQ RI VDPSOHV IRU ORFDO YV. FHQWUDO DQD\\VLV.
6WXG\ ❢HVLJQ	6\QRSVLV (6WXG\ ❢❒Q), 6HFWLRQ 3.1	$GGHG WKH IROORZLQJ QHZ WH[W GHVFULELQJ WKH VSDUVH SKDUPDFRNLQHWLF (3.) VDPSOLQJ WKDW ZLOO EH SHUIRUPHG GXULQJ 3KDVH 2: **%ORRG VDPSOHV ZLOO DOVR EH FROOHFWHG IURP SDWLHQWV DW SDUWLFLSDWLQJ VLWHV LQ WKH 3KDVH 2 VHJPHQW IRU VSDUVH 3. VDPSOLQJ.**	7LPH SRLQWV IRU 3. EORRG VDPSOLQJ ZHUH DGGHG WR WKH 3KDVH 2 VWXG\ VHJPHQW.
6WXG\ 'HVLJQ	6\QRSVLV (6WXG\ 'HVLJQ), 6HFWLRQ 3.1, 6HFWLRQ 4.7	$GGHG WKH IROORZLQJ QHZ WH[W: **3DWLHQWV ZKR ZLWKGUDZ IURP WKH VWXG\ DUH WR DWWHQG D ILQDO ❢XG\ YLVLW 30 GD\V (□ 3 GD\V) DIWHU WKH ODVW GRVH RI**	7R FODULI\ WLPLQJ RI ILQDO VWXG\ YLVLW DQG WKH DVVHVVPHQWV WR EH SHUIRUPHG XSRQ GLVFRQWLQXDWLRQ IURP ❢XG\ WUHDWPHQW IRU 3' RU

3URWRFRO ,WHP	/RFDWLRQ RI &KDQJHV	'HVFULSWLRQ RI &KDQJHV LQ $PHQGPHQW 1, 7 $SULO 2014	5DWLRQDOH IRU &KDQJH
		VWXG\ GUXJ LI SRVVLEOH. (6\QRSVLV, 6HFWLRQ 3.1) **,I SDWLHQWV DUH WUHDWHG ZLWK DQ DOWHUQDWH 00 WKHUDS\ EHIRUH WKH 30 GD\ YLVLW, DVVHVVPHQWV IRU WKH 30 GD\ YLVLW VKRXOG EH SHUIRUPHG SULRU WR LQLWLDWLRQ RI WKH DOWHUQDWH WKHUDS\.** (6HFWLRQ 3.1, 6HFWLRQ 4.7) **3DWLHQWV ZKR GLVFRQWLQXH VWXG\ WUHDWPHQW GXH WR UHDVRQV RWKHU WKDQ 3' ZLOO DOVR EH IROORZHG IRU HIILFDF\ DVVHVVPHQWV (DVVHVVPHQW RI UHVSRQVH, H[WUDPHGXOODU\ SODVPDF\WRPD DVVHVVPHQW, TXDQWLWDWLYH VHUXP LPPXQRJOREXOLQ OHYHOV, 63(3 DQG 83(3 RI 0-SURWHLQ OHYHOV, VHUXP DQG XULQH ,)(, DQG 6)/& DQDO\VLV) XQWLO 3', RU LQLWLDWLRQ RI DQ DOWHUQDWH 00 WKHUDS\.** (6\QRSVLV, 6HFWLRQ 3.1) **6XEVHTXHQW WKHUDSLHV VKRXOG EH FROOHFWHG XQWLO GHDWK RU HQG RI 5 \HDU IROORZ XS SHULRG. 6XUYLYDO IROORZ XS PD\ EH GRQH YLD SKRQH. 6HULRXV DGYHUVH HYHQWV (6$(V) ZLOO EH IROORZHG XQWLO 30 GD\V DIWHU VWXG\ WUHDWPHQW GLVFRQWLQXDWLRQ.** (6HFWLRQ 3.1)	DQ\ RWKHU UHDVRQ.
6WXG\ 'HVLJQ, 'RVH-OLPLWLQJ 7R[LFLW\	6\QRSVLV (6\XG\ 'HVLJQ, 6HFWLRQ 5.2.6)	$GGHG WKH IROORZLQJ WH[W: *+HPDWRORJLF WR[LFLW\:* • *UDGH 4 QHXWURSHQLD (DEVROXWH QHXWURSKLO FRXQW >$1&@ < 500/ȝ/) **ODVWLQJ ! 5 GD\V**, *RU* **UDGH 3 RU 4 $&<-1215-UHODWHG QRQ-KHPDWRORJLF WR[LFLW\:* • **$OO RWKHU *UDGH 3 RU 4 QRQ-KHPDWRORJLF WR[LFLWLHV ZLWK WKH H[FHSWLRQ RI:** • ***UDGH 3 RU 4 QDXVHD, YRPLWLQJ RU GLDUUKHD«**	7R FODULI\ WKH FULWHULD IRU GHWHUPLQDWLRQ RI ▼/7
6WXG\ 'HVLJQ/2YHUDOO 'HVLJQ DQG 3ODQ RI WKH 6\XG\	6\QRSVLV (6\XG\ 'HVLJQ), 6HFWLRQ 3.1, 6HFWLRQ 5.2.5	0RGLILHG WH[W DV IROORZV: 3DWLHQWV ZKR GLVFRQWLQXH ~~WUHDWPHQW~~ **IURP WKH VWXG** IRU UHDVRQV ~~XQUHODWHG WR $(V ZLWKLQ WKH ILUVW 28 GD\V RI WUHDWPHQW~~ **RWKHU WKDQ '/7 (H.J., QRQ-FRPSOLDQFH, SDWLHQW UHTXHVW) EHIRUH FRPSOHWLQJ &\FOH 1** ZLOO EH UHSODFHG.	7R V\QFKURQL]H \WXG\ GHVLJQ WH[W WKDW DSSHDUV LQ WKH V\QRSVLV ZLWK WH[W LQ 6HFWLRQ 4.6.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Study Design/Overall Design and Plan of the Study/Study Drug Dose and Administration	Synopsis (Study Design), Section 5.2, Section 5.2.5	Deleted the following text: ~~Following completion of the first cycle, patients may continue the study at their assigned dose of ACY-1215.~~	Redundant
Study Design	Synopsis (Study Design)	Modified text as follows: For all patients enrolled in the Phase 1b MTD segment, following the completion of Cycle 1, efficacy assessments will be conducted every ~~56 days (± a 2-day window)~~ **2 cycles** for the duration of the treatment period.	To reduce the likelihood of protocol deviations if a response assessment occurs outside the 56 day (± a 2-day) window.
