PROTOCOL

TITLE:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma
PROTOCOL NUMBER:	ACE-MY-001
STUDY DRUG:	ACP-196 (acalabrutinib)
IND NUMBER:	118717
EUDRACT NUMBER	2014-003587-21
SPONSOR MEDICAL MONITOR:	[redacted] Acerta Pharma BV [redacted] [redacted]
SPONSOR:	Acerta Pharma BV Kloosterstraat 9 5349 AB Oss The Netherlands
PROTOCOL DATE:	Version 0.0 - 11 July 2014
AMENDMENT 1 DATE:	Version 1.0 - 20 March 2015
AMENDMENT 2 DATE:	Version 2.0 - 13 January 2016

PROTOCOL APPROVAL PAGE

I have carefully read Protocol ACE-MY-001 entitled "An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP), all applicable regulatory requirements, and the ethical principles laid down in the Declaration of Helsinki. Furthermore, I understand that the Sponsor, Acerta Pharma, and the IRB/IEC must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma BV requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Acerta Pharma BV representative is authorized to sign the protocol and any amendments:

[redacted]

SUMMARY OF AMENDMENT 2

This protocol is being amended to add hepatitis serology testing at screening. For subjects who test positive for latent hepatitis B infection at screening (or who have a known history of hepatitis B infection), this protocol will now require monthly monitoring for potential hepatitis B reactivation. The reason for this amendment is hepatitis B reactivation has occurred in patients treated with Btk inhibitors including 1 subject receiving ACP-196 (Ngoma 2015).

Clarifying edits and typographical changes have been made throughout the protocol. In addition, the following substantive changes were made as part of this amendment:

Change	Rationale
In various parts of the protocol, the nonproprietary name for ACP-196 was introduced.	The nonproprietary name of acalabrutinib was recently approved for use.
Title Page Sponsor address changed from: Molenstraat 110 5342 CC Oss The Netherlands to new address of: Kloosterstraat 9 5349 AB Oss The Netherlands	Administrative change
Synopsis Updated to reflect changes made throughout the protocol.	To ensure consistency between the body of the protocol and the synopsis.
Section 3.4.2 Exclusion Criteria Revised text as follows (**bold** is new text): 11. **Known history of human immunodeficiency virus (HIV), serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction**	As hepatitis B virus (HBV) reactivation has occurred in 1 subject on ACP-196 treatment, this exclusion criterion was further clarified to state that subjects who are hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative PCR result before enrolling, and subjects who are hepatitis B surface antigen positive or hepatitis B PCR positive, and those who are hepatitis C PCR positive are excluded from the study.

Change	Rationale
(PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded. ~~Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.~~	
Section 3.7.2 Hepatitis B Virus Reactivation New section and corresponding language was added: **Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with ACP-196. Therefore, subjects who are hepatitis B core antibody (anti-HBc) positive, or have a known history of hepatitis B virus (HBV) infection, should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of ACP-196. Any subject with a rising viral load (above lower limit of detection) should discontinue ACP-196 and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming ACP-196 in subjects who develop HBV reactivation.** **Section 4.1.16 Hepatitis B and C Testing** New section and corresponding language was added: **Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and hepatitis C (HCV) antibody. Since intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, subjects who are receiving prophylactic IVIG and have positive**	As HBV reactivation has occurred in 1 subject on ACP-196 treatment, this language is being added to ensure adequate monitoring of patients who are anti-HBc positive or with a history of HBV. Subsequent sections were renumbered accordingly.

Change	Rationale
HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see Appendix 5 and exclusion criterion #11). Testing will be done by local or central laboratory. **Refer to Section 3.7.2 and Appendix 5 regarding monitoring of subjects who are anti-HBc positive or have a known history of HBV**	
Appendix 5. Schedule of Assessments The schedule of assessments and footnotes were revised, as appropriate, to match the body of the protocol as described above regarding hepatitis serology testing at screening and monthly HBV PCR testing.	Revised to be consistent with this amendment.

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ABBREVIATIONS

ACP-196	acalabrutinib
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
anti-HBc	hepatitis B core antibody
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BID	twice a day (dosing)
Btk	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CR	complete remission (response)
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FIH	first-in-human (trial)
FLC	(serum) free light chains
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HBsAb	hepatitis B surface antibody

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
ICF	informed consent form
IEC	Independent Ethics Committee
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IRB	Institutional Review Board
IVIG	intravenous immunoglobulins
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
ORR	overall response rate
PBMC(s)	peripheral blood mononuclear cells
PCR	polymerase chain reaction
PD	pharmacodynamics
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetics
PR	partial remission (response)
QD	once a day (dosing)
QM	every month
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SD	stable disease
SFLC	serum free light chains
SIFE	serum immunofixation electrophoresis
SPD	sum of the products of the perpendicular diameters (of lymph nodes)
SPEP	serum protein electrophoresis

SUSAR	Suspected Unexpected Serious Adverse Reaction (report)
T_{max}	time to maximum drug concentration
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine serum protein electrophoresis
VGPR	very good partial response
WHO	World Health Organization

STUDY SYNOPSIS

Protocol Number:	ACE-MY-001
Study Drug:	ACP-196 (acalabrutinib)
Protocol Title:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma
Phase:	Phase 1b
Comparator:	None
Background and Rationale for Study	Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton tyrosine kinase (Btk) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Preclinical studies have shown that Btk inhibition significantly reduces in vivo multiple myeloma (MM) cell growth and MM cell-induced osteolysis in a murine model (Tai 2012). Data on the utility of Btk targeted therapy in patients with MM is very preliminary, but suggests there are subsets of patients with malignant plasma cell clones in which Btk is active as evidenced by expression of phosphorylated Btk (p-Btk), and that these cancers may be particularly responsive to Btk inhibitor therapy. Acerta Pharma BV (Acerta Pharma) has developed a novel second generation Btk inhibitor, ACP-196, that achieves significant oral bioavailability and potency in preclinical models. ACP-196 monotherapy is currently in multiple Phase 1/2 studies in subjects with chronic lymphocytic leukemia (CLL) and other indications. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and activity of ACP-196 administration with and without dexamethasone in subjects with relapsed MM. The study will explore the concept of whether biomarkers may help identify patients with MM that are particularly likely to benefit from Btk inhibitor therapy.
Study Design:	This study is a multicenter, open-label, randomized, parallel-group study to be conducted at approximately 20 sites in 2 countries (United Kingdom and United States). Forty subjects will be equally randomized (1:1 ratio) into 2 cohorts to receive ACP-196, with and without dexamethasone: • Cohort 1: ACP-196 100 mg twice per day (BID) continuously • Cohort 2: ACP-196 100 mg BID continuously and dexamethasone 40 mg once weekly Twenty-eight days of study drug administration is 1 cycle. Treatment may be continued for > 28 days until disease

	progression or an unacceptable drug-related toxicity occurs. For subjects in Cohort 1, if documented disease progression occurs, then dexamethasone can be added to the treatment regimen. Additional dose modification provisions are provided in the study protocol. Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1 and Cycle 2. Tumor assessments will be done at 8- to 12-week intervals during the trial. Refer to Appendix 5 for a comprehensive list of study assessments and their timing. The end of trial is defined as the point when the last subject on the study exits the study for any reason.
Study Objectives:	**Primary Objective:** • To characterize the safety profile of ACP-196 with and without dexamethasone in subjects with relapsed or refractory MM **Secondary Objectives:** • To characterize the PK profile of ACP-196 with and without dexamethasone and the PK profile of dexamethasone with concomitant ACP-196 administration • To evaluate the PD effects of ACP-196 with and without dexamethasone • To evaluate the activity of ACP-196 with and without dexamethasone as measured by overall response rate, duration of response, clinical benefit rate, disease control rate, and progression-free survival • To explore the relationship between biological markers in MM cells and response to therapy
Safety Parameters:	Type, frequency, severity, timing of onset, duration, and relationship to study drug (ie, ACP-196, dexamethasone, or both) of any adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of study treatment.

Efficacy Parameters:	• Overall response rate (ORR) • Duration of response • Clinical benefit rate • Disease control rate • Progression-free survival
Pharmacokinetic Parameters:	The plasma PK of ACP-196 will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes: • AUC_{0-t}: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t). • AUC_{0-12}: Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation. • $AUC_{0-\infty}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant. • $AUC_{0-24calc}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}. • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • CL/F: Oral clearance
Pharmacodynamic Parameters:	The occupancy of Btk by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) and in bone marrow, when available, with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.
Sample Size:	Forty subjects with 20 subjects in each cohort.

Inclusion Criteria:	• Men and women ≥ 18 years of age.
	• A confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥ 1 prior therapy for MM, and is progressing at the time of study entry.
	• Evaluable myeloma at screening, defined as the presence of at least one of the following:
	  ○ Serum M-protein ≥ 0.5 g/dL
	  ○ Urine M-protein ≥ 200 mg/24 hours

	○ In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) **and** an abnormal serum kappa/lambda ratio ○ For subjects whose disease can only be reliably measured by serum quantitative immunoglobulin A (IgA), IgA ≥ 750 mg/dL (0.75 g/dL) • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. • Agreement to use acceptable methods of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children. • Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug. • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).
Exclusion Criteria:	• Plasma cell leukemia or circulating plasma cells ≥ 2 x 10^9/L • Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor. • A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ACP-196, or put the study outcomes at undue risk. • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec. • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Any immunotherapy within 4 weeks of first dose of study drug. • The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s). • Prior exposure to a B-cell receptor (BCR) inhibitor (eg, Btk, phosphoinositide-3 kinase [PI3K], or Syk inhibitors) or BCL-2 inhibitors (eg, ABT-199).

	• Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MM or other conditions. Note: Subjects may use topical or inhaled corticosteroids as therapy for comorbid conditions. During study participation, subjects may receive systemic or enteric corticosteroids as needed for MM therapy or treatment-emergent comorbid conditions. • Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation. • Known history of human immunodeficiency virus (HIV), serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded. • Major surgery within 4 weeks before first dose of ACP-196. • Known history of a bleeding diathesis (eg, hemophilia, von Willebrand disease) • History of stroke or intracranial hemorrhage within 6 months before the first dose of ACP-196. • Requires or receiving anti-coagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 28 days of first dose of study drug. • Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) • ANC < 0.75 x 10^9/L or platelet count < 50 x 10^9/L. For subjects with > 50% plasma cells in the marrow, ANC < 0.50 x 10^9/L or platelet count < 30 x 10^9/L. • Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN; or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN. • Breastfeeding or pregnant. • Concurrent participation in another therapeutic clinical trial.
Dosage Form and Strength:	ACP-196 is provided as 100-mg hard gelatin capsules prepared using standard pharmaceutical grade excipients.
Dose Regimen/Route of Administration:	ACP-196 is an orally administered product. ACP-196 can be administered with or without food. <u>Regimens:</u> • Cohort 1 (BID): 100 mg ACP-196 (1 x 100-mg capsule) administered 12 hours apart (BID dosing = 200-mg total daily dose)

	• Cohort 2 (BID + dexamethasone): 100 mg ACP-196 (1 x 100-mg capsule) administered 12 hours apart (BID dosing = 200-mg total daily dose) plus 40 mg dexamethasone administered once weekly (weekly dosing = 40-mg total weekly dose)
Concomitant Medications:	The effect of agents that reduce gastric acidity (eg, proton pump inhibitors, H2-receptor antagonists, or antacids) on ACP-196 absorption is currently being evaluated in a healthy volunteer study (ACE-HV-004). Preliminary results from this study suggest subjects should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids or calcium supplements) and short-acting H2-receptor antagonists for a period of at least 2 hours before and after taking ACP-196. Use of omeprazole or esomeprazole or any other long-acting proton pump inhibitors while taking ACP-196 is not permitted due to a potential decrease in study drug exposure; however, if a subject requires treatment with a long-acting proton pump inhibitor while on study (eg, to treat an ulcer), treatment options should be discussed with the Medical Monitor. Concomitant use of strong inhibitors/inducers of CYP3A should be avoided when possible. If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities.
Statistics:	Subjects meeting the stated eligibility requirements will be enrolled onto the study. Subjects will be randomized in a 1:1 ratio into the 2 regimens (ACP-196 with and without dexamethasone). With a sample size of 19 subjects per cohort, the power to detect the difference between a null-hypothesis response rate of 15% and an alternative response rate of 40% with a 0.025 one-sided significance level is 0.69 using a one-group, exact binomial test. A sample size of 19 subjects per cohort will also provide a 97.5% one-sided confidence interval centered around an expected ORR of 40% that excludes an ORR of 18.6% as a lower bound. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data, as appropriate.

1.0 BACKGROUND INFORMATION

1.1 ROLE OF BTK IN LYMPHOID CANCERS

Bruton tyrosine kinase (Btk) is a non-receptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Mohamed 2009, Bradshaw 2010). Functional null mutations of Btk in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells (Vihinen 2000). Conversely, Btk activation is implicated in the pathogenesis of several B-cell malignancies (Buggy 2012). Taken together, these findings have suggested that inhibition of Btk may offer an attractive strategy for treating B-cell neoplasms.

Ibrutinib (IMBRUVICA™), a first-generation oral, small-molecule Btk inhibitor has been approved for the treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) and is being evaluated for activity in other B-cell neoplasms including multiple myeloma (MM). Preclinical studies have shown that Btk inhibition with ibrutinib significantly reduces in vivo multiple myeloma (MM) cell growth and MM cell-induced osteolysis in a murine model (Tai 2012).

While current therapies have provided substantial benefit to patients, MM remains incurable; for patients who experience disease relapse after application of existing therapies, the prognosis is dismal and new drugs and therapeutic strategies are required for continued disease control (Romano 2014). Inhibition of Btk may simultaneously address the MM-related bone complications as well improve patient outcome in MM (Edwards 2012).

While highly potent in inhibiting Btk, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in Btk to which the drug covalently binds. The inhibition of epidermal growth factor receptor (EGFR) is also observed in cellular assays and may be the cause of ibrutinib-related adverse events (AEs) of diarrhea and rash (IMBRUVICA® package insert). In addition, ibrutinib is a substrate for CYP3A4; inhibition of CYP3A causes a 29-fold increase in maximum concentration (C_{max}) and 24-fold increase in area under the curve (AUC) for ibrutinib (IMBRUVICA® package insert). This increases the possibility of drug-drug interactions in combination therapies with drugs currently used in management of subjects with

cancer. These liabilities support the development of alternative Btk inhibitors for use in the therapy of B-cell malignancies.

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of ACP-196 (also known as acalabrutinib), an orally bioavailable, new chemical entity that covalently inhibits Btk and shows encouraging activity and acceptable safety in nonclinical studies. Within the class of Btk inhibitors, ACP-196 is a more selective inhibitor of Btk than ibrutinib. Key nonclinical differentiators of ACP-196 versus ibrutinib are:

- ACP-196 has been evaluated against ibrutinib in EGFR expressing cell lines. Ibrutinib is a potent covalent inhibitor of EGFR (EC50 = 50 to 70 nM). ACP-196 does not inhibit EGFR even at the highest concentration tested (10 μM).
- ACP-196 has been evaluated against ibrutinib in in vitro antibody-dependent cell-mediated cytotoxicity (ADCC) assays. At physiologic concentrations, ibrutinib, but not ACP-196, reduced natural killer (NK) cell-mediated lysis of Raji and autologous CLL tumor cells and significantly inhibited rituximab-induced NK cell cytokine secretion ($P<0.05$).
- ACP-196 has been evaluated against ibrutinib in an in vivo thrombus formation model. At physiologic concentrations, ibrutinib, but not ACP-196, significantly inhibited thrombus formation ($P=0.001$).

The nonclinical and toxicology results of ACP-196 suggest it may have an improved therapeutic window relative to ibrutinib; it may be more readily combined with other agents for the treatment of cancer.

1.2 PRECLINICAL STUDIES

Summaries of preclinical studies are provided below. For more detailed information please refer to the Investigator's Brochure.

1.2.1 Chemistry

[redacted] ACP-196 is orally bioavailable in humans and is suitable for formulating in capsules. For clinical testing, ACP-196 has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

1.2.2 Efficacy Pharmacology

Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to Btk inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). ACP-196 is currently being evaluated in an ongoing dose-escalation study in canine spontaneous B-cell lymphoma. Fourteen dogs, all of which had diffuse large B-cell lymphoma (DLBCL) confirmed by histology, have been treated with ACP-196 for at least 2 weeks. The dosages have ranged from 2.5 to 20 mg/kg once (QD) or twice (BID) per day. To date, per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), partial responses (PRs) been observed in 4 of 14 dogs (29%) and stable disease has been observed in 8 of 14 dogs (57%). No ACP-196-related adverse events (AEs) have been reported to date in this study. These findings are preliminary and similar to the clinical responses (ie, 1 dog with PR out of 5 dogs treated with suspected or confirmed DLBCL) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

Preliminary results assessing Btk occupancy using a biotin-tagged analogue of ACP-196 show near complete Btk occupancy over 24 hours with both BID and QD dosing in canine tumor tissue (Table 1-1).