Number of Patients Planned	Synopsis, (Number of Patients Planned), Section 4.1	Modified text as follows: "… a total of up to ~~105~~ **125** patients are planned to be enrolled, including up to 30 patients in the Phase 1b segment and up to ~~75~~ **95** patients in the Phase 2 segment."	To reflect that the patient population may be expanded based on the outcome of the interim analysis (per revised statistical text).
Inclusion Criteria	Synopsis (Inclusion Criteria), Section 4.2	Added text to Inclusion Criteria 7 as follows: 7. Must have measurable levels of myeloma paraprotein in serum (≥ 0.5 g/dL) or urine (≥ 0.2 g/24 hours). **Patients who do not have myeloma paraprotein must have SFLC concentration of > 10 mg/dl provided SFLC ratio is abnormal. Nonsecretory myeloma is excluded.**	To expand enrollment to patients with non-secretory Multiple Myeloma
Inclusion Criteria	Synopsis (Inclusion Criteria), Section 4.2	Revised the following Inclusion Criteria 10: *Old text:* FCBP must have a negative serum or urine pregnancy test ~~with a sensitivity of at least 25 mIU/mL within 10—14 days prior to, and again within 24 hours of starting pomalidomide~~ and must either commit to continued abstinence from heterosexual intercourse or ~~begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking pomalidomide. FCBP must also agree to ongoing pregnancy testing (see Section 6.1.7.3). Men must agree to use a latex condom during sexual contact~~	To update the pregnancy testing and birth control requirements based on the RevAid® program.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
		~~with a FCBP even if they have had a vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix 9.3.1 Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix 9.3.2 Education and Counseling Guidance Document.~~ *New text:* FCBP must have a negative serum **(for study participants in Canada)** or urine pregnancy test, **as described in Appendix** 9.3 **for the POMALYST REMS™ program (study participants in the US)** and **Appendix** 9.4 **for the RevAid® program (study participants in Canada). FCBP and males** must either commit to continued abstinence from heterosexual intercourse or **must abide by** birth control **requirements as described in Appendix 9.3 for the POMALYST REMS™ program (study participants in the US) and Appendix 9.4 for the RevAid® program (study participants in Canada).**	
Inclusion Criteria	Synopsis (Inclusion Criteria), Section 4.2	Added the following new Inclusion Criteria 13: **13. Must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program (or RevAid® for study participants in Canada).**	To clarify that patients in the United States (US) must register with the POMALYST REMS™ program and patients in Canada must register with the RevAid® program.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Added the following new text to Exclusion Criterion 2: 2. Any serious concurrent medical conditions, **laboratory abnormality, or psychiatric illness** that might make the patient non-evaluable, ~~or~~ put the patient's safety at risk, **or prevent the patient from following the study requirements**.	To clarify the exclusion of potentially non-compliant patients.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Added the following new text to Exclusion Criterion 4: 4. Prior therapy with HDAC inhibitor **or pomalidomide.**	To exclude patients with prior pomalidomide therapy.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Revised Exclusion Criteria 5 as follows: 5. Platelet count < ~~75~~**50**,000/ µL for patients in whom < 50% of bone marrow nucleated cells are plasma cells~~; or a platelet count < 30,000/ µL for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells~~.	To increase patient safety, given the definition of DLT at 25,000 platelets.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Added the following new text to Exclusion Criterion 5: 5. **Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted).**	To increase patient safety and exclude patients with low Hemoglobin.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Deleted the following new text from Exclusion Criterion 5: 5. ~~Serum creatinine ≥ 3.0 mg/dL.~~	To align with change below to Exclusion Criterion #4.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Added the following new text to Exclusion Criterion 5: 5. **Creatinine clearance < 45 mL/min according to Cockcroft-Gault formula. If creatinine clearance calculated from the 24-hour urine sample is ≥ 45 mL/min, patient will qualify for the trial.**	To align this criterion with current pomalidomide usage.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Deleted the following new text from Exclusion Criterion 7: 7. Corrected QT interval using Fridericia's formula (QTcF) value > 480 msec at Screening ~~and pre-dose on C1D1…~~	To clarify this exclusion criterion.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Revised Exclusion Criterion 8 as follows: 8. **Positive** human immunodeficiency virus (HIV), hepatitis B virus (HBV) and~~/or~~ **known or suspected active** hepatitis C virus (HCV) infection.	To clarify this exclusion criterion.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Added the following text to Exclusion Criterion 9: 9. Hypersensitivity to thalidomide, lenalidomide, or dexamethasone **(such as Steven Johnson Syndrome). Hypersensitivity, such as rash, that can be medically managed is allowable**.	To clarify this exclusion criterion.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Added the following new text to Exclusion Criterion 10. 10. Peripheral neuropathy ≥ Grade 2 **despite supportive therapy.**	To clarify this exclusion criterion.