Table 1-1. Assessment of ACP-196 Active-site Occupancy in Fine Needle Aspirates of Canine Lymph Node Tumors (N=4)

	Dog Identification and ACP-196 Dosing Regimen			
	DL-10	DL-12	DL-14	DL-16
	5 mg/kg BID	10 mg/kg QD	20 mg/kg QD	20 mg/kg QD
Timing	Btk Occupancy (% versus predose)			
Day 1 (3 hours after morning dose)	98%	99%	98%	99%
Day 7 (before morning dose)	80%	98%	77	93%

BID = twice per day; Btk = Bruton tyrosine kinase; QD = once per day

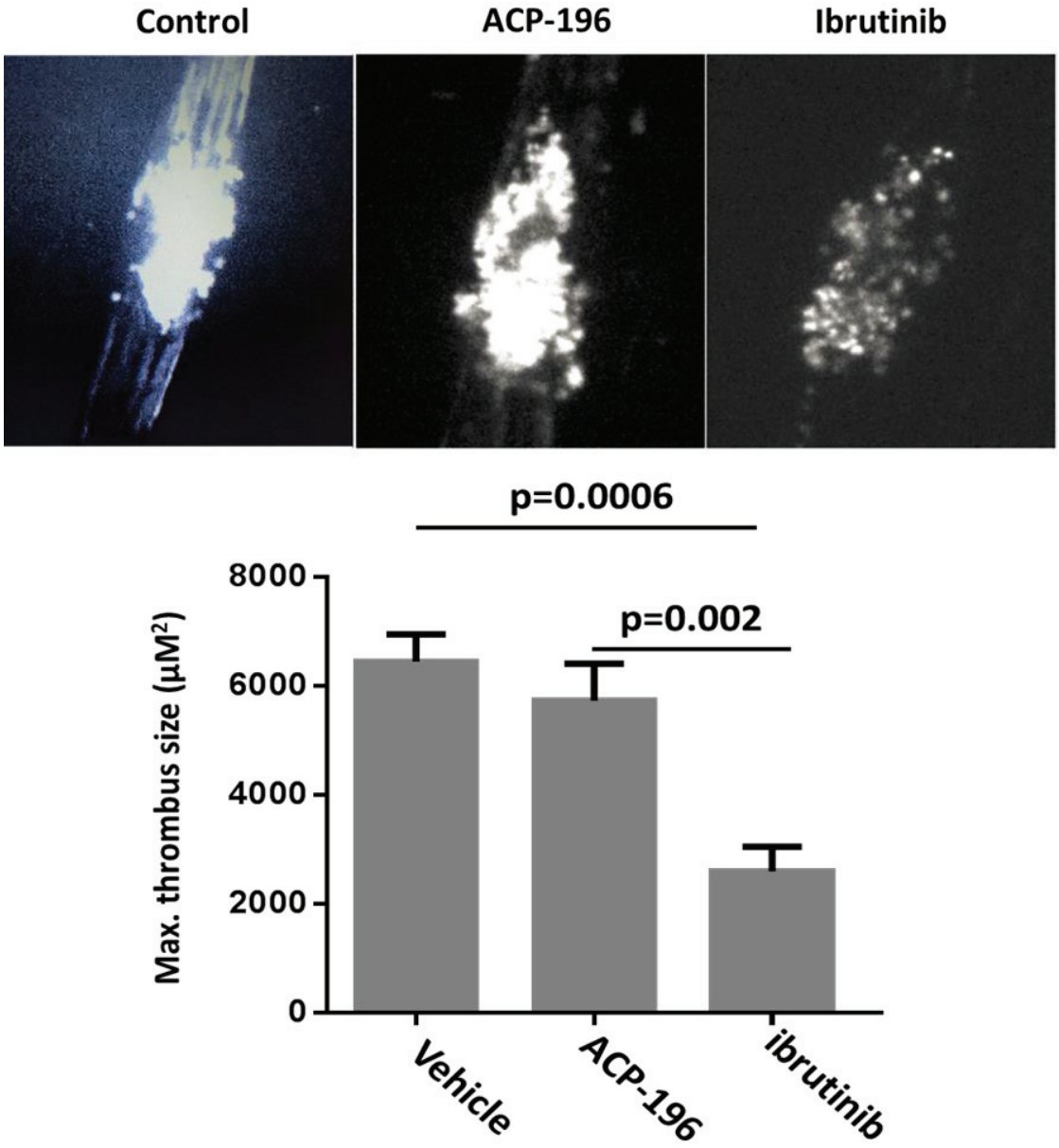
These canine data provide nonclinical support for the ability of ACP-196 to target Btk in vivo. The role of Btk expression in driving the proliferation and survival of malignant plasma cells in multiple myeloma (MM) has been less clear than among other lymphoid cancers. However, emerging, unpublished, preclinical data from the laboratory of Sagar Lonial (Emory University) suggest that Btk and phosphorylated Btk (p-Btk) expression is

present to varying levels in a standard panel of 12 myeloma cell lines, thus providing a basis for evaluating Btk inhibition as a therapy for MM.

1.2.3 ACP-196 and Thrombus Formation

Ibrutinib is associated with an increased risk of bleeding (Kamel 2014). Hence, the effects of ACP-196 and ibrutinib were evaluated on human platelet-mediated thrombosis by using the in vivo human thrombus formation in a VWF^{HA1} murine model, which has been previously described (Chen 2008). Purified human platelets were preincubated with various concentrations of ibrutinib and ACP-196 (0.1 µM, 0.5 µM, or 1 µM for each) or DMSO and then administered to VWF^{HA1} mice followed by laser-induced thrombus formation. Ibrutinib- and ACP-196-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Thrombus formation in response to laser-induced vascular injury was monitored in real time using 2-channel confocal intravital microscopy (Furie 2005) (Figure 1-1). Upon induction of arteriole injury, untreated platelets rapidly formed thrombi with a mean (± SEM) thrombus size of 6450 ± 292 mm^2. Similarly, ACP-196 (1 µM) treated platelets formed slightly smaller but not significantly different thrombi, with a mean thrombus size of 5733 ± 393 mm^2. In contrast, a significant reduction in thrombus size occurred in platelets pretreated with ibrutinib (1 µM); mean thrombus size was 2600 ± 246 mm^2, representing in a reduction in maximal thrombus size by approximately 61% compared with control (P=0.001). Similar results were obtained with platelets pretreated with 500 nM of ACP-196 or ibrutinib: mean thrombus sizes were 5946 ± 283 mm^2 and 2710 ± 325 mm^2, respectively. These preliminary results showing reduced thrombus formation for ibrutinib at physiologically relevant concentrations (0.5 to 1 µM) may provide some mechanistic background for the Grade ≥ 3 bleeding events (eg, subdural hematoma, gastrointestinal bleeding, hematuria, and post procedural hemorrhage) that have been reported in ≤ 6% of patients treated with ibrutinib. In addition, bleeding events of any grade, including bruising and petechiae, were reported in approximately half of patients treated with ibrutinib (IMBRUVICA® package insert).

Figure 1-1. Effect of ACP-196 (1 µM) and Ibrutinib (1 µM) on Thrombus Formation



1.2.4 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with ACP-196 have demonstrated a favorable nonclinical safety profile.

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, ACP-196 shows significant activity only against the

A3 adenosine receptor; follow-up dose-response experiments indicated a IC_{50} of 2.7 μM, suggesting a low clinical risk of off-target effects. ACP-196 at 10 μM showed no inhibition of in vitro epidermal growth factor receptor (EGFR) phosphorylation in an A431 human epidermoid cancer cell line, whereas ibrutinib had an IC_{50} of 66 nM.

The in vitro effect of ACP-196 on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. ACP-196 inhibited hERG channel activity by 25% at 10 μM, suggesting a low clinical risk that ACP-196 would induce clinical QT prolongation as predicted by this assay.

ACP-196 was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of ACP-196 at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that ACP-196 is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.2.5 Drug-drug Interaction Potential

The in vitro studies suggest CYP-mediated metabolism of ACP-196 appears to be catalyzed predominantly by CYP3A4/5. However, in elimination studies in preclinical species, the metabolic fate of ACP-196 is dominated by direct conjugation of ACP-196 with glutathione, providing evidence for a significant non-CYP mechanism of elimination. In a healthy volunteer study (ACE-HV-001), the effect of coadministration of a potent CYP3A and P-gP inhibitor, itraconazole, on the plasma levels of ACP-196 was evaluated. The mean plasma ACP-196 C_{max} and $AUC_{0\text{-last}}$ values increased 3.7- and 5.1-fold, respectively, in the presence of itraconazole relative to no pretreatment. In vitro studies also show that ACP-196 is a substrate for P-gp.

ACP-196 is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms.

Results from drug transporter studies suggest that ACP-196 is not anticipated to alter the PK of other therapeutic agents that are substrates for MDR1, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2. ACP-196 (100 mg BID) may alter the PK of BCRP substrates by inhibition of intestinal BCRP.

1.2.6 In Vivo General Toxicology

To date, the toxicology program has included 28-day GLP evaluations in rats and dogs. In the 28-day study in male and female Sprague-Dawley rats, animals received oral gavage ACP-196 dosages of 30, 100, and 300 mg/kg/day. In the 28-day study in male and female beagle dogs, animals received oral ACP-196 dosages of 3, 10, and 30 mg/kg/day. Both studies had 28-day recovery periods.

The no observable adverse effect level in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, 100 mg/kg/day was selected to conservatively represent the highest nonseverely toxic dose (HNSTD). In dogs at 30 mg/kg/day, no adverse effects on the pancreas were observed. In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the 28-day toxicology studies. However, in 5 of 6 rats from the 300-mg/kg dose group that died early in the study, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts. These findings were most likely incidental postmortem changes.

1.3 CLINICAL EXPERIENCE

Table 1-2 lists the studies currently being conducted with ACP-196 monotherapy.

Table 1-2. ACP-196 Clinical Studies as of January 2015

Protocol	Design	Subjects Enrolled	Status
ACE-CL-001 (NCT02029443)	• First-in-human • Open label • Dose escalation (ACP-196 100-400 mg QD and 100-200 mg BID) • Subjects with relapsed/refractory CLL • Expansion cohorts: o treatment-naive subjects o subjects with Richter's syndrome o subjects who are intolerant to ibrutinib treatment o subjects who are relapsed/refractory to ibrutinib treatment	125	• Cohort 1 (100 mg QD) enrolled and no DLTs observed. • Cohort 2a (175 mg QD) enrolled and no DLTs observed. • Cohort 3 (250 mg QD) enrolled and no DLTs observed. • Cohort 4a (400 mg QD) enrolled and no DLTs observed. • Cohort 2b (100 mg BID now enrolling) and no DLTs observed. • Expansion cohorts now enrolling.
ACE-HV-001	• Open label • Single-dose escalation (ACP-196 2.5-50 mg BID and 100 mg QD) • Food effect (ACP-196 75 mg QD) • Drug-drug interaction with itraconazole (ACP-196 50 mg QD) • Healthy volunteers	59	• Enrollment completed. • No adverse laboratory, vital signs, or ECGs findings observed. • 1 event each of constipation, feeling cold, somnolence (each Grade 1) was reported as related to study drug.
ACE-HV-004	• Open label • ACP-196 100 mg • Drug-drug interaction: o Calcium carbonate o Omeprazole o Rifampin • Healthy volunteers	72	• Enrollment completed. • No adverse laboratory, vital signs, or ECGs findings observed. • Other analyses pending.
ACE-LY-002 (NCT02112526)	• Open label • ACP-196 100 mg BID • Activated B-cell subtype of diffuse large B-cell lymphoma	6	• Enrollment recently begun
ACE-WM-001 (NCT02180724)	• Open label • ACP-196 100 mg BID and 200 mg QD • Waldenström macroglobulinemia	7	• Enrollment recently begun
ACE-LY-003 (NCT02180711)	• Open label • ACP-196 100 mg BID and 200 mg QD • Follicular lymphoma	1	• Enrollment recently begun
15-H-0016 (NIH study)	• Open label • ACP-196 200 mg QD and 100 mg BID • CLL	0	• Enrollment recently begun
ACE-ST-003	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic pancreatic cancer	0	• Protocol in study start up

AE = adverse event; BID = twice per day; CLL = chronic lymphocytic leukemia; DLT = dose-limiting toxicity; ECGs = electrocardiograms; QD = once per day

Table 1-2. ACP-196 Clinical Studies as of January 2015 (continued)

Protocol	Design	Subjects Enrolled	Status
ACE-ST-005 (NCT02351739)	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic bladder cancer	0	• Protocol in study start up
ACE-LY-004 (NCT02213926)	• Open label • ACP-196 100 mg BID • Mantle cell lymphoma	0	• Enrollment recently begun
ACE-CL-002 (NCT02157324)	• Open label • ACP-196 50 mg BID and ACP-319 25 mg BID • CLL	8	• Enrollment recently begun
ACE-LY-001 (NCT02328014)	• Open label • ACP-196 100 mg BID and ACP-319 25 to 100 mg BID • B-cell malignancies	1	• Enrollment recently begun
ACE-CL-003 (NCT02296918)	• Open label • ACP-196 200 mg QD and Obinutuzumab per label • CLL	2	• Enrollment recently begun
ACE-HI-001	• Hepatic impairment study • ACP-196 50 mg QD	18	• Enrollment ongoing
ACE-LY-005	• Open label • ACP-196 100 mg BID and pembrolizumab 2 mg/kg IV Q3W • B-cell malignancies	None	• Protocol in study start up
ACE-ST-006	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic head & neck cancer	0	• Protocol in study start up
ACE-ST-007	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic non-small cell lung cancer	0	• Protocol in study start up

AE = adverse event; BID = twice per day; CLL = chronic lymphocytic leukemia; DLT = dose-limiting toxicity; ECGs = electrocardiograms; IV = intravenous; Q3W = once every 3 weeks; QD = once per day

1.3.1 Pharmacokinetics and Pharmacodynamics of ACP-196 in Healthy Volunteers

ACE-HV-001 was a dose-ranging, food-effect, and drug-drug interaction study evaluating BID and QD dosing for 1 or 2 days in healthy volunteers. The starting dose for ACP-196 was 2.5 mg BID. This study has been completed and no adverse laboratory, vital signs, or ECG findings were observed (2.5 to 50 mg BID; 50 to 100 mg QD). Three AEs related to ACP-196 were reported. Each AE was Grade 1 and resolved

without treatment. The AEs were constipation (2.5 mg BID), feeling cold (75 mg QD), and somnolence (75 mg QD).

In Part 1, PK properties of ACP-196 were evaluated after oral administration of 2 daily doses of 2.5 to 50 mg and a single dose of 100 mg. Of the 30 subjects evaluated, all had measurable systemic concentrations of ACP-196. ACP-196 plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts and independent of the dose level. The increase in mean maximum concentration (C_{max}) values was greater than dose proportion based on the increases of C_{max} from the first dose administered. When evaluating area under the concentration curve (AUC_{0-12}, AUC_{0-24} or AUC_{0-inf}), the mean values increased in a dose proportional manner based on the increases of the total dose administered. Mean half-life ($t_{1/2}$) values ranged from 0.97 to 2.1 hours, and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (Vz/F: 233 to 612 L) appeared to be independent of the dose administered.

ACP-196 was not detected in the urine of subjects who received the 2.5- or 5.0-mg BID doses of ACP-196. ACP-196 was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose dependent manner.

In Part 2, the effect of food on the PK of ACP-196 (75 mg) after a single oral administration was evaluated in 6 men and 6 women. Median ACP-196 plasma T_{max} values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma ACP-196 C_{max} values decreased to 27.3% of the values observed in the fasted state. In contrast, the relative exposure of ACP-196 (AUC) remained mostly unchanged in both states. Per FDA guidance on food-effect studies (FDA 2002), this decrease in exposure is not clinically significant, and therefore, ACP-196 can be taken with or without food.

In Part 3, after administration of a single dose of ACP-196 (50 mg), the effect of itraconazole on the PK was evaluated in 17 subjects. No difference in ACP-196 T_{max} values was observed in the presence or absence of itraconazole.

Mean ACP-196 exposures (as assessed by C_{max}, AUC_{0-last}, AUC_{0-24}, and AUC_{0-inf}) increased in the presence of itraconazole. The mean plasma ACP-196 C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma AUC_{0-last}, AUC_{0-24}, and AUC_{0-inf} values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and Vz/F values decreased in the presence of itraconazole

(CL/F: 217 vs 44 L/h; Vz/F: 1190 vs 184 L). No differences in half-life values were observed (3.3 vs 2.5 hours).