Exclusion Criteria	Synopsis (Exclusion Criteria), Section 4.3	Added the following new text to Exclusion Criteria 13: 13. Inability or unwillingness to comply with birth control requirements **or any of the Pomalyst REMS or RevAid requirements (region-specific), per Appendix 9.3 and Appendix 9.4, respectively**.	To update this exclusion criterion based on the requirements of the RevAid® program.
Test Products, Doses and Mode of Administration/ Study Drug Supply and Storage: Pomalidomide and Dexamethasone	Synopsis (Study Design, Test Products, Doses and Mode of Administration), Section 5.1.2	Added the following new text: Celgene will supply pomalidomide 4**, 3, 2, and 1 mg** for PO administration	To specify that different concentrations of pomalidomide will be available.
Test Products, Doses and Mode of Administration/ Study Drug Supply and Storage: ACY-1215	Synopsis (Study Design, Test Products, Doses and Mode of Administration), Section 5.1.21	Added the following new text: **If Dose level 2 is well tolerated, Dose Level 3 of 160 mg BID will be explored.** Deleted the following new text: ~~If Dose level 1 is well tolerated, Dose Level 3 of 160 mg BID will be explored after completion of the highest daily dose cohort.~~	To correct the language to better describe dose escalation during Phase 1b.
Test Products, Doses and Mode of Administration/ Study Drug Supply and Storage: Pomalidomide	Synopsis (Study Design, Test Products, Doses and Mode of Administration), Section 5.2.2	Added the following new text: **Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal.**	To add instructions for Pomalidomide dosing

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Statistical Methods/Justification of Sample Size	Synopsis (Statistical Methods), Section 7.1	Revised the Justification of Sample Size text: *Old text:* The corresponding expected 95% confidence interval for the response rate ~~is (0.3, 0.56) which would surpass the reference response rate~~ of 0.29. Assuming a 10% dropout rate, a study with n=~~75~~ would be sufficient. *New text:* **Equivalently,** the corresponding expected **one-sided** 95% confidence interval **(CI)** for the response rate **will exclude 0.29 with 80% of chance. In order to have a robust study, a single interim analysis will be conducted when there are 30 evaluable patients. The SRC will use the totality of information from the interim analysis to recommend whether the study should proceed as planned, be terminated for superiority or futility, or extended to allow for 86 evaluable patients.** Assuming a 10% dropout rate, a study with n=**95** would be sufficient**.**	To clarify how the interim analysis will be used by the SRC to make critical decisions regarding the future of the study.
Statistical Methods/Interim Analysis	Synopsis (Statistical Methods), Section 7.5.1	Edited the text describing the Interim Analysis: *Old text:* ~~An interim analysis of response will be conducted by an independent statistician after 30 patients have been treated for at least 4 months in the Phase 2 segment. Accrual will continue during the interim analysis, and the sample size may be adjusted based on the 95% confidence intervals around the observed response rate. Prediction analysis is planned for the final 95% confidence interval for the response rate with the planned sample size. If the lower bound of the interval includes 0.29, a sample size adjustment will be considered. The size adjustment will depend upon the predicted 0.95~~	To clarify the statistical methods that will be used for the interim analysis.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
		~~confidence interval estimates under various scenarios.~~ *New text:* **There will be a single, scheduled interim analysis of when there are 30 evaluable patients available in order to determine if the study should proceed as planned, be terminated, or extended to allow for 86 evaluable patients. Assuming a 10% dropout rate, a study with n=95 would be sufficient**. (Section 7.5.1) **The interim analysis with the first 30 evaluable patients will be conducted using a one-sided 95% CI estimate for the response rate. If the lower bound of the 95% CI estimate with the 30 patients is ≥ 29%, the SRC may recommend either terminating the study at the interim based on treatment superiority, or continuing the study as planned. If the lower bound is < 29%, various predicted lower bounds of one-sided 95% CIs for the response rate will be constructed to further guide the SRC's recommendation. For example, assuming a true response rate of 44% for the remaining 36 patients, the expected lower bound of one-sided 95% CI with 66 evaluable patients will be calculated. If the expected lower bound is ≥ 29%, the SRC may recommend continuing the study as planned. If the expected lower bound with 66 evaluable patients is < 29%, another simulation will be run with 86 evaluable patients. If the resulting lower bound is acceptable (e.g., close to or ≥ 29%), the SRC may recommend expanding the sample size by 20 patients. If the resulting lower bound is not acceptable (e.g., < 29%), the SRC may recommend terminating the study for futility. In addition, the expected lower bound of the one-sided 95% CI when the true response rate is equal to the observed value at**	

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
		the interim analysis will be calculated. The resulting scenario will be similar to the previous one: if the expected lower bound is ≥ 29%, the SRC may recommend continuing the study as planned, if the lower bound is < 29%, the SRC may recommend expanding the sample size by 20 patients. Additional simulations with other possible response rates (for example, assuming a 40% response rate), with or without adaptation, will also be conducted; the SRC will review all simulation results to make a recommendation at the interim. Furthermore, with the potential adaptations at the interim, we find via an extensive simulation study the final CI estimate would have the accurate coverage level. Therefore, no statistical penalty or adjustment will be needed for the final inferential statistical procedure for the response rate.	

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Statistical Methods/Safety Analysis	Synopsis (Statistical Methods)	Revised text as follows: ~~AEs~~ **SAEs, treatment-emergent AEs, frequency of DLTs,** vital sign measurements, clinical laboratory information, and concomitant medications will be tabulated and summarized for each dose cohort when appropriate.	To clarify the tabulation of safety data.
Statistical Methods/Safety Analysis	Synopsis (Statistical Methods), Section 7.6.6	Added the following new text: **AEs leading to dose reduction or interruption will also be tabulated.**	To clarify the tabulation of safety data.