The pharmacodynamics (PD) profile of ACP-196 was evaluated using a Btk occupancy assay and correlated with a functional assay that determines the level of Btk inhibition by measuring expression of CD69 and CD86 on B-cells. A dose-dependent increase in Btk occupancy and corresponding decrease in CD69/86 expression was observed in this study. Full Btk occupancy (≥ 90%) and complete CD86 and CD69 inhibition (≥ 90%) occurred in the 75- and 100-mg single dose cohorts 1 to 3 hours after administration. However, only the 100 mg cohort maintained high Btk occupancy (91.5%) and high BCR functional inhibition (CD86: 86 ± 3% and CD69: 78 ± 8%) at 24 hours. For subjects who received a second dose of ACP-196 12 hours after the first administration, full Btk target occupancy was observed 3 hours after the second dose for the 50 mg dose cohort (Btk occupancy 97 ± 4%).

1.3.2 Clinical Experience of ACP-196 in CLL

ACE-CL-001 (NCT02029443), an ongoing Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL or Richter's syndrome, has a sequential, dose-escalation design. As of 22 January 2015, 125 subjects have received ACP-196 at dosages from 100 to 400 mg QD or 100 to 200 mg BID.

To date, ACP-196 has been well tolerated at all dose levels evaluated. No dose-limiting toxicities (DLTs) have occurred at any dose level. The MTD was not reached in this study; however, per the protocol, dose escalation was stopped once a plateau in PK was observed (ie, between 250 and 400 mg).

Preliminary data from ACE-CL-001 show that Btk occupancy with ACP-196, in peripheral blood cells, is > 95% at 4 hours but decreases to < 95% at 24 hours, while with BID dosing complete Btk occupancy (97% to 99%) is maintained over 24 hours at steady state (Table 1-3). These data suggest that synthesis of de novo Btk may occur within 24 hours.

Table 1-3. Btk Occupancy in Peripheral Blood of Subjects from ACE-CL-001 (December 2014)

	Subjects with Relapsed/Refractory CLL			
Timepoint*	**100 mg QD (n=8)**	**175 mg QD (n=8)**	**250 mg QD (n=6)**	**100 mg BID (n=17)**
Day 7: Median % Occupancy 24 h	89.0	86.9	93.5	**97.4**
Day 8: Median % Occupancy 4 h	98.6	98.7	100	**98.8**

Abbreviations: BID = twice per day; CLL = chronic lymphocytic leukemia; QD = once per day
*Note: 24-h timepoint on BID regimen represents 24 hours after first dose and 12 hours after second dose on Day 7. The 4-h timepoint on the BID regimen represents 4 hours after the first dose on Day 8.

Preliminary PK data from Day 8 show dose linearity from 100 to 250 mg and no accumulation with repeat dosing (Table 1-4).

Table 1-4. Preliminary Day 8 PK Results from ACE-CL-001 (October 2014)

Cohort	**Mean C_{max} ± SD (ng/mL)**	**Mean $AUC_{0\text{-last}}$ ± SD (ng•h/mL)**
100 mg QD (N=8)	529 ± 286	634 ± 197[a]
175 mg QD (N=7)	800 ± 692	1240 ± 789
250 mg QD (N=7)	1350 ± 933	2170 ± 1180
400 mg QD (N=6)	932 ± 576	1870 ± 1040
100 mg BID (N=22)	716 ± 658	837 ± 485[b]

Timepoints: Predose, 0.25, 0.50, 0.75, 1.0, 2.0, 4.0, and 6.0 postdose.
[a] N=7 for AUC calculations in 100 mg QD dose group.
[b] BID regimens were not sampled during the second daily dose interval; 0-24 h exposures are expected to be approximately 2-fold the $AUC_{0\text{-}6}$ values shown.
AUC = area under the curve; BID = twice per day; C_{max} = maximum concentration; SD = standard deviation

To date, 31 subjects have been evaluated for tumor response, by investigators, based on International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include partial response with treatment-induced lymphocytosis. Based on preliminary, unaudited data an overall response rate (ORR) of 94% (71% PR + 23%

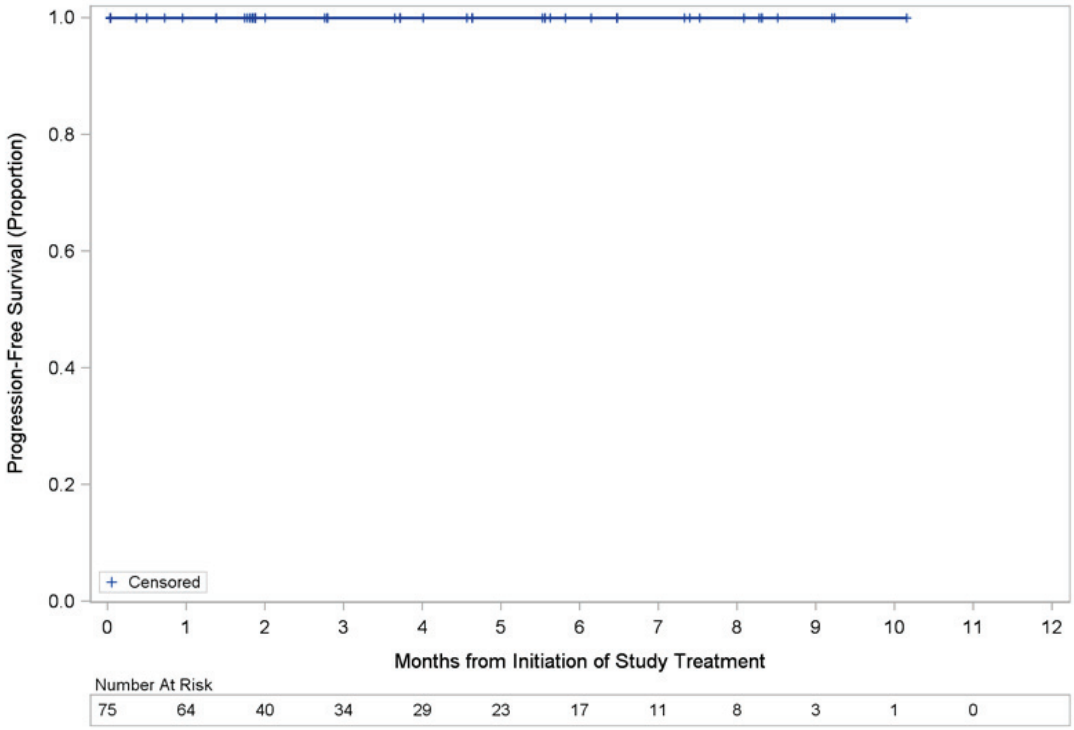
PR with lymphocytosis) has been observed (Table 1-5). Of the 31 subjects assessed, nearly half (15 of 31) have 17p del. Of the 15 subjects with 17p del, 80% (12/15) have PR and 20% (3/15) have PR with lymphocytosis. The median follow-up for the ACP-196 subjects evaluated for response is 7.3 cycles (range 3.0 to 10.8) and each cycle is 28 days. No primary disease progression has occurred on study (N = 75; Figure 1-2).

Table 1-5. Best Response by Cohort from ACE-CL-001 (23OCT2014)

n (%)	All Cohorts (N=31)	100 mg QD (N=8)	175 mg QD (N=8)	250 mg QD (N=7)	100 mg BID (N=3)	400 mg QD (N=5)
PR	22 (71)	7 (88)	5 (71)	4 (57)	3 (100)	2 (40)
PR+L	7 (23)	0 (0)	3 (38)	2 (29)	0 (0)	2 (40)
SD	2 (6)	1 (12)	1 (13)	0 (0)	0 (0)	1 (20)
PD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
			Median (range) Cycles			
	7.3 (3.0-10.8)	10.0 (9.0-10.8)	8.6 (3.0-8.8)	7.0 (7.0-7.3)	5.2 (4.7-5.5)	5.0 (4.8-5.5)

BID = twice per day; PD = progressive disease; PR = partial response; PR+L = partial response with lymphocytosis; QD = once per day; SD = stable disease

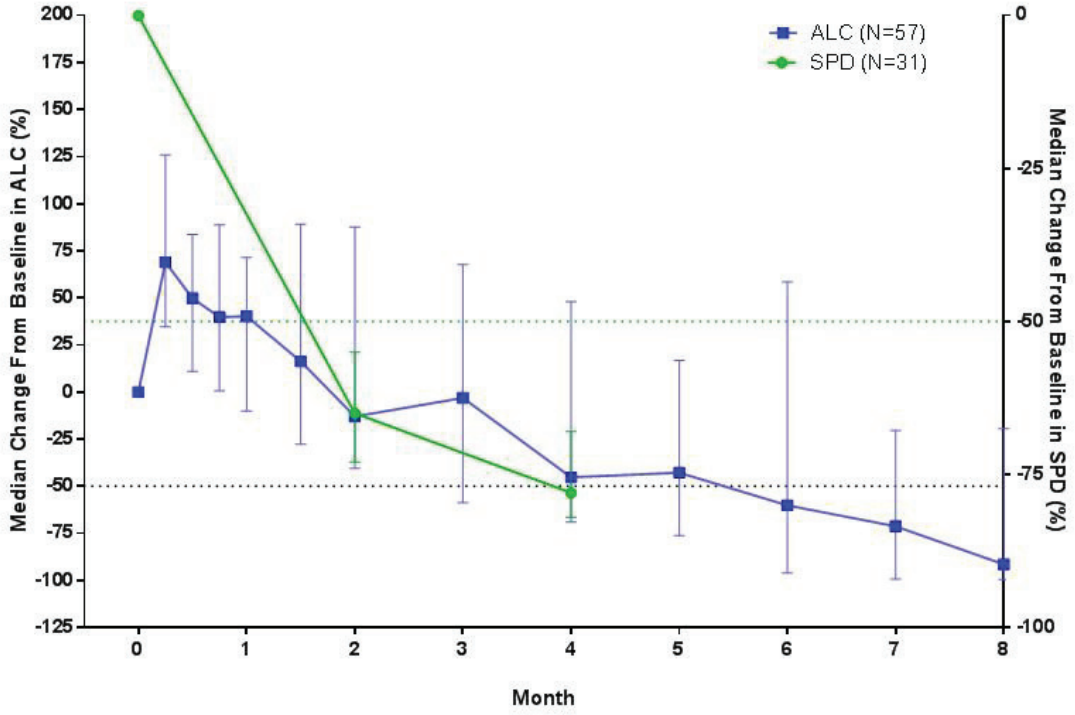
Figure 1-2. Kaplan-Meier Curves for Progression-free Survival by Investigator Assessment for ACE-CL-001 (N=75; excludes Richter's Syndrome Cohort and Ibrutinib R/R Cohort)



These results compare favorably with the Phase 3 results of ibrutinib, the first generation Btk inhibitor, when administered at dosages of 420 mg QD in subjects with relapsed/refractory CLL (N=195). In the ibrutinib study, Byrd and colleagues (2014) report a PR rate of 43%, a PR with lymphocytosis rate of 20%—for an ORR of 63%—an SD rate of 32%, and a progressive disease (PD) rate of 3% (Byrd 2014) based on independent review. The median follow-up time reported for the ibrutinib study was 9.5 months (range 0.1 to 16.6).

Figure 1-3 shows the change from baseline in sum of the product of the diameters (SPD) (N=31) and in absolute lymphocyte count (ALC) (N=57) over time. As shown in the figure, substantial reductions in lymphadenopathy have been observed despite the fact that three-quarters of the evaluable subjects have high-risk cytogenetics (17p del, 11q del, or both). As mentioned above, the observed reductions in lymphadenopathy are consistent with the clinical results for ibrutinib (Byrd 2013, Byrd 2014). However, the reduced drug-induced lymphocytosis and the rapid time to resolution of lymphocytosis with ACP-196 treatment varies greatly from that reported for ibrutinib. Per the IMBRUVICA package insert, 77% of patients with CLL treated with ibrutinib experienced lymphocytosis, which occurred during the first month of therapy and resolved by a median of 23 weeks (range 1 to 104+ weeks). With ACP-196 treatment, the onset of lymphocytosis, if it occurs, is within the first week of treatment and resolves by a median of 8 weeks (range 0 to 24+ weeks).

Figure 1-3. Median (95% CI) Change from Baseline in ALC/SPD Over Time



ALC = absolute lymphocyte count; CI = confidence interval; SPD = sum of the products of the perpendicular diameters (of lymph nodes).

1.4 BENEFIT/RISK

ACP-196 is a potent, orally available small-molecule inhibitor of Btk. A PK/PD study has been completed with ACP-196 in healthy volunteers (ACE-HV-001; Section1.3.1). The safety results showed no identified safety risks in healthy subjects receiving 1 or 2 days of ACP-196 ≤ 100 mg. In study ACE-CL-001, a study of ACP-196 in subjects with relapsed/refractory or previously untreated CLL or Richter's syndrome, no DLTs have been reported at dosages of ≤ 400 mg QD or 100 and 200 mg BID. The overall response rate in the evaluable subjects for this study is currently 94% with some subjects obtaining PRs after only 2 cycles of therapy. Based on these robust results in subjects with CLL, the evaluation of ACP-196 in subjects with relapsed or refractory MM is warranted.

1.5 SUMMARY AND CONCLUSIONS

This study comprises a pilot evaluation of the safety and activity of the potent, second-generation Btk inhibitor, ACP-196, in patients with relapsed or refractory MM. The design

and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with lymphoid cancers; knowledge of the efficacy and safety of the first-generation BCR inhibitor (eg, ibrutinib) in subjects with hematologic cancers; and the available nonclinical and clinical information regarding ACP-196. Preclinical studies are ongoing in parallel to identify biomarkers that may be evaluated in this clinical trial as correlates of response to Btk-directed therapy and that may permit selection of patients who are particularly likely to benefit from ACP-196 treatment for MM.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To characterize the safety profile of ACP-196 with and without dexamethasone in subjects with relapsed or refractory MM

2.2 SECONDARY OBJECTIVES:

- To characterize the PK profile of ACP-196 with and without dexamethasone and the PK profile of dexamethasone with concomitant ACP-196 administration
- To evaluate the PD effects of ACP-196 with and without dexamethasone
- To evaluate the activity of ACP-196 with and without dexamethasone as measured by overall response rate, duration of response, clinical benefit rate, disease control rate, and progression-free survival
- To explore the relationship between biological markers in MM cells and response to therapy

3.0 STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This study is a multicenter, open-label, randomized, parallel-group study to be conducted at approximately 20 sites in 2 countries (United Kingdom and United States). Forty subjects will be randomized 1:1 into the following 2 cohorts to receive ACP-196, with and without dexamethasone:

- Cohort 1: ACP-196 100 mg BID continuously
- Cohort 2: ACP-196 100 mg BID continuously and 40 mg dexamethasone once weekly

Twenty-eight days of study drug administration is 1 cycle. Treatment may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. For subjects in Cohort 1, if documented disease progression occurs, then dexamethasone can be added to the treatment regimen. Additional dose modification provisions are provided in Section 3.5.5. Note: temporary withholding of study drug for

as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe.

All subjects will have standard hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1 and Cycle 2. Tumor assessments will be done at 8- to 12-week intervals during the trial.

Refer to Appendix 5 for a comprehensive list of study assessments and their timing. The end of trial is defined as the point when the last subject on the study exits the study for any reason.

3.2 STUDY PARAMETERS

3.2.1 Safety Parameters

The safety of ACP-196 with and without dexamethasone will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug (ie, ACP-196, dexamethasone, or both) of any treatment-emergent AEs or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation or dose reduction of study treatment.

For consistency of interpretation, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Standard definitions for seriousness will be applied (see Section 6.1).

3.2.2 Efficacy Parameters

Standardized response and progression criteria have been established for MM (Rajkumar 2011); assessments of ACP-196 efficacy in this study will be based on these criteria. Efficacy endpoints will include:

- Overall response rate (ORR)
- Duration of response
- Clinical benefit rate
- Disease control rate

- Progression-free survival

3.2.3 Pharmacokinetic and Pharmacodynamic Parameters

Standard PK parameters for ACP-196 and dexamethasone in plasma will be evaluated in this study. A full description of the PK parameters is provided in Section 5.5.4.

The occupancy of Btk by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, when available, with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.

3.3 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.3, preliminary data from the ongoing Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL have shown that ACP-196 is well tolerated at dosages of 100 to 400 mg QD and 100 to 200 mg BID. In addition, preliminary PD data from ACE-CL-001 show that Btk occupancy with ACP-196, in peripheral blood, is > 95% at 4 hours after QD dosing but decreases to < 95% at 24 hours with QD dosing, while with BID dosing complete Btk occupancy (95% to 99%) is maintained over 24 hours at steady state (Table 1-3). These data suggest that de novo synthesis of Btk can occur within 24 hours in peripheral blood cells. BID dosing may ensure Btk inhibition for the entire 24 hours and thus may be beneficial in terms of increasing efficacy and/or decreasing development of resistance to ACP-196. In addition, having information regarding the safety and pharmacology of a BID schedule may support future combination studies with other drugs that are administered BID.