Statistical Methods/Efficacy Analysis	Synopsis (Statistical Methods), Section 7.5.1, Section 7.6.7	Revised text as follows: **The ITT Population will include all treated patients, and the EE Population will include all patients who meet eligibility criteria, receive at least 14 doses of study drug (i.e., ACY-1215, pomalidomide and low-dose dexamethasone), and have at least 1 post-baseline efficacy assessment**. The primary analysis will be based on the ~~ITT principle~~ **EE population**, and will use the **Investigator-assessed** response data evaluated according to consensus recommendations from the IMWG criteria.	To clarify the statistical methods to be used for the efficacy analysis.
Statistical Methods/Efficacy Analysis	Synopsis (Statistical Methods), Section 7.6.7	Added the following new text: Response rate will be percent of patients who achieve **at least** partial response (PR) at the recommended Phase 2 dose. **Percent of patients achieving MR or better will also be collected as clinical benefit response.**	To clarify the methods used for evaluation of the primary efficacy endpoint of objective response.
Statistical Methods/Efficacy Analysis	Synopsis (Statistical Methods), Section 7.6.7	Added the following new text: Duration of Response (DOR) will be defined as the time from the first PR or CR to the first documentation of ~~disease progression~~ **PD or death, whichever occurs earlier.**	To clarify the methods used for evaluation of DOR.

3URWRFRO ,WHP	/RFDWLRQ RI &KDQJHV	'HVFULSWLRQ RI &KDQJHV LQ $PHQGPHQW 1, 7 $SULO 2014	5DWLRQDOH IRU &KDQJH
6WDWLVWLFDO OHWKRGV/3KDUPDFRNLQHWLF $QDO\VLV	6\QRSVLV (6WDWLVWLFDO 0HWKRGV), 6HFWLRQ 7.6.8	5HYLVHG WH[W DV IROORZV: 6\XG\ GUXJ VHUXP FRQFHQWUDWLRQV RI $&<-1215 DQG SRPDOLGRPLGH ZLOO EH GHWHUPLQHG DW DOO SUH- DQG SRVW-GRVH ~~(0.5, 1, 2, 4, DQG 6 KRXUV)~~ WLPH -SRLQWV **VSHFLILHG LQ WKH 6FKHGXOH RI $VVHVVPHQWV.**	7R FODUL\ WH[W GHVFULELQJ 3. FROOHFWLRQ WLPH SRLQWV.
62$, &OLQLFDO /DERUDWRU\ 7HVWV	6FKHGXOH RI $VVHVVPHQWV (62$), DQG)RRWQRWH 8, 6HFWLRQ 6.1.6.1	5HPRYHG WKH FROOHFWLRQ RI EORRG IRU WK\URLG IXQFWLRQ WHVWV,)RRWQRWH 8 DQG GHOHWHG WKH IROORZLQJ WH[W: ~~%ORRG VDPSOHV IRU WK\URLG IXQFWLRQ WHVWV DUH WR EH FROOHFWHG IRU DOO SDWLHQWV DW 6FUHHQLQJ, DQG DW VWXG\ WUHDWPHQW GLVFRQWLQXDWLRQ.~~	7K\URLG IXQFWLRQ WHVWV DUH QRW FXUUHQW\ UHTXLUHG IRU SRPDOLGRPLGH WKHUDS\.
6DIHW\ $VVHVVPHQWV	6\QRSVLV (6DIHW\ $VVHVVPHQWV), 62$, 6HFWLRQ 6.1.4, 6HFWLRQ 7.6.6, $SSHQGL[9.7	5HSODFHG WKH .DUQRIVN\ 3HUIRUPDQFH 6WDWXV (.36) ZLWK WKH (DVWHUQ 2QFRORJ\ *URXS ((&2*) SHUIRUPDQFH VWDWXV LQ WKH 62$ DQG UHYLVHG WH[W DV IROORZV: • ~~.DUQRIVN\~~ **(&2*** SHUIRUPDQFH VWDWXV (V\QRSVLV) • **(&2* S.DUQRIVN\ 3HUIRUPDQFH 6WDWXV (.36,** ~~>$SSHQGL[9.4@) LV WR EH GRFXPHQWHG IRU DOO SDWLHQWV DW 6FUHHQLQJ, RQ 'D\~~ 1 RI HYHU\ WUHDWPHQW F\FOH, XSRQ **'** DQG DW VWXG\ WUHDWPHQW GLVFRQWLQXDWLRQ. (6HFWLRQ 6.1.4) • ~~**(&2* S.DUQRIVN\ SHUIRUPDQFH VWDWXV ZLOO EH VXPPDUL]HG IRU FKDQJHV IURP %DVHOLQH WR WUHDWPHQW GLVFRQWLQXDWLRQ; .DUQRIVN\ SHUIRUPDQFH VWDWXV RQ 'D\ 1 RI HYHU\ WUHDWPHQW F\FOH ZLOO EH SUHVHQWHG LQ GDWD OLVWLQJ IRUPDW.~~ (6HFWLRQ 7.6.6) • **❮DVWHUQ &RRSHUDWLYH 2QFRORJ\ *URXS ((&2*) 3HUIRUPDQFH 6WDWXV**~~7DEOH RI .DUQRIVN\ 3HUIRUPDQFH 6WDWXV 6FDOH~~ ($SSHQGL[~~9.4~~ 9.7)	5HSODFHG WKH .36 DVVHVVPHQW ZLWK WKH (&2* SHUIRUPDQFH VWDWXV DVVHVVPHQW.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Study Design	SOA and Footnote 18, Section 6.2.6	Modified text as follows: Response will be assessed every ~~56 days (± a 2-day window)~~ **2 cycles** while on study drug treatment, and at study treatment discontinuation. Assessment of response will include measurement of serum M-protein by electrophoresis, **SFLC analysis**, and IFE studies (see footnotes 10-12).	To reduce the likelihood of protocol deviations if a response assessment occurs outside the 56 day (± a 2-day) window. Protocol now allows patients with free light chain myeloma.