Evaluation of dexamethasone as a combination partner for ACP-196 builds on known antineoplastic activity of this drug in patients with MM. Dexamethasone therapy is commonly coadministered with targeted agents for MM (Ocio 2014). The dosing regimen of 40 mg weekly to be used in this study has been established based on randomized trial data showing the superiority of this method of administration (Rajkumar 2009). Combined use of ACP-196 and dexamethasone provides an all oral, non-cytotoxic regimen that may have increased efficacy relative to administration of the individual agents alone. While dexamethasone can increase CYP3A4 activity and thus might enhance ACP-196 metabolism, it is considered a weak inducer of this isoenzyme and has not substantially altered the disposition of other CYP3A4 substrates (eg, bortezomib) that are commonly used in the therapy of MM (Hellmann 2011). The

randomized design of this pilot study will allow the potential for drug-drug interactions between ACP-196 and dexamethasone to be assessed.

3.4 SELECTION OF STUDY POPULATION

3.4.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥ 18 years of age.
2. A confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥ 1 prior therapy for MM, and is progressing at the time of study entry.
3. Evaluable myeloma at screening, defined as the presence of at least one of the following:
   - Serum M-protein ≥ 0.5 g/dL
   - Urine M-protein ≥ 200 mg/24 hours
   - In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) **and** an abnormal serum kappa/lambda ratio
   - For subjects whose disease can only be reliably measured by serum quantitative immunoglobulin A (IgA), IgA ≥ 750 mg/dL (0.75 g/dL)
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
5. Agreement to use acceptable methods of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children.
6. Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug.
7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local patient privacy regulations).

3.4.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Plasma cell leukemia or circulating plasma cells ≥ 2 x 10^9/L
2. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor.
3. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with

the absorption or metabolism of ACP-196, or put the study outcomes at undue risk.

4. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec.
5. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
6. Any immunotherapy within 4 weeks of first dose of study drug.
7. The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s).
8. Prior exposure to a B-cell receptor (BCR) inhibitor (eg, Btk, phosphoinositide-3 kinase [PI3K], or Syk inhibitors) or BCL-2 inhibitors (eg, ABT-199).
9. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MM or other conditions. Note: Subjects may use topical or inhaled corticosteroids as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids as needed for MM therapy or treatment-emergent comorbid conditions.
10. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
11. Known history of human immunodeficiency virus (HIV), serologic status reflecting active hepatitis B or C infection, or any uncontrolled active systemic infection. Subjects with hepatitis B core antibody positive who are surface antigen negative or who are hepatitis C antibody positive will need to have a negative PCR result before enrollment. Those who are hepatitis B surface antigen positive or hepatitis B PCR positive and those who are hepatitis C PCR positive will be excluded.
12. Major surgery within 4 weeks before first dose of ACP-196.
13. Known history of a bleeding diathesis (eg, hemophilia, von Willebrand disease)
14. History of stroke or intracranial hemorrhage within 6 months before the first dose of ACP-196.
15. Requires or receiving anti-coagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 28 days of first dose of study drug.
16. Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
17. ANC < 0.75 x 10^9/L or platelet count < 50 x 10^9/L. For subjects with >50% marrow involvement with plasma cells, ANC < 0.50 x 10^9/L or platelet count < 30 x 10^9/L.
18. Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN; and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN.
19. Breastfeeding or pregnant.

20. Concurrent participation in another therapeutic clinical trial.

3.4.3 Replacement of Subjects

Any subject who does not complete Cycle 2 may be replaced at the discretion of the study investigators and sponsor.

3.4.4 Enrollment and Randomization Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

- Notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled in the study.
- To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the form is faxed/emailed to the sponsor.
- An Enrollment Confirmation Form will be completed and faxed/emailed to the study center by the sponsor within 24 hours.
- The Enrollment Confirmation Form will contain cohort allocation per the randomization scheme generated by the sponsor.

Treatment must begin within the screening window (Section 4.1) and after the site has received the cohort allocation from the sponsor. Study treatment is not blinded on this study.

3.5 STUDY DRUG

3.5.1 Premedications

No specific premedications or supporting medications are required in conjunction with ACP-196 administration.

3.5.2 Formulation, Packaging, and Storage

3.5.2.1 ACP-196

ACP-196 is manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. ACP-196 should be stored according to the instructions on the label that is affixed to the package containing the drug product.

ACP-196 capsules is provided as hard gelatin capsules containing 100 mg drug substance. ACP-196 will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative.

Refer to the Investigator's Brochure for additional information regarding the drug product to be used in this trial.

3.5.2.2 Dexamethasone

This study will use commercially available dexamethasone tablets for oral administration. The Sponsor will either directly supply sites with dexamethasone or the sites will be reimbursed to prescribe dexamethasone; this will be detailed separately in each site's clinical trial agreement. Per the U.S. dexamethasone package insert (Appendix 4), tablets are to be stored at room temperature (20° to 25°C) and protected from moisture and light. Please refer to the appropriate dexamethasone package insert for further storage and handling instructions.

3.5.3 Administration of Study Drug

3.5.3.1 ACP-196

Investigators are prohibited from supplying ACP-196 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators on FDA Form 1572. The investigator must ensure that subjects receive ACP-196 only from personnel who fully understand the procedures for administering the drug.

ACP-196 is intended to be administered orally with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice and Seville orange juice due to CYP3A4 inhibition). ACP-196 may be taken with or without food. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. .

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the following dose. If it has been greater than 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.3.2 Dexamethasone

This study will use commercially available dexamethasone tablets for oral administration. At the time of weekly dexamethasone administration, the subject should take the dexamethasone tablets simultaneously with the ACP-196 capsules and with 8 ounces (approximately 240 mL) of water. The dexamethasone tablets should be swallowed intact and subjects should not attempt to chew them or dissolve them in water.

If a dexamethasone dose is missed, it can be taken up to 3.5 days (84 hours) days after the scheduled time with a return to the normal schedule the following week. If the interval of missed dosing has been > 3.5 days (84 hours), the dexamethasone dose should not be taken and the subject should take the next dose at the scheduled time in the following week. The missed dexamethasone dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.4 Assuring Subject Compliance

During cycle 1, subjects will receive their Day 1, 8, 15, 22, and 28 doses (for Cohort 2 this includes the dexamethasone dose) in the clinic. For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other treatments will be taken at home. Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining ACP-196 capsules and dexamethasone tablets to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules and tablets were administered. Any remaining or returned capsules and tablets will be counted and recorded as described in Section 7.7. Returned capsules or tablets must not be redispensed to another subject. The study staff will resupply the subject with the correct number of ACP-196 capsules and dexamethasone tablets needed for use until the next visit.

3.5.5 Study Treatment Regimen and Dose Modifications

3.5.5.1 ACP-196

Dose Delays

Treatment with ACP-196 should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Medical Monitor.

Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances.

Dose Modification and Discontinuation

The actions in Table 3-1 should be taken for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded on the electronic case report form [eCRF]).
- Grade 3 platelets in the presence of significant bleeding
- Grade 4 platelets
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

Table 3-1. Drug Discontinuation Actions for ACP-196

Occurrence	Action
1st - 2nd	Hold ACP-196 until recovery to Grade ≤ 1 or baseline; may restart at original dose level
3rd	Hold ACP-196 until recovery to Grade ≤ 1 or baseline; restart at 100 mg once daily
4th	Discontinue ACP-196

Subjects in Cohort 1 (ACP-196 monotherapy) who do not experience at least an minimal response (MR) after 2 cycles of study treatment may have dexamethasone (40 mg once weekly) added to their treatment.

Whenever possible, any dose adjustment of ACP-196, including adding dexamethasone to subjects in Cohort 1, should be discussed between the investigator and the Acerta Pharma medical monitor before implementation. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level. Any changes to the dosing regimen must be recorded in the appropriate eCRF.

3.5.5.2 Dexamethasone

This study will use commercially available dexamethasone. Dosing of dexamethasone will be 40 mg once weekly. For subjects who experience intolerable dexamethasone-related adverse effects, dexamethasone may be reduced to 20 mg once weekly.

3.6 CONCOMITANT THERAPY

3.6.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

For subjects considered at risk for tumor lysis syndrome: Administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

3.6.2 Guideline for Use of CYP Inhibiting/Inducing Drugs

At the systemic exposure levels expected in this study, ACP-196 inhibition of CYP metabolism is not anticipated. However, as discussed in Section 1.3.1, concomitant administration of ACP-196 with a strong CYP3A4 inhibitor increased exposure by approximately 5-fold. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (Appendix 3) should be avoided when possible. If a subject requires a strong CYP3A4 inhibitor while on study, monitor the subject closely for potential toxicities.

3.6.3 Guideline for Use of Drugs that Affect Gastric pH

The effect of agents that reduce gastric acidity (eg, proton pump inhibitors, H2-receptor antagonists or antacids) on ACP-196 absorption is currently being evaluated in a healthy volunteer study (ACE-HV-004). Preliminary results from this study suggest subjects

should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids or calcium supplements) for a period of at least 2 hours before and after taking ACP-196.

Subjects should also avoid the use of H2-receptor antagonists for a period at least 2 hours before and after taking ACP-196. Use of omeprazole, esomeprazole, lansoprazole or any other long-acting proton pump inhibitors while taking ACP-196 is not permitted due to a potential decrease in study drug exposure. However, if a subject requires treatment with a long-acting proton pump inhibitor while on study (eg, to treat an ulcer), discuss treatment options with the Medical Monitor.

3.6.4 Prohibited Concomitant Therapy

Any chemotherapy, immunotherapy, kinase inhibitors, bone marrow transplantation, experimental therapy, and radiotherapy are prohibited (see Section 3.4.2).

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids, per the dexamethasone package insert (Appendix 4). Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.

3.7 PRECAUTIONS

3.7.1 Dietary Restrictions

Because ACP-196 may be metabolized by CYP3A4/3A5 (see Section 1.2.4), subjects should be strongly cautioned against excessive consumption of grapefruit, grapefruit juice, Seville oranges, or Seville orange juice (which contain potent CYP3A4 inhibitors) or using herbal remedies or dietary supplements (in particular, St. John's Wort, which is a potent CYP3A4 inducer).

ACP-196 may be taken with or without food.

3.7.2 Hepatitis B Virus Reactivation

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with ACP-196. Therefore, subjects who are hepatitis B core antibody (anti-HBc) positive, or have a known history of hepatitis B virus (HBV) infection, should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of ACP-196. Any subject with a rising viral load (above lower limit of detection) should discontinue ACP-196 and have antiviral

therapy instituted and a consultation with a physician with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming ACP-196 in subjects who develop HBV reactivation.

3.7.3 Surgery

Susceptibility to bleeding has been observed with the first generation Btk inhibitor, ibrutinib [IMBRUVICA package insert]. As a precaution, it is suggested that ACP-196 be held for 3 days before and after any major surgical procedure.

3.7.4 Infections

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals (dexamethasone package insert, Appendix 4). Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions.

3.7.5 Reproductive Toxicity

Definitive reproductive toxicity studies with ACP-196 are pending. Therefore, subjects with reproductive potential who are sexually active must use acceptable methods of contraception during the study and for 30 days after the last dose of ACP-196. Examples of acceptable methods of contraception include condoms, implants, injectables, combined oral contraceptives, intrauterine devices, true sexual abstinence, or sterilized partner. Note that periodic abstinence, eg, calendar, ovulation, symptothermal, or postovulation methods, or withdrawal, are not acceptable methods of contraception.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue ACP-196 immediately. Pregnancy in a female subject or a male subject's partner must be reported (see Section 6.2.3). Male subjects must agree to refrain from sperm donation during the study and for 30 days after the last dose of study drug.

3.7.6 Overdose Instructions

For any subject experiencing an ACP-196 overdose (administration of a dose ≥ 1.5 times the highest intended dose level in the clinical study protocol), observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematologic parameters should be followed closely (consistent with the protocol or more

frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

The Acerta Pharma Medical Monitor should be contacted if a study drug overdose occurs.

3.8 STOPPING RULES

All study participants may receive ACP-196 indefinitely as long as they are safely benefitting. However:

- Any subject has the right to withdraw from the study at any time.
- Any subject who has objective evidence of definitive MM progression while receiving study treatment at the highest individual tolerable dose level allowed in the protocol (see Section 3.5.5) should be withdrawn from the study treatment. Note: If there is uncertainty regarding whether there is MM progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 4- to 8-week intervals) pending confirmation of progression. In particular, transient worsening of disease during temporary interruption of study therapy (eg, for intercurrent illness, drug-related toxicity, or surgery) may not indicate definitive disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.
- Any subject who is unable to tolerate rechallenge at the lowest protocol-described, dose-modified levels (see Section 3.5.5) should be withdrawn from the study treatment unless continued therapy is permitted by the Acerta Pharma medical monitor.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the Acerta Pharma medical monitor. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be removed from study treatment.

- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.
- The investigator, in consultation with the Acerta Pharma medical monitor, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Subjects who discontinue study therapy will continue on study for safety (Section 4.3) unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate posttherapy period unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from study treatment or from the study and the reason for discontinuation will be recorded and also should be described on the appropriate eCRF.

3.9 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Quarterly conference calls with the investigators will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs, and deaths).

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 5. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are required. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. Such unscheduled assessments will be captured in the protocol-specific database as appropriate.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand and sign the IRB/IEC approved ICF confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information.

4.1.2 Medical History

The subject's complete history should be collected and recorded through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1 All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

All concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug should be documented.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.4. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 1.

4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes,

ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams, including tumor assessments by palpation, will be done during the treatment period and at the safety follow-up visits.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.

4.1.8 Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at screening or up to 30 days before the main screening procedures. Per the current response criteria (Rajkumar 2011), a bone marrow aspirate/biopsy will also be required at any time on study to confirm a complete response (CR). The baseline bone marrow aspirate/biopsy will used for immunohistochemistry and/or flow cytometry, cytogenetics, and FISH. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

When available, any unused bone marrow tissue will be used for PD testing. PD testing will be done by the sponsor.

4.1.9 Electrocardiogram

Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.

4.1.10 Urine Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound. Testing will be done by the central laboratory.

4.1.11 Hematology

Hematology studies must include complete blood count (CBC) with differential and platelet and reticulocyte counts. Testing will be done by the central laboratory.

4.1.12 Serum Chemistry

Serum chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride,

creatinine, C-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by the central laboratory.

4.1.13 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, N-terminal telopeptide, and glucose. Testing will be done by the central laboratory.

4.1.14 T/B/NK Cell Count

Flow cytometry testing will include $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD16/56^+$ cells. Testing will be done by the central laboratory.

4.1.15 Disease Markers

Testing for serum M-protein levels (by serum protein electrophoresis [SPEP] and serum immunofixation electrophoresis [SIFE]), serum free light chains (SFLC), urine M-protein levels (by urine serum protein electrophoresis [UPEP] and urine immunofixation electrophoresis [UIFE]), and serum β2-microglobulin will be done by the central laboratory.

4.1.16 Hepatitis B and C Testing

Hepatitis serology testing must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), anti-HBc, and hepatitis C (HCV) antibody. Since intravenous immunoglobulins (IVIG) may cause false positive hepatitis serology, subjects who are receiving prophylactic IVIG and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see Appendix 5 and exclusion criterion #11). Testing will be done by local or central laboratory.

Refer to Section 3.7.2 and Appendix 5 regarding monitoring of subjects who are anti-HBc positive or have a known history of HBV.

4.1.17 Skeletal Survey

Standard lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri are required at screening or baseline (ie, before the first dose of study drug). Radiographic imaging and

analysis will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

4.1.18 Pharmacodynamics

Blood samples and bone marrow, when available, will be used for PD testing (eg, Btk occupancy and B-cell activation). Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be done by the sponsor.

4.1.19 Pharmacokinetics

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at the central clinical laboratory. Leftover plasma samples may be used for exploratory ACP-196 metabolite analyses. The PK sampling timepoints are provided in Table 4-1.

Table 4-1. Pharmacokinetic Sample Schedule

			HOURS POSTDOSE					
Cycle	**Day**	**Predose**	**0.5 (±5 min)**	**0.75 (±5 min)**	**1 (±5 min)**	**2 (±10 min)**	**4 (±10 min)**	**6 (±10 min)**
1	**1**	X	X	X	X	X	X	X
	8	X			X			
	15	X			X			
	22	X	X	X	X	X	X	X
	28	X			X			

Note: These timepoints are relative to the morning dose.