SOA	SOA, Footnote 2	Added new Footnote 2: **Pregnancy tests may be conducted locally for patients who are unable to attend the 30 day follow-up visit at the study center; all other assessments may be conducted via phone.**	To clarify how the 30-day follow-up visits may be conducted.
SOA	SOA, Footnote 3, Section 6.1.1	Added new text to existing Footnote 3: **Subsequent therapies should be collected until death or the end of the 5 year follow-up period. Survival follow-up may be done via phone.**	To clarify extent and methods of follow-up assessments.
SOA, Demographics and Medical History	SOA, (former) Footnote 3	Deleted the following text: ~~As part of the patient's MM treatment history, study centers are to submit a local cytogenetics report and fluorescence in situ hybridization (FISH) analysis report obtained prior to enrollment, if available; ideally, the FISH report collected should include assessment of t(4;14); t(11;14); t(6;14); t(14;16); t(14;20); and del 17p. These data will be submitted for centralized review.~~	Deleted instruction as it is no longer applicable for this study.
SOA	SOA, Footnote 5	Revised as follows: A bone marrow aspirate ~~and/or at least a unilateral biopsy~~ is to be performed **at Screening and a sample sent for central cytogenetic and fluorescence in situ hybridization (FISH) analysis (a bone marrow biopsy is needed only if the marrow is unable to be aspirated). A bone marrow biopsy/aspirate may be done as clinically indicated, at the discretion of the treating physician for** ~~and when~~ **assessment of disease**.	To clarify that FISH analysis will be performed centrally.

3URWRFRO ,WHP	/RFDWLRQ RI &KDQJHV	'HVFULSWLRQ RI &KDQJHV LQ $PHQGPHQW 1, 7 $SULO 2014	5DWLRQDOH IRU &KDQJH
62$	62$,)RRWQRWH 7	$GGHG QHZ WH[W WR H[LVWLQJ)RRWQRWH 7: +HPDWRORJ\ ZLOO LQFOXGH KHPDWRFULW, KHPRJORELQ, UHG EORRG FHOO (5%&) FRXQW, LQWHUQDWLRQDO QRUPDOL]HG UDWLR (,15), **DEVROXWH QHXWURSKLO FRXQW ($1&), DEVROXWH O\PSKRF\WH FRXQW ($/&),** ZKLWH EORRG FHOO (:%&) FRXQW ZLWK GLIIHUHQWLDO, SODWHOHW FRXQW, UHWLFXORF\WH FRXQW, DQG PHDQ FRUSXVFXODU YROXPH.	7KHVH SDUDPHWHUV ZHUH PLVWDNHQO\ RPLWWHG IURP WKH IRRWQRWH LQ WKH SULRU YHUVLRQ RI WKH SURWRFRO.
62$	62$,)RRWQRWH 13, 14	)RRWQRWHV 13-145 ZHUH XSGDWHG WR UHIOHFW WKH SUHJQDQF\ WHVWLQJ DQG ELUWK FRQWURO UHTXLUHPHQWV RI ERWK WKH 320$/<67 5(06□ DQG 5HY$LG□ SURJUDPV.	7R XSGDWH WKH SUHJQDQF\ WHVWLQJ DQG ELUWK FRQWURO UHTXLUHPHQWV EDVHG RQ ERWK WKH UHJLRQ-VSHFLILF 320$/<67 5(06□ DQG 5HY$LG□ SURJUDPV.
62$	62$,)RRWQRWH 17	$GGHG QHZ WH[W WR H[LVWLQJ)RRWQRWH 17: **&RUUHFWHG 47 LQWHUYDO DW VFUHHQLQJ (47F)) PXVW EH ! 480 PVHF DW 6FUHHQLQJ.**	7R XSGDWH WKLV IRRWQRWH EDVHG RQ ([FOXVLRQ &ULWHULRQ 6.
3KDUPDFRNLQHWLF 0HDVXUHPHQWV	6FKHGXOH RI $VVHVVPHQWV ()RRWQRWH 25), 6HFWLRQ 6.3	$GGHG QHZ 3. WLPH SRLQWV IRU SDWLHQWV SDUWLFLSDWLQJ LQ 3KDVH 2 RI WKH WXG\: 6HULDO EORRG VDPSOHV IRU 3. DVVHVVPHQWV DUH WR EH FROOHFWHG IURP DOO SDWLHQWV GXULQJ &\FOH 1 RI WKH 3KDVH 1E DQG IURP SDWLHQWV DW SDUWLFLSDWLQJ VLWHV LQ WKH 3KDVH 2 VHJPHQW DW WKH IROORZLQJ WLPH SRLQWV: • **3KDVH 2, &1'1: SUH-GRVH, 0.5 DQG 1 KRXU SRVW GRVH** • **3KDVH 2, &1'22: 24 KRXUV SRVW PRUQLQJ GRVH RI 'D\ 21,** • **3KDVH 2, 'D\ 1 RI &\FOHV 2-6, DW OHDVW 1 KRXU SRVW GRVH**	7R FROOHFW DGGLWLRQDO 3. EORRG VDPSOHV GXULQJ 3KDVH 2 RI WKH VWXG\.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Pharmacokinetic Measurements	Schedule of Assessments (Footnote 25), Section 6.3	Modified text as follows: PK samples ~~are to~~ **should** be collected as close to the scheduled time as possible: ≤ 1 hour before drug administration, ±5 minutes through 6 hours post dose **and ±1 hour at the 24 hour post dose. If deviations in timing occur, the timing of the sample collection should be clearly marked.**	To clarify timing of PK blood collection sampling.
Overall Design and Plan of the Study	Section 3.1	Deleted the following text: "…and 12-lead electrocardiograms (ECGs) ~~taken in triplicate, with the average of the 3 ECGs used to calculate the corrected QT interval (QTc).~~	Clarification of text describing 12-lead ECG recordings.
Overall Design and Plan of the Study	Section 3.1	Revised text as follows: **All safety and efficacy laboratory tests will be analyzed by local laboratories.** A central laboratory will analyze **duplicate samples** of serum immunoglobulin levels, SPEP and UPEP of M-protein levels, serum and urine immunofixation (IFE) studies, **and SFLC analysis**~~. bone marrow biopsy/aspirate, and fluorescence in situ hybridization (FISH)/cytogenetic.~~ **A bone marrow aspirate sample will be centrally analyzed for fluorescence in situ hybridization (FISH)/cytogenetics. Results from the central efficacy analysis will not be shared with sites**	Clarification of how the safety and efficacy analyses will be conducted.
Justification of the Study Design	Section 3.4	Added the following new text: **Sparse PK sampling in Phase 2 will be analyzed to determine relationship of drug exposure to response and potential adverse events.**	Time points for PK blood sampling were added to the Phase 2 study segment.

3URWRFRO ,WHP	/RFDWLRQ RI &KDQJHV	'HVFULSWLRQ RI &KDQJHV LQ $PHQGPHQW 1, 7 $SULO 2014	5DWLRQDOH IRU &KDQJH
3DWLHQW ,GHQWLILFDWLRQ DQG 5HJLVWUDWLRQ	6HFWLRQ 4.5	0RGLILHG WH[W DV IROORZV: • **7KH SDWLHQW ZLOO EH DVVLJQHG D VHTXHQWLDO DQG XQLTXH SDWLHQW QXPEHU. 2QFH D SDWLHQW QXPEHU KDV EHHQ DVVLJQHG, LW FDQQRW EH UHXVHG.** • 7KH ,QYHVWLJDWRU RU WKH ,QYHVWLJDWRU¶V UHVHDUFK VWDII ZLOO SURYLGH HOLJLELOLW\ LQIRUPDWLRQ WR $FHW\ORQ. ~~7KH SDWLHQW ZLOO EH UHJLVWHUHG E\ $FHW\ORQ DQG DVVLJQHG D VHTXHQWLDO DQG XQLTXH SDWLHQW QXPEHU.~~ $V FRQILUPDWLRQ, $FHW\ORQ ZLOO SURYLGH WKH ,QYHVWLJDWRU ZLWK ZULWWHQ YHULILFDWLRQ RI HDFK SDWLHQW¶V UHJLVWUDWLRQ. ~~2QFH D~~ **1R** SDWLHQW ~~QXPEHU KDV EHHQ DVVLJQHG, LW FDQQRW~~ **PD** EH~~UHXVHG.~~**HQUROOHG RU EHJLQ WUHDWPHQW SULRU WR $FHW\ORQ UHJLVWUDWLRQ.** • ~~1R SDWLHQW PD\ EH HQUROOHG RU EHJLQ WUHDWPHQW SULRU WR $FHW\ORQ UHJLVWUDWLRQ DQG DVVLJQPHQW RI D SDWLHQW QXPEHU.~~	7R FODULI\ PHWKRGV RI SDWLHQW LGHQWLILFDWLRQ DQG UHJLVWUDWLRQ.
; LWKGUDZDO DQG 5HSODFHPHQW RI 3DWLHQWV	6HFWLRQ 4.6	$GGHG QHZ WH[W DV IROORZV: • **1RQ-DGKUHQFH WR WKH 320$/<67 5(06 RU 5HY$LG 3URJUDPV,**	7R LQGLFDWH WKDW SDWLHQWV PD\ EH ZLWKGUDZQ IRU QRQ-FRPSOLDQFH WR WKH UHVHFWLYH UHTXLUHPHQWV RI WKH 320$/<67 5(06 RU 5HY$LG 3URJUDPV.
3DWLHQW 0DQDJHPHQW	6HFWLRQ 4.7	0RGLILHG WH[W DV IROORZV: 3DWLHQWV ZLOO EH HYDOXDWHG DW WKH VWXG\ FHQWHU RQ 'D\V 1, 2, 8, 15, DQG 22 RI ~~HYHU\~~ F\FOH 1. **'XULQJ F\FOH 2, SDWLHQWV ZLOO EH HYDOXDWHG DW WKH VWXG\ FHQWHU RQ 'D\V 1 DQG 15.**)RU DOO VXEVHTXHQW F\FOHV, SDWLHQWV ZLOO EH HYDOXDWHG DW WKH VWXG\ FHQWHU RQ 'D\ 1. 3DWLHQWV ZKR ZLWKGUDZ IURP WKH VWXG\ DUH WR EH IROORZHG XS HLWKHU LQ SHUVRQ RU E\ SKRQH 30 GD\V (□3 GD\V) DIWHU WKH ODVW GRVH ~~RI~~ VWXG\ GUXJ. ~~RU ODWHU~~ LI ~~GUXJ UHODWHG $(V KDYH QRW UHVROYHG DW WKDW WLPH.~~	7R FODULI\ WLPLQJ RI WXG\ FHQWHU YLVLWV.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Patient Management	Section 4.7	Added new text as follows: **Upon discontinuation from the study for PD or any other reason, patients will be assessed 3 times per year (e.g., April, August, and December), for up to 5 years for survival, subsequent anti-myeloma therapies, and monitoring of second primary malignancies as outlined in Table 1. SAEs will be followed until 30 days after study treatment discontinuation. Subsequent therapies should be collected until death or end of the 5 year follow-up period. Survival follow up may be done via phone, when relevant. Patients who discontinue study treatment due to reasons other than PD will also be followed for efficacy assessments (see Section 6.2) until PD, death, or initiation of an alternate MM therapy, whichever occurs first.** **Patients who have been contacted at least 3 times without success (at least 1 month apart) should be sent a certified letter. If no contact is established, the patient will be deemed lost to follow up. A similar process will be followed for patients being followed up by phone. All attempted contact should be documented in the patient's medical chart.**	To clarify methods of patient follow-up after patients following study discontinuation as well as define parameters for Loss to Follow Up.