4.1.20 Tumor Assessment

Baseline myeloma assessments will consist of:

- M-protein determination using both of the following procedures:
  - serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE)
  - Urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE), all using the same 24-hour urine collection
- SFLC

- Plasmacytoma evaluation
- Bone marrow to quantify percent myeloma cell involvement (aspirate and biopsy required at baseline)
- Skeletal survey: lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri
- β2-microglobulin

On-study myeloma assessments will consist of:

- SPEP and/or UPEP (if results were measurable at baseline); quantitative immunoglobulins if used to follow disease; immunofixation to confirm a complete response
- SFLC
- Plasmacytoma evaluation (if only measurable disease at baseline)
- Bone marrow aspirate and/or trephine bone biopsy (to confirm a complete response or if clinically indicated).

4.1.21 Study Drug Accountability

See Section 7.7.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

Subjects will be evaluated by investigator review for disease response and progression according to the current guidelines proposed by the International Myeloma Workshop Consensus Panel 1 (Rajkumar 2011) and European Group for Blood and Marrow Transplant (EBMT; Bladé 1998)as listed below in . Response categories include sCR, CR, VGPR, PR, SD, and progressive disease. In addition, the number of subjects achieving the response category of MR will also be evaluated and reported. Subjects will be considered evaluable for response if they have a baseline and ≥1 adequate on-study myeloma assessment obtained ≥4 weeks from the start of therapy.

Table 4-2. Response Criteria (derived from Rajkumar 2011 and Bladé 1998)

Response Subcategory	Response Criteria[a]
Complete response (CR)	• Negative immunofixation of serum and urine and • Disappearance of any soft tissue plasmacytomas and

	• < 5% plasma cells in bone marrow[b].
Stringent complete response (sCR)	• CR as defined above plus • Normal FLC ratio and • Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry.
Very good partial response (VGPR)	• Serum and urine M-component detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 h.
Partial response (PR)	• ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h • If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minimal response (MR)	• Requires all of the following: ○ ≥ 25% to ≤ 49% reduction of serum M-protein and ○ 50% to 89% reduction in 24-hour urine M-protein and ○ If present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas and ○ No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease (SD)	• Not meeting criteria for CR, VGPR, MR, PR or progressive disease
Progressive disease	Any of the following: • Increase of ≥ 25% from lowest response value[c] in: ○ Serum M-component (absolute increase must be ≥ 0.5 g/dL)[d] ○ Urine M-component (absolute increase must be ≥ 200 mg/24 h) ○ Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) ○ Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels

	bone marrow plasma cell percentage (absolute increase must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Abbreviations: FLC = (serum) free light chains
Note: in subjects in whom the only measurable disease is by serum FLC levels, CR requires a normal FLC ratio of 0.26-1.65 in addition to negative serum and urine immunofixation. VGPR in such subjects is defined as a > 90% decrease in the difference between involved and uninvolved free light chain FLC levels

a. All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at ≥4 weeks after the start of study therapy and any time before the institution of any new therapy after study therapy; CR, sCR, VGPR, PR, and SD 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.
b. Bone marrow assessments need not be confirmed.
c. Lowest response value does not need to be a confirmed value.
d. For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

4.3 EARLY TERMINATION/SAFETY FOLLOW-UP VISIT

An early termination visit is required for any subjects who permanently discontinue study drug early for any reason including disease progression. Each subject should be followed for 30 (±7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.5) and to document the occurrence of any new events; unless, the subject receives a new anticancer therapy within this timeframe. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Appendix 5) describes the procedures required for the safety follow-up.

4.4 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate. Analyses will be done by dosing regimen and overall.

5.2 SAMPLE SIZE CONSIDERATIONS

This study will assess safety, PK, PD, and antitumor activity of ACP-196 alone or in combination with dexamethasone. Subjects will be equally randomized into 1 of the 2 dosing regimens (ACP-196 monotherapy or ACP-196 + dexamethasone) as an efficient method for allocating patients into these regimens. The study is not formally designed to compare these regimens but rather to obtain descriptive information that can be used in support of further ACP-196 development.

While the primary objective of this study is to determine the safety in each of the 2 dosing cohorts, the sample size has been determine to independently evaluate the activity of each dosing regimen. The trial seeks to exclude an uninteresting ORR of $\leq$ 15% (ie, the response rate that might be associated with single-agent dexamethasone therapy [Anderson 2013]) in favor a target response rate of $\geq$ 40%. Considering a sample size of 19 subjects per cohort, the power to detect the difference between a null-hypothesis response rate of 15% and an alternative-hypothesis response rate of 40% with a 0.025 one-sided significance level is 69% using a one-group, exact binomial test. A sample size of 19 subjects per cohort will also provide a 97.5% 1-sided confidence interval centered around an expected ORR of 40% that excludes an ORR of 18.6% as a lower bound.

5.3 DEFINITION OF ANALYSIS POPULATIONS

The following definitions will be used for the analysis populations:

- **Safety population:** All enrolled subjects who receive ≥ 1 dose of study drug.
- **Intent-to-treat (ITT) population**: All subjects who have been randomized.

The safety population will be used for evaluating the safety parameters in this study. The ITT population will be analyzed for efficacy parameters in this study.

5.4 MISSING DATA HANDLING

General Considerations: Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation.

Duration of Response and Progression-free Survival: Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy.

Safety: Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules. No other imputation of values for missing data will be performed.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event (per CTCAE, v4.03) and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments and physical exams will be tabulated and summarized.

5.5.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

5.5.3 Analysis of Efficacy Parameters

5.5.3.1 Overall Response Rate

Tumor control will be documented at each assessment by response category (eg, CR, sCR, VGPR, PR, MR, SD, and disease progression) as defined for each response parameter, date that response is first documented, and date of MM disease progression.

The overall response rate (ORR) will be defined as the proportion of subjects who achieve a CR, sCR, VGPR, or PR. ORR will be calculated and the corresponding 95% two-sided confidence interval will be derived.

5.5.3.2 Duration of Response

The duration of response (DOR) defined as the interval from the first documentation of CR, sCR, VGPR, or PR to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quantiles (including the median). Data from surviving, nonprogressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of definitive MM progression was objectively documented. Data from subjects who have MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time before the missing assessments that lack of MM progression was objectively documented.

5.5.3.3 Clinical Benefit Rate

Clinical benefit rate (CBR) will be defined as the proportion of subjects who achieve a CR, sCR, VGPR, PR, or MR. CBR will be calculated and the corresponding 95% two-sided confidence interval will be derived.

5.5.3.4 Disease Control Rate

Disease control rate (DCR) will be defined as the proportion of subjects who achieve a CR, sCR, VGPR, PR, MR, or SD. DCR will be calculated and the corresponding 95% two-sided confidence interval will be derived.

5.5.3.5 Progression-free Survival

Progression-free survival (PFS) is defined as the interval from the date of randomization to the earlier of the first documentation of objective MM disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of MM progression was objectively documented. Data from subjects who have MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of MM progression was objectively documented.

5.5.4 Analysis of Pharmacokinetic/Pharmacodynamic Parameters

The plasma PK of ACP-196 and dexamethasone will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of ACP-196:

- AUC_{0-t} Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t).
- AUC_{0-12} Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.
- $AUC_{0-\infty}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.
- $AUC_{0-24calc}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}.
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- CL/F Oral clearance

Missing dates or times may be imputed for PK and PD samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. If PK and PD sampling for a given subject is not performed according to protocol instructions that subject may be excluded from the PK and PD analyses.

The PK parameters will be tabulated and summarized using descriptive statistics.

For each PD variable, the concentration at each assessment will be described. The change from baseline to each assessment will be summarized. The best change from baseline during the study will also be summarized. As appropriate, the on-treatment values will be compared with the pretreatment baseline values using paired t-tests.

5.5.5 Exploratory or Correlative Analyses

Additional PK or PD analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques. Such evaluations may assist in determining if baseline parameters or early changes in PD biomarkers are predictive of response to Btk inhibition.

6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other

laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

6.1 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MM that were not present before the AE reporting period (see Section 6.2.1)
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values should not be reported as AEs; however, any clinically significant laboratory values (defined as requiring treatment, discontinuation from study, or dose modification) should be reported as AEs.

6.1.2 Serious Adverse Event

The terms "severe" and "serious" are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). "Serious" is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).

- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on the SAE/Product Complaint form (see Section 6.2.4).

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study medication and ends with the safety follow-up visit (or last on-treatment visit if the safety follow-up visit is not done), or when the subject receives a new anticancer therapy. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. Fatal AEs occurring within 30 days after the last dose of ACP-196 ***AND*** assessed by the investigator as related to ACP-196 must be reported as a SAEs.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE/Product Complaint form.

Disease progression itself is not considered an adverse event; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (ie, ACP-196, dexamethasone, or both; see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' Answer Yes or No.

See Appendix 2 for more detail on assessing relationship.

6.2.3 Pregnancy

The investigator should report all pregnancies in study subjects and in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be

reported using the SAE report form, according to the usual timelines and directions for SAE reporting (Section 6.2.4).

Any uncomplicated pregnancy that occurs in a subject or a partner of a treated subject during this study will be reported for tracking purposes only, if agreed to by the subject or the partner of the subject in this study. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 30 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner is willing to participate in follow-up.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE/Product Complaint form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving ACP-196 who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

6.2.4 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discover. All initial SAE reports and follow-up information will be reported using the protocol-specific electronic data capture system. If electronic SAE reporting is not available, paper SAE/Product Complaint forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. Acerta Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator's Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the SAE to all investigators. Each investigator must then notify his or her IRB/IEC of the SAE.

Drug Safety Contact Information	
Fax:	[redacted]
Email:	[redacted]

6.2.5 Type and Duration of Follow-up of Subjects After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the event as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination include:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failure to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 REGULATORY AND ETHICAL COMPLIANCE

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations Title 21 and

European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.

7.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the ICF, Investigator's Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed FDA 1572 form (Statement of Investigator form) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agencies, as appropriate, before the implementation of changes in this study.

7.3 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved ICF must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.12), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance with individual local and national patient privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study Sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected

health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.4 SUBJECT SCREENING LOG

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.5 CASE REPORT FORMS

Authorized study site personnel (see Section 7.12) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed within 5 days of each subject's visit (unless required earlier for SAE reporting). The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed, in accordance with the record retention policies in Section 7.8.

7.6 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits by the sponsor, regulatory authorities, or ethics committees.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology,

pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.7 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

ACP-196 capsules must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply ACP-196 capsules to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Acerta Pharma.

Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and regulatory authorities at any time.

Each shipment of study drug will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. If it is used, the Drug Re-order Form (provided in the pharmacy binder) must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of study drug capsules. Then the designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/emailing address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-MY-001)
2. subject identification number
3. lot number(s) of ACP-196 dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its representative, for return of unused investigational product. Before

disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.8 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, and all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or returned to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

7.9 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must

be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.10 PUBLICATION OF STUDY RESULTS

Acerta Pharma may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. The study is being conducted as part of a multicenter clinical trial. Data from all study centers shall be pooled and analyzed for publication in a final report (Primary Publication). The investigator agrees that the Primary Publication, which will be coordinated by Acerta Pharma, will be the first publication to present the pooled study results. After the Primary Publication, or if the Primary Publication is not published within 1 year of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement subject to providing Acerta Pharma with the opportunity to review the contents of any proposed presentation, abstract or publication about such work, including any results of this study, 90 days in advance of any presentation or submission for publication. Within that 90-day period, Acerta Pharma may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, Acerta Pharma may elect an additional review period not to exceed 60 days.

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2014).

7.11 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been obtained according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.12 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. Electronic CRF pages are completed within 5 days of each subject's visit (unless required earlier for SAE reporting).
11. All IND Safety Reports/ Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge and to the IRB/IEC per their requirements.

8.0 REFERENCES

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9.0 APPENDICES

Appendix 1. Performance Status Scores

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, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

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

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

Appendix 2. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug?

No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix 3. Known Strong in Vivo Inhibitors of CYP3A4

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	carbamazepine[f]
clarithromycin[b]	phenytoin[f]
conivaptin[b]	rifampin[f]
grapefruit juice[c]	St John's wort[f]
indinavir	
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (eg, high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Medical Monitor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix 4. Dexamethasone Prescribing Information

The United States label for dexamethasone tablets (Roxane Laboratories 2007) is provided for reference. The United States label will also serve as the Reference Safety Information for dexamethasone for this study. Country-specific labels will be provided to investigative sites as appropriate.

4047401//04

Roxane Laboratories, Inc.
Columbus, Ohio 43216

DEXAMETHASONE Tablets USP, DEXAMETHASONE Oral Solution, and DEXAMETHASONE *Intensol*™ Oral Solution (Concentrate)

℞ only

DESCRIPTION

Dexamethasone Tablets 0.5, 0.75, 1, 1.5, 2, 4 and 6 mg USP, Dexamethasone Oral Solution, 0.5 mg per 5 mL and Dexamethasone *Intensol*™ Oral Solution (Concentrate), 1 mg per mL are for oral administration.

Each tablet contains:
Dexamethasone ..... 0.5, 0.75, 1, 1.5, 2, 4, or 6 mg
Each 5 mL of Oral Solution contains:
Dexamethasone ..... 0.5 mg
Each mL of *Intensol*™ Oral Solution (Concentrate) contains:
Dexamethasone ..... 1 mg
Alcohol 30%

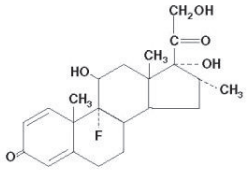
Inactive Ingredients

The tablets contain lactose monohydrate, magnesium stearate, starch, sucrose, cosmetic ochre (1 mg), D&C Yellow No. 10 (0.5, 4 mg), FD&C Blue No. 1 (0.75, 1.5 mg), FD&C Green No. 3 (4, 6 mg), FD&C Red No. 3 (1.5 mg), FD&C Red No. 40 (1.5 mg), and FD&C Yellow No. 6 (0.5, 4 mg).

The oral solution contains citric acid, disodium edetate, flavoring, glycerin, methylparaben, propylene glycol, propylparaben, sorbitol and water.

The *Intensol*™ oral solution contains alcohol, benzoic acid, citric acid, disodium edetate, propylene glycol, and water.

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water. The molecular formula is $C_{22}H_{29}FO_5$. The molecular weight is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene,3,20-dione and the structural formula is:



CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, and serum sickness.

Dermatologic Diseases

Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, and severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; may be used in conjunction with synthetic mineralocorticoid analogs where applicable; in infancy mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, and nonsuppurative thyroiditis.

Gastrointestinal Diseases

To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic Disorders

Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia.

Miscellaneous

Diagnostic testing of adrenocortical hyperfunction, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic Diseases

For the palliative management of leukemias and lymphomas.

Nervous System
Acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy, or head injury.
Ophthalmic Diseases
Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
Renal Diseases
To induce a diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.
Respiratory Diseases
Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.
Rheumatic Disorders
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute rheumatic carditis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

CONTRAINDICATIONS

Contraindicated in systemic fungal infections (see **WARNINGS**: **Infections**: *Fungal Infections*) and patients with known hypersensitivity to the product and its consituents.

WARNINGS

General
Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).
Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.
Cardio-Renal
Average and large doses of corticosteroids can cause elevation of blood pressure, sodium and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.
Endocrine
Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment. Adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased.
Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.
Infections
General: Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.
Fungal Infections: Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **PRECAUTIONS**: **Drug Interactions**: *Amphotericin B injection and potassium-depleting agents*).
Special Pathogens: Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Toxoplasma.*
It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.
Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.
Corticosteroids should not be used in cerebral malaria.
Tuberculosis: The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.
Vaccination: **Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.** Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.
Viral infections: Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.
Ophthalmic
Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

The lowest possible dose of corticosteroids should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with corticosteroids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-Renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy.

Neuro-Psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision. As prolonged use may cause adrenal insufficiency and make patients dependent on corticosteroids, they should advise any medical attendants that they are taking corticosteroids and they should seek medical advice at once should they develop an acute illness including fever or other signs of infection. Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including, myalgia, arthralgia, and malaise.

Persons who are on corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

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 (see **Drug Interactions**: *Hepatic Enzyme Inducers, Inhibitors and Substrates*).

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 dexamethasone suppression test (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-adminstration 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 (NSAIDS): Concomitant use of aspirin (or other nonsteroidal antiinflammatory 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.

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 (see **WARNINGS: Infections***: Vaccination*).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects: Pregnancy Category C.: Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (patients >2 years of age), and aggressive lymphomas and leukemias (patients >1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, the increased risk of diabetes mellitus, fluid retention and hypertension in elderly patients treated with corticosteroids should be considered.

ADVERSE REACTIONS
(listed alphabetically, under each subsection)

The following adverse reactions have been reported with dexamethasone or other corticosteroids:

Allergic Reactions

Anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS: Cardio-Renal**), edema, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic

Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, erythema, impaired wound healing, increased sweating, rash, striae, suppression of reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine

Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal

Abdominal distention, elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic

Negative nitrogen balance due to protein catabolism.