Study Drug Supply and Storage/Pomalidomide and Dexamethasone	Section 5.1.2	Pomalidomide will be dispensed by pharmacists to patients for the duration of their participation in this study at no charge to them or their insurance provider**, through the region-specific POMALYST REMS™ or RevAid® program. Patients will have to be registered in such a program and follow the required procedures to receive pomalidomide supply.** Only enough pomalidomide for one cycle of therapy will be supplied to the patient every cycle. Pomalidomide capsules are to be stored ~~at room temperature (20–25° C or 68–77° F),~~ **per the package insert** ~~away from direct sunlight and protected from excessive heat and cold. Additional storage conditions and dose dispensing instructions will be provided in detail within the Pharmacy Manual~~.	To update registration methods of for receipt of pomalidomide and storage conditions for pomalidomide.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Study Drug Dose and Administration/ACY-1215	Section 5.2.1	Modified text as follows: **On study center visit days requiring PK/pharmacodynamic blood draws, ACY-1215 must be taken in the study center. On other** study drug administration days that coincide with scheduled study center visits, ACY-1215 ~~will~~**may** be administered at the study center **or at home**. If ACY-1215 is being given BID, pomalidomide and dexamethasone are to be given with the first dose of ACY-1215. ~~When taking~~ **The** ACY-1215 BID, doses should be taken approximately every twelve hours. **A plus or minus 2 hour window is acceptable for BID dosing.**	To clarify how ACY-1215 will be administered.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Study Drug Dose and Administration/Pomalidomide	Synopsis (Test Products, Doses and Mode of Administration), Section 5.2.2	Added new text: **Pomalidomide (POMALYST®) will be provided to research patients for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ or RevAid® program. Per the standard POMALYST REMS™ and RevAid® program requirements, all physicians who prescribe pomalidomide for research patients enrolled into this trial, and all research patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ and RevAid® program. Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for Investigational New Drug studies. Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ and RevAid® programs.** If it is missed for the entire day, it should not be made up, **rather it should be taken at the next scheduled time point.** **Pomalidomide will be sent to the patients' home via the POMALYST REMS™ and RevAid® programs (see Appendix 9.3 and Appendix 9.4, respectively).**	To update how pomalidomide will be provided to patients in the POMALYST REMS and RevAid Programs and how the dose will be administered.
Dose Modifications/ ACY-1215	Section 5.2.8.1	Added new text: **Patients should receive 80% of planned doses for to be evaluable for SRC review.**	To clarify evaluation of DLT.
Dose Modifications/ Pomalidomide	Section 5.2.8.2	Added new text: Hold the pomalidomide dose for remainder of cycle. If the patient was not receiving GCSF therapy, initiate GCSF therapy **at the discretion of the treating physician.** **(Note, ANC must be ≥1000/ µL to restart dosing).**	To clarify text describing initiation of GCSF therapy for patients with neutropenia and resumption of pomalidomide dosing.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Dose Modifications/ Pomalidomide	Section 5.2.8.2	Added new text: **(Note, platelet count must recover to ≥ 50,000/ µL to restart dosing).**	To clarify text describing resumption of pomalidomide dosing in patients with Grade 4 thrombocytopenia.
Packaging and Labeling	Section 5.3.2	Added new text: **• Canada: Investigational Drug to be used by qualified investigators only.**	To update packaging and labeling to reflect approval of pomalidomide in Canada.
Packaging and Labeling	Section 5.3.2	Revised text as follows: **Celgene will provide pomalidomide 4, 3, 2, and 1 mg for PO administration. Pomalidomide will be dispensed to patients for the duration of their participation in this study at no charge to them or their insurance providers, through the region-specific POMALYST REMS™ or RevAid® program (see Appendix 9.3 and Appendix 9.4).** ~~Pomalidomide will be distributed to patients at the same time they receive ACY-1215. Bottles will contain a sufficient number of capsules for one cycle of dosing~~, **respectively).** **Pomalidomide capsules are to be stored, per the package insert (47, 52).**	To update packaging and labeling to reflect approval of pomalidomide in Canada.

3URWRFRO ,WHP	/RFDWLRQ RI &KDQJHV	'HVFULSWLRQ RI &KDQJHV LQ $PHQGPHQW 1, 7 $SULO 2014	5DWLRQDOH IRU &KDQJH
([FOXGHG 0HGLFDWLRQ DQG 6XEVWDQFHV	6HFWLRQ 5.6.2	$GGHG QHZ WH[W DV IROORZV: **7KH &DQDGLDQ SRPDOLGRPLGH SDFNDJH LQVHUW VWDWHV WKDW QR IRUPDO GUXJ LQWHUDFWLRQ VWXGLHV KDYH EHHQ FRQGXFWHG; KRZHYHU, SRPDOLGRPLGH LV D VXEVWUDWH RI 3 JO\FRSURWHLQ (3J-S) DQG LV SDUWO\ PHWDEROL]HG E\ &<31$2 DQG &<33$4.>52@:** • **7KH XVH RI SRPDOLGRPLGH ZLWK FRQFRPLWDQW VWURQJ &<31$2 LQKLELWRUV DQG VWURQJ &<33$4 LQKLELWRUV WRJHWKHU VKRXOG EH DYRLGHG.** • **,I VWURQJ LQKLELWRUV RI &<31$2 DUH FRDGPLQLVWHUHG ZLWK SRPDOLGRPLGH, SDWLHQWV VKRXOG EH FORVHO\ PRQLWRUHG IRU WKH RFFXUUHQFH RI $(V.** • **7KH ULVN RI WKURPERHPEROLF HYHQWV PD\ EH LQFUHDVHG ZLWK WKH VLPXOWDQHRXV XVH RI SRPDOLGRPLGH ZLWK HU\WKURSRLHWLF DJHQWV, KRUPRQH UHSODFHPHQW WKHUDS\ RU KRUPRQDO FRQWUDFHSWLYHV.** • **&LJDUHWWH VPRNLQJ PD\ UHGXFH WKH H|SRVXUH WR SRPDOLGRPLGH.** • **3RPDOLGRPLGH PD\ SRVVLEO\ LPSDLU PHQWDO DQG/RU SK\VLFDO DELOLWLHV UHTXLUHG IRU WKH SHUIRUPDQFH RI KD|DUGRXV WDVNV, VXFK DV GULYLQJ D FDU RU RSHUDWLQJ RWKHU FRPSOH[RU GDQJHURXV PDFKLQHU\.** P **'UXJV WKDW PD\ LQWHUDFW ZLWK SRPDOLGRPLGH LQFOXGH:** P **IOXYR|DPLQH, +RUPRQDO 5HSODFHPHQW 7KHUDS\, DQG** P **+RUPRQDO &RQWUDFHSWLYHV (HVWURJHQV DQG SURJHVWLQV).**	7R XSGDWH H[FOXGHG PHGLFDWLRQV DQG VXEVWDQFHV, SHU WKH &DQDGLDQ SRPDOLGRPLGH SDFNDJH LQVHUW.
6DIH\W\ 0HDVXUHPHQWV/ 3UHJQDQF\ 7HVWLQJ DQG &RXQVHOLQJ	6HFWLRQ 6.1.6..3	$GGHG QHZ WH[W DV IROORZV: **)&%3 PX\W FRPPLW HLWKHU WR DEVWDLQ FRQWLQXRXV\ IURP KHWHURVH[XDO VH|XDO LQWHUFRXUVH RU WR XVH 2 PHWKRGV RI UHOLDEOH ELUWK FRQWURO VLPXOWDQHRXV\ (RQH KLJKO**	7R XSGDWH WKH SUHJQDQF\ WHVWLQJ DQG SUHJQDQF\ FRQVHOLQJ UHTXLUHPHQWV EDVHG RQ WKH 320$/<67 5(06 DQG

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
		effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. **All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. For additional requirements of the POMALYST REMS™ Program regarding pregnancy testing, counseling, and acceptable methods of birth control, see Appendix 9.3.** **RevAid® Program (Canada)** **A FCBP is any female patient who: 1) is still menstruating; or 2) who is amenorrheic from previous chemotherapy treatments; 3) who is premenopausal.** **FCBP must have two medically supervised negative pregnancy tests prior to the first dispensed prescription of pomalidomide. Pregnancy tests must be performed in a licensed laboratory (serum test with a sensitivity of at least 25 mIU/mL) must occur 7 to 14 days and again within 24 hours prior to initiation of study drug. The dates and results of pregnancy tests must be documented. FCBP with regular or no menstruation must have a pregnancy test weekly for the first month of treatment, monthly thereafter during treatment (or every 2 weeks if menses are irregular) and for 4 weeks after discontinuation of treatment. FCBP must use at least 2 effective methods of contraception at the same time for at least 4 weeks before starting treatment, during interruptions of treatment, for at least 4 weeks after stopping treatment.** **All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks.**	RevAid® programs.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
		The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. For additional requirements of the RevAid® Program regarding pregnancy testing, counseling, and acceptable methods of birth control, see Appendix 9.4.	
Efficacy Measurements/ Bone Marrow Examination	Section 6.2.3	Revised text as follows: A bone marrow aspirate is to be performed at Screening **and when clinically indicated at the discretion of the treating physician. A biopsy is needed only if the marrow is unable to be aspirated. A bone marrow aspirate sample collected at Screening will be sent for central cytogenetic and FISH analysis** ~~and when clinically indicated at the discretion of the treating physician. A biopsy is needed only if the marrow is unable to be aspirated.~~ ~~Additionally, all bone marrow samples collected will be used for pharmacodynamic assessments (see Section 6.4).~~	To clarify that bone marrow aspirate samples will be centrally analyzed for FISH/cytogenetics.
Appendix	Appendix 9.3	Replaced former Appendix 9.3 "Pomalidomide Pregnancy Risk Minimization Plan with the following: **9.3. POMALYST REMS™ Program (United States)** **The full prescribing information, Pregnancy Testing Guideline and Pregnancy Risk Minimization Plan for FCBP and male patients in the US taking pomalidomide can be accessed using the following web link:** **http://www.pomalystrems.com/**	To reference the weblink containing all the relevant resources for the POMALYST REMS program.

Protocol Item	Location of Changes	Description of Changes in Amendment 1, 7 April 2014	Rationale for Change
Appendix	Appendix 9.4	Added the following new Appendix 9.4: **9.4. RevAid® Complete Guide for Health Care Practitioners (Canada)** **The full prescribing information, Pregnancy Testing Guideline and Pregnancy Risk Minimization Plan for FCBP and male patients in Canada taking pomalidomide can be accessed using the following web link:** **https://www.revaid.ca/revaid/**	To reference the weblink containing all the relevant resources for the RevAid program.