Musculoskeletal
Aseptic necrosis of femoral and humeral heads, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures.
Neurological/Psychiatric
Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.
Ophthalmic
Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.
Other
Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE

Treatment of overdosage is by supportive and symptomatic therapy. In the case of acute overdosage, according to the patient's condition, supportive therapy may include gastric lavage or emesis.

DOSAGE AND ADMINISTRATION

For Oral Administration
The initial dosage varies from 0.75 to 9 mg a day depending on the disease being treated.
It Should Be Emphasized That Dosage Requirements Are Variable And Must Be Individualized On The Basis Of The Disease Under Treatment And The Response Of The Patient.
After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that maintains an adequate clinical response is reached.
Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.
In the treatment of acute exacerbations of multiple sclerosis, daily doses of 30 mg of dexamethasone for a week followed by 4 to 12 mg every other day for one month have been shown to be effective (see **PRECAUTIONS: Neuro-Psychiatric**).
In pediatric patients, the initial dose of dexamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02 to 0.3 mg/kg/day in three or four divided doses (0.6 to 9 mg/m^2bsa/day).
For the purpose of comparison, the following is the equivalent milligram dosage of the various corticosteroids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.
In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:
Dexamethasone sodium phosphate injection, 4 mg per mL
First Day: 1 or 2 mL, intramuscularly
Dexamethasone tablets, 0.75 mg
Second Day: 4 tablets in two divided doses
Third Day: 4 tablets in two divided doses
Fourth Day: 2 tablets in two divided doses
Fifth Day: 1 tablet
Sixth Day: 1 tablet
Seventh Day: No treatment
Eighth Day: Follow-up visit
This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.
In *cerebral edema*, dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by 4 mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with either dexamethasone sodium phosphate injection or dexamethasone tablets in a dosage of 2 mg two or three times daily may be effective.
Dexamethasone Suppression Tests
1. Tests for Cushing's syndrome
   Give 1.0 mg of dexamethasone orally at 11:00 p.m. Blood is drawn for plasma cortisol determination at 8:00 a.m. the following morning.
   For greater accuracy, give 0.5 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.
2. Test to distinguish Cushing's syndrome due to pituitary ACTH excess from Cushing's syndrome due to other causes.
   Give 2.0 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

Proper Use of an Intensol™
An Intensol is a concentrated oral solution as compared to standard oral liquid medications. It is recommended that an Intensol be mixed with liquid or semi-solid food such as water, juices, soda or soda-like beverages, applesauce and puddings.
Use only the calibrated dropper provided with this product. Draw into the dropper the amount prescribed for a single dose. Then squeeze the dropper contents into a liquid or semi-solid food. Stir the liquid or food gently for a few seconds. The Intensol formulation blends quickly and completely. The entire amount of the mixture, of drug and liquid or drug and food, should be consumed immediately. Do not store for future use.

HOW SUPPLIED

Dexamethasone Tablets USP:
0.5 mg yellow, scored tablets (Identified 54 299).
NDC 0054-8179-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4179-25: Bottles of 100 tablets.
0.75 mg pale blue, scored tablet (Identified 54 960).
NDC 0054-8180-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4180-25: Bottles of 100 tablets.
1 mg yellow, scored tablets (Identified 54 489).
NDC 0054-8174-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4181-25: Bottles of 100 tablets.
1.5 mg pink, scored tablets (Identified 54 943).
NDC 0054-8181-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4182-25: Bottles of 100 tablets.
NDC 0054-4182-31: Bottles of 1000 tablets.
2 mg white, scored tablets (Identified 54 662).
NDC 0054-8176-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4183-25 Bottles of 100 tablets.
4 mg green, scored tablets (Identified 54 892).
NDC 0054-8175-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4184-25: Bottles of 100 tablets.
6 mg aqua, scored tablets (Identified 54 769).
NDC 0054-8183-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4186-25: Bottles of 100 tablets.

Store and Dispense
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF.

Dexamethasone Oral Solution, 0.5 mg per 5 mL:
NDC 0054-3177-57: Bottles of 240 mL.
NDC 0054-3177-63: Bottles of 500 mL.

Store and Dispense
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP/NF.

Dexamethasone *Intensol*™ Oral Solution (Con-centrate), 1 mg per mL:
NDC 0054-3176-44: Bottles of 30 mL with calibrated dropper [graduations of 0.25 mL (0.25 mg), 0.5 mL (0.5 mg), 0.75 mL (0.75 mg), and 1 mL (1 mg), on the dropper].

Store and Dispense
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze. Do not use if solution contains a precipitate. Dispense only in this bottle and only with the calibrated dropper provided. Discard opened bottle after 90 days.

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Revised September 2007

Boehringer Ingelheim
Roxane Laboratories

Appendix 5. Schedule of Assessments

	Screening[a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12[b]	ET/Safety Follow Up[c]
		Days (± 2)					Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	
		1	8	15	22	28	15	28	28	28	28	
Informed consent	x											
Confirm eligibility	x											
Medical history	x											
PE[d]/Vital signs[e]/Weight	x	x	x	x	x	x	x	x	x	x	x	x
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x
ECG[f]	x	x										x
Lab assessments:												
Urine pregnancy test[g]	x											x
Hematology[h]	x	x[q]	x	x	x	x	x	x	x	x	x	x
Serum chemistry[i]	x	x[q]	x	x	x	x	x	x	x	x	x	x
Urinalysis[j]	x					x		x	x	x	Every 2 mos	
T/B/NK cell count[k]		x[q]	x	x		x		x			Every 6 mos	
Disease markers[l]	x			x		x		x	x	x	Every 2 mos	x
Bone marrow (aspirate/biopsy) /Skeletal survey[p]	x								As clinically indicated or to confirm a CR	As clinically indicated or to confirm a CR	As clinically indicated or to confirm a CR	
Hepatitis serology[r]	x											
HBV PCR[s]						x		x	x	x	QM	QM
Pharmacodynamics		x[m]	x[m]			x[n]		x[n]				x
Pharmacokinetics[o]		x	x	x	x	x						
ACP-196/ dexamethasone dispensed		x	x	x	x	x	x	x	x	x	x	
Study drug compliance		x	x	x	x	x	x	x	x	x	x	
Tumor assessment[p]	x					x		x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x

Abbreviations: anti-HBc = hepatitis B core antibody; CR = complete remission; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET = early termination; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; Ig = immunoglobulin; IVIG = intravenous immunoglobulins; mos = months; PCR = polymerase chain reaction; PE = physical exam; QM = every month.

Footnotes for ACE-MY-001 Schedule of Study Activities:

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. Any subjects who have not progressed while receiving study drug treatment, may be eligible to enroll into a long-term follow up study and continue to receive ACP-196.
c. An early termination visit is required for any subjects who permanently discontinue study drug early for any reason including disease progression. A 30-day (± 7 days) safety follow-up visit is required when subjects discontinue study drug unless they start another anticancer therapy within that timeframe.
d. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter.
e. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
f. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.
g. Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
h. Hematology includes complete blood count with differential and platelet and reticulocyte counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days.
i. Serum chemistry: albumin, alkaline phosphatase, bone-specific alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, C-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 5 days.
j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, N-terminal telopeptide, and glucose.
k. T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD16/56). During Cycle 5-12, only done at end of Cycle 6 and 12.
l. Refer to Section 4.1 for a list of myeloma disease markers.
m. Pharmacodynamic samples are drawn predose and 4 hours (±10 minutes) postdose on the days indicated. Note: These timepoints are relative to the morning dose.
n. Pharmacodynamic samples are drawn predose on the days indicated.
o. Pharmacokinetic samples are drawn per Table 4-1.
p Refer to Section 4-2. Bone marrow aspirate/biopsy and skeletal survey are required at baseline (ie, before the first dose of study drug). Thereafter they are required as indicated in the table above.
q. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.
r. Hepatitis serology must include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), hepatitis B core antibody (anti-HBc), and hepatitis C (HCV) antibody. Subjects who are receiving prophylactic intravenous immunoglobulins (IVIG) and have positive HBsAg or anti-HBc must have negative hepatitis B DNA to be eligible. In addition, any subjects testing positive for any hepatitis serology, must have PCR testing (see exclusion criterion #11).
s. Subjects who are anti-HBc positive (or have a known history of HBV infection) should be monitored monthly with a quantitative PCR test for HBV DNA. Monthly monitoring should continue until 12 months after last dose of ACP-196. Any subject with a rising viral load (above lower limit of detection) should discontinue ACP-196 and have antiviral therapy instituted and a consultation with a physician with expertise in managing hepatitis B.

PROTOCOL

TITLE:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma
PROTOCOL NUMBER:	ACE-MY-001
STUDY DRUG:	ACP-196
IND NUMBER:	118717
EUDRACT NUMBER	2014-003587-21
SPONSOR MEDICAL MONITOR:	[redacted] Acerta Pharma BV [redacted] [redacted]
SPONSOR:	Acerta Pharma BV Molenstraat 110 5342 CC Oss The Netherlands
PROTOCOL DATE:	Version 0.0 - 11 July 2014
AMENDMENT 1 DATE:	Version 1.0 - 20 March 2015

Confidentiality Statement

PROTOCOL APPROVAL PAGE

I have carefully read Amendment 1 of Protocol ACE-MY-001 entitled "An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP), all applicable regulatory requirements, and the ethical principles laid down in the Declaration of Helsinki. Furthermore, I understand that the Sponsor, Acerta Pharma, and the IRB/IEC must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma BV requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Acerta Pharma BV representative is authorized to sign the protocol and any amendments:

[redacted]

SUMMARY OF AMENDMENT 1

Acerta Pharma is amending this protocol to provide updated background information on ACP-196 and to assure consistency in eligibility criteria and other study requirements across studies.

This amendment also reflects the memo to file dated 09 October 2014 clarifying the concomitant use of agents that reduce gastric acidity.

Clarifying edits and typographical changes have been made throughout the protocol. In addition, the following substantive changes were made as part of this amendment:

Change	Rationale
Title Page: changed Medical Monitor	Sandeep Inamdar, MBBS, is now the Acerta Pharma Medical Monitor for the study.
Synopsis: Revised text	The synopsis was updated to reflect the changes made throughout the protocol.
Section 1.1 Role of BTK in Lymphoid Cancers: Added background information on ibrutinib	Information added to provide context of ACP-196 development compared with other BTK inhibitors such as ibrutinib.
Section 1.2.2 Efficacy Pharmacology: Revised Table 1-1	Table updated to reflect new preclinical data.
Section 1.2.4 ACP-196 and Thrombus Formation: New section added.	An in vivo murine model of human thrombus formation showed that the thrombi formed by platelets treated with ACP-196 were not significantly different than untreated platelets. In contrast, ibrutinib-treated platelets showed reduced thrombus formation, which may provide some mechanistic background for the bleeding events seen in patients treated with ibrutinib.
Section 1.2.6 Drug-drug Interaction Potential: Revised text throughout section	Section updated to reflect new clinical data.
Section 1.3 Clinical Experience: Revised Table 1-2; updated text and added new subsections 1.3.1 Pharmacokinetics and Pharmacodynamics of ACP-196 and 1.3.2 Clinical Experience of ACP-196 in CLL	Section updated to reflect current clinical data from ACE-CL-001.
Section 1.4 Benefit/Risk: New section added.	Section added to summarize the risk/benefit to subjects in this study.
Section 2.2 Secondary Objective: Added endpoints of clinical benefit rate (CBR) and disease control rate (DCR), and deleted time-to-next treatment.	In addition to the endpoint of overall response rate (ORR), which includes complete responses and partial responses, the activity of ACP-196 will be evaluated by assessing clinical benefit rate (overall response plus minimal responses) and disease control rate (clinical benefit plus stable disease). Time-to-next treatment analysis was removed, as subjects who experience disease progression on study are expected to move quickly on to a new anticancer regimen.
Section 3.1 Description of Study: Added	Sites/countries added to clarify study

Change	Rationale
number of planned sites and countries and defined end of trial.	structure. End of trial defined for reporting purposes
Section 3.2.2 Efficacy Parameters: Added clinical benefit rate and disease control rate, deleted time-to-next treatment.	Revised to reflect changes in Section 2.2 Secondary Objectives, as noted above.
Section 3.3 Rationale for Study Design and Dosing Regimen: updated Btk occupancy data.	Updated to reflect current data from ACE-CL-001.
Section 3.4.1 Inclusion Criteria: Added new inclusion criteria: • Evaluable myeloma at screening, defined as the presence of at least one of the following: o Serum M-protein ≥ 0.5 g/dL o Urine M-protein ≥ 200 mg/24 hours o In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) **and** an abnormal serum kappa/lambda ratio o For subjects whose disease can only be reliably measured by serum quantitative immunoglobulin A (IgA), IgA ≥ 750 mg/dL (0.75 g/dL)	Subjects must have measurable disease at screening to allow adequate evaluation of response on study.
Section 3.4.2 Exclusion Criteria: Added 3 new criteria: • Plasma cell leukemia or circulating plasma cells ≥ 2 x 10^9/L • Known history of a bleeding diathesis (eg, hemophilia, von Willebrand disease) • Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) Revised exclusion criteria as follows: • Removed ECG exclusion criteria, except that QTc > 480 msec was moved to cardiovascular disease exclusion criteria • Added gastric bypass • Added phosphoinositide-3 kinase [PI3K], Syk, and BCL-2 receptors • Added vitamin K antagonist (phenprocoumon) within 28 days • Added specific criteria for absolute	Subjects with plasma cell leukemia are excluded due to the distinct clinical course compared to primary multiple myeloma. The other exclusion criteria have been revised for consistency with other ACP-196 protocols. Susceptibility to bleeding has been observed with the first generation Btk inhibitor, ibrutinib [IMBRUVICA package insert]; therefore, subjects with a known history of a bleeding diathesis will be excluded from this study. Preliminary results from a healthy volunteer study suggest subjects should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids and calcium supplements) and short-acting H2 receptor antagonists for a period of at least 2 hours before and after taking ACP-196. Use of omeprazole, esomeprazole, or any other long-acting proton pump inhibitors while taking ACP-196 is not permitted due to a potential decrease in study drug exposure. However, if a subject requires treatment with

Change	Rationale
neutrophil count (ANC) and platelet count in subjects with bone marrow involvement: ANC < 0.50 x 10^9/L or platelet count < 30 x 10^9/L • Changed aspartate aminotransferase (AST) and alanine aminotransferase (ALT) limits from > 2.5 x upper limit of normal (ULN) to > 3.0 x ULN and removed exception for disease-related abnormalities for bilirubin and ALT/AST	a long-acting proton pump inhibitor while on study (eg, to treat an ulcer), treatment options should be discussed with the Medical Monitor. Based on the safety results observed in the ongoing first-in-human study of ACP-196, the ECG exclusion criteria have been narrowed to exclude QTc > 480 msec at screening.
Section 3.5.2.1 ACP-196: Removed 25-mg capsule information; deleted inactive excipients and bottle size	This section updated as Acerta Pharma is phasing out the 25-mg strength capsule.
Section 3.5.2.2 Dexamethasone: Added information about supply and storage of dexamethasone.	Acerta Pharma will either directly supply sites with dexamethasone or the sites will be reimbursed to prescribe dexamethasone; this will be detailed separately in each site's clinical trial agreement. Per the US dexamethasone package insert (Appendix 4), tablets are to be stored at room temperature (20° to 25°C) and protected from moisture and light.
Section 3.5.5.1 Study Treatment Regimen and Dose Modifications, ACP-196: Revised text and Table 3-1: New Section Dose Delays states: Treatment with ACP-196 should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Medical Monitor. Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.9 for more information on assessing disease progression under these circumstances. New Section Dose Modification and Discontinuation states: The actions in Table 3-1 should be taken for	This section is now 2 sections. Data from the ongoing study of ACP-196 in subjects with CLL (Section1.3.2) suggest full Btk occupancy (> 90%) over 24 hours occurs with 200 mg QD and 100 mg BID, so dose escalation to 200 mg BID is not currently supported for this protocol. Therefore this section was revised to remove language that allowed escalation to 200 mg BID for subjects who were not responding to ACP-196 treatment. To better allow evaluation of single-agent activity of ACP-196, subjects in Cohort 1 must have received at least 2 cycles of study treatment and not experienced at least an MR in order to have dexamethasone added to their treatment.

Change	Rationale
the following toxicities: • Grade 4 absolute neutrophil count (ANC) (< 500/µL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded on the electronic case report form [eCRF]). • Grade 3 platelets in the presence of significant bleeding • Grade 4 platelets • Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy • Any other Grade 4 toxicity or unmanageable Grade 3 toxicity. Table 3-1 states: Occurrence→Action 1st - 2nd→Hold ACP-196 until recovery to Grade ≤ 1 or baseline; may restart at original dose level 3rd→Hold ACP-196 until recovery to Grade ≤ 1 or baseline; restart at 100 mg once daily 4th→Discontinue ACP-196 Specified that subjects in Cohort 1 (ACP-196 monotherapy) who do not experience at least an minimal response (MR) after 2 cycles of study treatment may have dexamethasone (40 mg once weekly) added to their treatment.	
Section 3.6.2 Guideline for Use of CYP Inhibiting/Inducing Drugs: New section added	Language regarding monitoring of subjects on CYP3A inhibitors/inducers was moved (formerly appeared under Precautions/Drug-drug Interactions) and revised for clarity and consistency with other studies. At the systemic exposure levels expected in this study, ACP-196 inhibition of CYP metabolism is not anticipated. However, as discussed in Section 1.3.1, concomitant administration of ACP-196 with a strong CYP3A4 inhibitor increased exposure by approximately 5-fold. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (Appendix 3) should be avoided when possible. If a subject requires a strong CYP3A4 inhibitor while on

Change	Rationale
	study, monitor the subject closely for potential toxicities.
Section 3.6.3 Guideline for Use of Drugs that Affect Gastric pH: New section added	Language regarding the use of drugs that affect gastric pH was added to reflect current findings on the effect of agents that reduce gastric acidity (eg, proton pump inhibitors, H2-receptor antagonists or antacids) on ACP-196 absorption in a healthy volunteer study (ACE-HV-004). Preliminary results from this study suggest subjects should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids or calcium supplements) for a period of at least 2 hours before and after taking ACP-196. Subjects should also avoid the use of H2-receptor antagonists for a period at least 2 hours before and after taking ACP-196. Use of omeprazole, esomeprazole, lansoprazole or any other long-acting proton pump inhibitors while taking ACP-196 is not permitted due to a potential decrease in study drug exposure. However, if a subject requires treatment with a long-acting proton pump inhibitor while on study (eg, to treat an ulcer), discuss treatment options with the Medical Monitor.
Section 3.6.4 Prohibited Concomitant Therapy: Added live or live attenuated vaccines.	Per the dexamethasone package insert, administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.
Section 3.7.1 Dietary Restrictions: • Added caution against excessive consumption of grapefruit or Seville oranges or use of herbal remedies such as St. John's Wort. • Added that ACP-196 can be taken with or without food.	Because ACP-196 may be metabolized by CYP3A4/3A5, subjects are cautioned against ingesting these known CYP3A inhibitors and inducers.
Section 3.7.2 Drug-drug Interactions: Section removed.	Information about drug-drug interactions with CYP inhibitors/inducers was moved to the Concomitant Medications section of the protocol (Section 3.6.2).
Section 3.7.2 Surgery: New section added.	Susceptibility to bleeding has been observed with the first generation Btk inhibitor, ibrutinib [IMBRUVICA package insert]. As a precaution, it is suggested that ACP-196 be held for 3 days before and after any major surgical procedure.
Section 3.7.3 Infections: New section added.	Per the dexamethasone package insert, patients who are on corticosteroids are more susceptible to infections than are healthy individuals. Corticosteroids may exacerbate systemic fungal infections and therefore

Change	Rationale
	should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions.
Section 3.8 Stopping Rules • Edited section to clarify the assessment of response if there is uncertainty regarding whether there is cancer progression • Revised instruction for discontinuation as follows: Any subject who is unable to tolerate ~~a second~~ rechallenge ~~with~~ at the lowest protocol-described, dose-modified levels (see Section 3.5.5) should be withdrawn from the study treatment unless continued therapy is permitted by the Acerta Pharma medical monitor.	Clarified disease assessment in the event that transient worsening of disease is observed during temporary interruption of study therapy. Revised instructions for study discontinuation to be consistent with the dose modification instructions in Section 3.5.5.
Section 4.1 Description of Procedures: Revised as noted: - Electrocardiograms (ECGs) – changed screening ECG from triplicate to single, and added a single ECG to 30-day Safety Follow-up visit - Tumor Assessments – text added - Routine Clinical Assessments – new text section added	- ECG criteria were revised for consistency with other protocols - Tumor assessment requirements were further clarified. - Routine Clinical Assessments section added to clarify non-radiology assessments needed to support overall response.
Section 4.2 Investigator's Assessment of Response: Updated Table 4-1.	Response criteria updated to reflect the latest criteria (Rajkumar 2011), including removal of near complete response (nCR) category.
Section 4.3 Early Termination/Safety Follow-up Visit: Specified that an early termination visit is required for any subjects who permanently discontinue study drug early for any reason including disease progression.	Clarifying edit.
Section 5.2 Sample Size Considerations: Deleted power calculation based on chi square test (no change in power based on exact binomial test).	Clarifying edits; no substantive change in sample size calculations.
Section 5.3 Definition of Analysis Populations: Replaced per-protocol analysis set with intent-to-treat ITT population for efficacy endpoints.	Efficacy analyses will be done on randomized subjects (ie, the ITT population) for this study. PK/PD analyses will be further defined in a separate statistical analysis plan.
Section 5.4 Missing Data Handling: Revised text	Clarified and specified missing data handling procedures for response and safety parameters.
Section 5.5.3.1 Overall Response Rate: removed nCR and MR from this endpoint; replaced 97.5% one-sided confidence interval with 95% two-sided confidence interval.	Per the current guidelines (Rajkumar 2011), nCR is not defined, and minimal response rate should be considered separately from ORR.
Section 5.5.3.2 Duration of Response: removed nCR and MR from this endpoint.	Per the current guidelines (Rajkumar 2011), nCR is not defined, and minimal response

Change	Rationale
	rate should be considered separately from overall response.
Section 5.5.3.3 Clinical Benefit Rate: Added new section.	Added endpoint of CBR, defined as the proportion of subjects who achieve a CR, sCR, VGPR, PR, or MR.
Section 5.5.3.4 Disease Control Rate: Added new section.	Added endpoint of DCR, defined as the proportion of subjects who achieve a CR, sCR, VGPR, PR, MR, or SD.
Section 5.5.3.5 Progression-free Survival: defined start of PFS interval as the date of randomization, rather than the start of ACP-196 therapy.	As the PFS analysis will be performed on the ITT population, the start randomization is a more appropriate timepoint for the PFS interval.
Section 5.5.3.4 Time-to-Next Treatment: Section deleted; long-term follow-up visits are no longer required.	Time-to-next treatment analysis was removed, as subjects who experience disease progression on study are expected to move quickly on to a new anticancer regimen.
Section 5.5.4 Analysis of Pharmacokinetic/Pharmacodynamic Parameters: Added AUC_{0-12} analysis and defined $AUC_{0-24calc}$ (calculated by doubling the value for AUC_{0-12})	PK parameters revised to be consistent with other studies that use BID dosing.
Section 6.2.1 Adverse Event Reporting Period: Added underlined text: The AE reporting period for this study begins when the subject receives the first dose of study and ends with the safety follow-up visit (<u>or last on-treatment visit if the safety follow-up visit is not done) or if the subject receives a new anticancer therapy.</u>	Added text to clarify the end of the AE reporting period.
Section 6.2.3 Pregnancy: Revised reporting procedures to reflect single-part form	Clarifying edits
Section 6.2.4 Expedited Reporting Requirements for Serious Adverse Events: Instructions clarified to emphasize use of the electronic reporting system (no substantive change in reporting procedures).	Clarifying edits
Section 7.1 Regulatory and Ethical Compliance: New section added (with subsequent re-numbering of sections 7.2-7.12). New text reads: <u>This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations Title 21 and European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.</u>	Added explicit statement that the study will be implemented in accordance with appropriate regulatory guidelines.
Section 7.10 Publication of Study Results: Revised text to specify that authorship will follow ICMJE recommendations.	Clarifying edits
Section 8.0 References	Updated to reflect new references throughout the protocol.

Change	Rationale
Appendix 3 Known Strong in Vivo Inhibitors and Inducers of CYP3A4: Replaced table	Replaced with current FDA list of strong CYP3A inhibitors/inducers
Appendix 4: Dexamethasone Prescribing Information: Added new appendix.	The United States label for dexamethasone tablets (Roxane Laboratories 2007) is provided for reference. The United States label will also serve as the Reference Safety Information for dexamethasone for this study. Country-specific labels will be provided to investigative sites as appropriate
Appendix 5: Schedule of Assessments: Revised throughout, including deletion of bone marrow requirement at Cycle 2	Schedule updated to reflect changes as described above, including deletion of long-term follow-up visit. Bone marrow assessments were corrected to match the existing text (ie, required only at screening and as clinically indicated/to confirm a CR).

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ABBREVIATIONS

AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BID	twice a day (dosing)
Btk	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CR	complete remission (response)
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FIH	first-in-human (trial)
FLC	(serum) free light chains
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene

HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
ICF	informed consent form
IEC	Independent Ethics Committee
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minimal response
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
ORR	overall response rate
PBMC(s)	peripheral blood mononuclear cells
PD	pharmacodynamics
PI3K	phosphoinositide-3 kinase
PK	pharmacokinetics
PR	partial remission (response)
QD	once a day (dosing)
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SD	stable disease
SFLC	serum free light chains
SIFE	serum immunofixation electrophoresis
SPD	sum of the products of the perpendicular diameters (of lymph nodes)
SPEP	serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction (report)
T_{max}	time to maximum drug concentration
UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine serum protein electrophoresis
VGPR	very good partial response
WHO	World Health Organization

STUDY SYNOPSIS

Protocol Number:	ACE-MY-001
Study Drug:	ACP-196
Protocol Title:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma
Phase:	Phase 1b
Comparator:	None
Background and Rationale for Study	Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton tyrosine kinase (Btk) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Preclinical studies have shown that Btk inhibition significantly reduces in vivo multiple myeloma (MM) cell growth and MM cell-induced osteolysis in a murine model (Tai 2012). Data on the utility of Btk targeted therapy in patients with MM is very preliminary, but suggests there are subsets of patients with malignant plasma cell clones in which Btk is active as evidenced by expression of phosphorylated Btk (p-Btk), and that these cancers may be particularly responsive to Btk inhibitor therapy. Acerta Pharma BV (Acerta Pharma) has developed a novel second generation Btk inhibitor, ACP-196, that achieves significant oral bioavailability and potency in preclinical models. ACP-196 monotherapy is currently in multiple Phase 1/2 studies in subjects with chronic lymphocytic leukemia (CLL) and other indications. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and activity of ACP-196 administration with and without dexamethasone in subjects with relapsed MM. The study will explore the concept of whether biomarkers may help identify patients with MM that are particularly likely to benefit from Btk inhibitor therapy.
Study Design:	This study is a multicenter, open-label, randomized, parallel-group study to be conducted at approximately 20 sites in 2 countries (United Kingdom and United States). Forty subjects will be equally randomized (1:1 ratio) into 2 cohorts to receive ACP-196, with and without dexamethasone: • Cohort 1: ACP-196 100 mg twice per day (BID) continuously • Cohort 2: ACP-196 100 mg BID continuously and dexamethasone 40 mg once weekly Twenty-eight days of study drug administration is 1 cycle. Treatment may be continued for > 28 days until disease

	progression or an unacceptable drug-related toxicity occurs. For subjects in Cohort 1, if documented disease progression occurs, then dexamethasone can be added to the treatment regimen. Additional dose modification provisions are provided in the study protocol. Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1 and Cycle 2. Tumor assessments will be done at 8- to 12-week intervals during the trial. Refer to Appendix 5 for a comprehensive list of study assessments and their timing. The end of trial is defined as the point when the last subject on the study exits the study for any reason.
Study Objectives:	**Primary Objective:** • To characterize the safety profile of ACP-196 with and without dexamethasone in subjects with relapsed or refractory MM **Secondary Objectives:** • To characterize the PK profile of ACP-196 with and without dexamethasone and the PK profile of dexamethasone with concomitant ACP-196 administration • To evaluate the PD effects of ACP-196 with and without dexamethasone • To evaluate the activity of ACP-196 with and without dexamethasone as measured by overall response rate, duration of response, clinical benefit rate, disease control rate, and progression-free survival • To explore the relationship between biological markers in MM cells and response to therapy
Safety Parameters:	Type, frequency, severity, timing of onset, duration, and relationship to study drug (ie, ACP-196, dexamethasone, or both) of any adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of study treatment.

Efficacy Parameters:	• Overall response rate (ORR) • Duration of response • Clinical benefit rate • Disease control rate • Progression-free survival
Pharmacokinetic Parameters:	The plasma PK of ACP-196 will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes: • AUC_{0-t}: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t). • AUC_{0-12}: Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation. • $AUC_{0-\infty}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant. • $AUC_{0-24calc}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}. • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • CL/F: Oral clearance
Pharmacodynamic Parameters:	The occupancy of Btk by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) and in bone marrow, when available, with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.
Sample Size:	Forty subjects with 20 subjects in each cohort.

Inclusion Criteria:	• Men and women ≥ 18 years of age.
	• A confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥ 1 prior therapy for MM, and is progressing at the time of study entry.
	• Evaluable myeloma at screening, defined as the presence of at least one of the following:
	  ○ Serum M-protein ≥ 0.5 g/dL
	  ○ Urine M-protein ≥ 200 mg/24 hours

	○ In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) **and** an abnormal serum kappa/lambda ratio ○ For subjects whose disease can only be reliably measured by serum quantitative immunoglobulin A (IgA), IgA ≥ 750 mg/dL (0.75 g/dL) • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. • Agreement to use acceptable methods of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children. • Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug. • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).
Exclusion Criteria:	• Plasma cell leukemia or circulating plasma cells ≥ 2 x 10^9/L • Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor. • A life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ACP-196, or put the study outcomes at undue risk. • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec. • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Any immunotherapy within 4 weeks of first dose of study drug. • The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s). • Prior exposure to a B-cell receptor (BCR) inhibitor (eg, Btk, phosphoinositide-3 kinase [PI3K], or Syk inhibitors) or BCL-2 inhibitors (eg, ABT-199).

	• Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MM or other conditions. Note: Subjects may use topical or inhaled corticosteroids as therapy for comorbid conditions. During study participation, subjects may receive systemic or enteric corticosteroids as needed for MM therapy or treatment-emergent comorbid conditions. • Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation. • Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection. • Major surgery within 4 weeks before first dose of ACP-196. • Known history of a bleeding diathesis (eg, hemophilia, von Willebrand disease) • History of stroke or intracranial hemorrhage within 6 months before the first dose of ACP-196. • Requires or receiving anti-coagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 28 days of first dose of study drug. • Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole) • ANC < 0.75 x 10^9/L or platelet count < 50 x 10^9/L. For subjects with > 50% plasma cells in the marrow, ANC < 0.50 x 10^9/L or platelet count < 30 x 10^9/L. • Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN; or aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN. • Breastfeeding or pregnant. • Concurrent participation in another therapeutic clinical trial.
Dosage Form and Strength:	ACP-196 is provided as 100-mg hard gelatin capsules prepared using standard pharmaceutical grade excipients.
Dose Regimen/Route of Administration:	ACP-196 is an orally administered product. ACP-196 can be administered with or without food. <u>Regimens:</u> • Cohort 1 (BID): 100 mg ACP-196 (1 x 100-mg capsule) administered 12 hours apart (BID dosing = 200-mg total daily dose) • Cohort 2 (BID + dexamethasone): 100 mg ACP-196 (1 x 100-mg capsule) administered 12 hours apart (BID dosing = 200-mg total daily dose) plus 40 mg dexamethasone administered once weekly (weekly dosing = 40-mg total weekly dose)

Concomitant Medications:	The effect of agents that reduce gastric acidity (eg, proton pump inhibitors, H2-receptor antagonists, or antacids) on ACP-196 absorption is currently being evaluated in a healthy volunteer study (ACE-HV-004). Preliminary results from this study suggest subjects should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids or calcium supplements) and short-acting H2-receptor antagonists for a period of at least 2 hours before and after taking ACP-196. Use of omeprazole or esomeprazole or any other long-acting proton pump inhibitors while taking ACP-196 is not permitted due to a potential decrease in study drug exposure; however, if a subject requires treatment with a long-acting proton pump inhibitor while on study (eg, to treat an ulcer), treatment options should be discussed with the Medical Monitor. Concomitant use of strong inhibitors/inducers of CYP3A should be avoided when possible. If a subject requires a strong CYP3A inhibitor while on study, monitor the subject closely for potential toxicities.
Statistics:	Subjects meeting the stated eligibility requirements will be enrolled onto the study. Subjects will be randomized in a 1:1 ratio into the 2 regimens (ACP-196 with and without dexamethasone). With a sample size of 19 subjects per cohort, the power to detect the difference between a null-hypothesis response rate of 15% and an alternative response rate of 40% with a 0.025 one-sided significance level is 0.69 using a one-group, exact binomial test. A sample size of 19 subjects per cohort will also provide a 97.5% one-sided confidence interval centered around an expected ORR of 40% that excludes an ORR of 18.6% as a lower bound. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data, as appropriate.

1.0 BACKGROUND INFORMATION

1.1 ROLE OF BTK IN LYMPHOID CANCERS

Bruton tyrosine kinase (Btk) is a non-receptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Mohamed 2009, Bradshaw 2010). Functional null mutations of Btk in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells (Vihinen 2000). Conversely, Btk activation is implicated in the pathogenesis of several B-cell malignancies (Buggy 2012). Taken together, these findings have suggested that inhibition of Btk may offer an attractive strategy for treating B-cell neoplasms.

Ibrutinib (IMBRUVICA™), a first-generation oral, small-molecule Btk inhibitor has been approved for the treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) and is being evaluated for activity in other B-cell neoplasms including multiple myeloma (MM). Preclinical studies have shown that Btk inhibition with ibrutinib significantly reduces in vivo multiple myeloma (MM) cell growth and MM cell-induced osteolysis in a murine model (Tai 2012).

While current therapies have provided substantial benefit to patients, MM remains incurable; for patients who experience disease relapse after application of existing therapies, the prognosis is dismal and new drugs and therapeutic strategies are required for continued disease control (Romano 2014). Inhibition of Btk may simultaneously address the MM-related bone complications as well improve patient outcome in MM (Edwards 2012).

While highly potent in inhibiting Btk, ibrutinib has also shown in vitro activity against other kinases with a cysteine in the same position as Cys481 in Btk to which the drug covalently binds. The inhibition of epidermal growth factor receptor (EGFR) is also observed in cellular assays and may be the cause of ibrutinib-related adverse events (AEs) of diarrhea and rash (IMBRUVICA® package insert). In addition, ibrutinib is a substrate for CYP3A4; inhibition of CYP3A causes a 29-fold increase in maximum concentration (C_{max}) and 24-fold increase in area under the curve (AUC) for ibrutinib (IMBRUVICA® package insert). This increases the possibility of drug-drug interactions in combination therapies with drugs currently used in management of subjects with

cancer. These liabilities support the development of alternative Btk inhibitors for use in the therapy of B-cell malignancies.

Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of ACP-196, an orally bioavailable, new chemical entity that covalently inhibits Btk and shows encouraging activity and acceptable safety in nonclinical studies. Within the class of Btk inhibitors, ACP-196 is a more selective inhibitor of Btk than ibrutinib. Key nonclinical differentiators of ACP-196 versus ibrutinib are:

- ACP-196 has been evaluated against ibrutinib in EGFR expressing cell lines. Ibrutinib is a potent covalent inhibitor of EGFR (EC50 = 50 to 70 nM). ACP-196 does not inhibit EGFR even at the highest concentration tested (10 µM).
- ACP-196 has been evaluated against ibrutinib in in vitro antibody-dependent cell-mediated cytotoxicity (ADCC) assays. At physiologic concentrations, ibrutinib, but not ACP-196, reduced natural killer (NK) cell-mediated lysis of Raji and autologous CLL tumor cells and significantly inhibited rituximab-induced NK cell cytokine secretion ($P<0.05$).
- ACP-196 has been evaluated against ibrutinib in an in vivo thrombus formation model. At physiologic concentrations, ibrutinib, but not ACP-196, significantly inhibited thrombus formation ($P=0.001$).

The nonclinical and toxicology results of ACP-196 suggest it may have an improved therapeutic window relative to ibrutinib; it may be more readily combined with other agents for the treatment of cancer.

1.2 PRECLINICAL STUDIES

Summaries of preclinical studies are provided below. For more detailed information please refer to the Investigator's Brochure.

1.2.1 Chemistry

[redacted] ACP-196 is orally bioavailable in humans and is suitable for formulating in capsules. For clinical testing, ACP-196 has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

1.2.2 Efficacy Pharmacology

Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to Btk inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail 2004). ACP-196 is currently being evaluated in an ongoing dose-escalation study in canine spontaneous B-cell lymphoma. Fourteen dogs, all of which had diffuse large B-cell lymphoma (DLBCL) confirmed by histology, have been treated with ACP-196 for at least 2 weeks. The dosages have ranged from 2.5 to 20 mg/kg once (QD) or twice (BID) per day. To date, per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), partial responses (PRs) been observed in 4 of 14 dogs (29%) and stable disease has been observed in 8 of 14 dogs (57%). No ACP-196-related adverse events (AEs) have been reported to date in this study. These findings are preliminary and similar to the clinical responses (ie, 1 dog with PR out of 5 dogs treated with suspected or confirmed DLBCL) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

Preliminary results assessing Btk occupancy using a biotin-tagged analogue of ACP-196 show near complete Btk occupancy over 24 hours with both BID and QD dosing in canine tumor tissue (Table 1-1).

Table 1-1. Assessment of ACP-196 Active-site Occupancy in Fine Needle Aspirates of Canine Lymph Node Tumors (N=4)

	Dog Identification and ACP-196 Dosing Regimen			
	DL-10	DL-12	DL-14	DL-16
	5 mg/kg BID	10 mg/kg QD	20 mg/kg QD	20 mg/kg QD
Timing	Btk Occupancy (% versus predose)			
Day 1 (3 hours after morning dose)	98%	99%	98%	99%
Day 7 (before morning dose)	80%	98%	77	93%

BID = twice per day; Btk = Bruton tyrosine kinase; QD = once per day

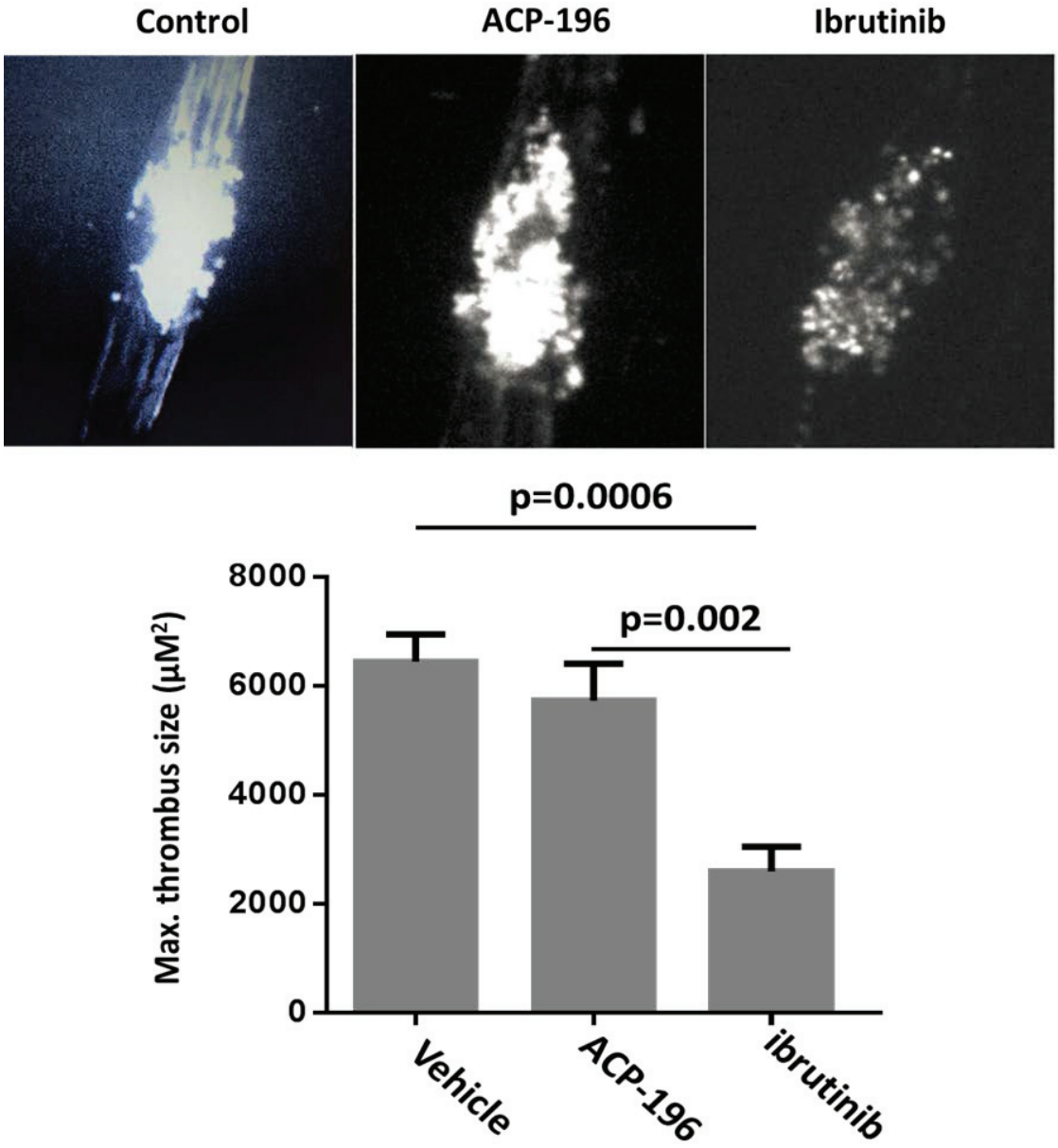
These canine data provide nonclinical support for the ability of ACP-196 to target Btk in vivo. The role of Btk expression in driving the proliferation and survival of malignant plasma cells in multiple myeloma (MM) has been less clear than among other lymphoid cancers. However, emerging, unpublished, preclinical data from the laboratory of Sagar Lonial (Emory University) suggest that Btk and phosphorylated Btk (p-Btk) expression is

present to varying levels in a standard panel of 12 myeloma cell lines, thus providing a basis for evaluating Btk inhibition as a therapy for MM.

1.2.3 ACP-196 and Thrombus Formation

Ibrutinib is associated with an increased risk of bleeding (Kamel 2014). Hence, the effects of ACP-196 and ibrutinib were evaluated on human platelet-mediated thrombosis by using the in vivo human thrombus formation in a VWF^{HA1} murine model, which has been previously described (Chen 2008). Purified human platelets were preincubated with various concentrations of ibrutinib and ACP-196 (0.1 µM, 0.5 µM, or 1 µM for each) or DMSO and then administered to VWF^{HA1} mice followed by laser-induced thrombus formation. Ibrutinib- and ACP-196-treated human platelets were fluorescently labeled and infused continuously through a catheter inserted into the femoral artery. Thrombus formation in response to laser-induced vascular injury was monitored in real time using 2-channel confocal intravital microscopy (Furie 2005) (Figure 1-1). Upon induction of arteriole injury, untreated platelets rapidly formed thrombi with a mean (± SEM) thrombus size of 6450 ± 292 mm^2. Similarly, ACP-196 (1 µM) treated platelets formed slightly smaller but not significantly different thrombi, with a mean thrombus size of 5733 ± 393 mm^2. In contrast, a significant reduction in thrombus size occurred in platelets pretreated with ibrutinib (1 µM); mean thrombus size was 2600 ± 246 mm^2, representing in a reduction in maximal thrombus size by approximately 61% compared with control (P=0.001). Similar results were obtained with platelets pretreated with 500 nM of ACP-196 or ibrutinib: mean thrombus sizes were 5946 ± 283 mm^2 and 2710 ± 325 mm^2, respectively. These preliminary results showing reduced thrombus formation for ibrutinib at physiologically relevant concentrations (0.5 to 1 µM) may provide some mechanistic background for the Grade ≥ 3 bleeding events (eg, subdural hematoma, gastrointestinal bleeding, hematuria, and post procedural hemorrhage) that have been reported in ≤ 6% of patients treated with ibrutinib. In addition, bleeding events of any grade, including bruising and petechiae, were reported in approximately half of patients treated with ibrutinib (IMBRUVICA® package insert).

Figure 1-1. Effect of ACP-196 (1 µM) and Ibrutinib (1 µM) on Thrombus Formation



1.2.4 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with ACP-196 have demonstrated a favorable nonclinical safety profile.

When screened at 10 µM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, ACP-196 shows significant activity only against the

A3 adenosine receptor; follow-up dose-response experiments indicated a IC_{50} of 2.7 µM, suggesting a low clinical risk of off-target effects. ACP-196 at 10 µM showed no inhibition of in vitro epidermal growth factor receptor (EGFR) phosphorylation in an A431 human epidermoid cancer cell line, whereas ibrutinib had an IC_{50} of 66 nM.

The in vitro effect of ACP-196 on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. ACP-196 inhibited hERG channel activity by 25% at 10 µM, suggesting a low clinical risk that ACP-196 would induce clinical QT prolongation as predicted by this assay.

ACP-196 was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of ACP-196 at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that ACP-196 is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.2.5 Drug-drug Interaction Potential

The in vitro studies suggest CYP-mediated metabolism of ACP-196 appears to be catalyzed predominantly by CYP3A4/5. However, in elimination studies in preclinical species, the metabolic fate of ACP-196 is dominated by direct conjugation of ACP-196 with glutathione, providing evidence for a significant non-CYP mechanism of elimination. In a healthy volunteer study (ACE-HV-001), the effect of coadministration of a potent CYP3A and P-gP inhibitor, itraconazole, on the plasma levels of ACP-196 was evaluated. The mean plasma ACP-196 C_{max} and $AUC_{0\text{-last}}$ values increased 3.7- and 5.1-fold, respectively, in the presence of itraconazole relative to no pretreatment. In vitro studies also show that ACP-196 is a substrate for P-gp.

ACP-196 is unlikely to be a perpetrator of a drug-drug interaction at the level of inhibition or induction of CYP isoforms.

Results from drug transporter studies suggest that ACP-196 is not anticipated to alter the PK of other therapeutic agents that are substrates for MDR1, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2. ACP-196 (100 mg BID) may alter the PK of BCRP substrates by inhibition of intestinal BCRP.

1.2.6 In Vivo General Toxicology

To date, the toxicology program has included 28-day GLP evaluations in rats and dogs. In the 28-day study in male and female Sprague-Dawley rats, animals received oral gavage ACP-196 dosages of 30, 100, and 300 mg/kg/day. In the 28-day study in male and female beagle dogs, animals received oral ACP-196 dosages of 3, 10, and 30 mg/kg/day. Both studies had 28-day recovery periods.

The no observable adverse effect level in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, 100 mg/kg/day was selected to conservatively represent the highest nonseverely toxic dose (HNSTD). In dogs at 30 mg/kg/day, no adverse effects on the pancreas were observed. In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the 28-day toxicology studies. However, in 5 of 6 rats from the 300-mg/kg dose group that died early in the study, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts. These findings were most likely incidental postmortem changes.

1.3 CLINICAL EXPERIENCE

Table 1-2 lists the studies currently being conducted with ACP-196 monotherapy.

Table 1-2. ACP-196 Clinical Studies as of January 2015

Protocol	Design	Subjects Enrolled	Status
ACE-CL-001 (NCT02029443)	• First-in-human • Open label • Dose escalation (ACP-196 100-400 mg QD and 100-200 mg BID) • Subjects with relapsed/refractory CLL • Expansion cohorts: o treatment-naive subjects o subjects with Richter's syndrome o subjects who are intolerant to ibrutinib treatment o subjects who are relapsed/refractory to ibrutinib treatment	125	• Cohort 1 (100 mg QD) enrolled and no DLTs observed. • Cohort 2a (175 mg QD) enrolled and no DLTs observed. • Cohort 3 (250 mg QD) enrolled and no DLTs observed. • Cohort 4a (400 mg QD) enrolled and no DLTs observed. • Cohort 2b (100 mg BID now enrolling) and no DLTs observed. • Expansion cohorts now enrolling.
ACE-HV-001	• Open label • Single-dose escalation (ACP-196 2.5-50 mg BID and 100 mg QD) • Food effect (ACP-196 75 mg QD) • Drug-drug interaction with itraconazole (ACP-196 50 mg QD) • Healthy volunteers	59	• Enrollment completed. • No adverse laboratory, vital signs, or ECGs findings observed. • 1 event each of constipation, feeling cold, somnolence (each Grade 1) was reported as related to study drug.
ACE-HV-004	• Open label • ACP-196 100 mg • Drug-drug interaction: o Calcium carbonate o Omeprazole o Rifampin • Healthy volunteers	72	• Enrollment completed. • No adverse laboratory, vital signs, or ECGs findings observed. • Other analyses pending.
ACE-LY-002 (NCT02112526)	• Open label • ACP-196 100 mg BID • Activated B-cell subtype of diffuse large B-cell lymphoma	6	• Enrollment recently begun
ACE-WM-001 (NCT02180724)	• Open label • ACP-196 100 mg BID and 200 mg QD • Waldenström macroglobulinemia	7	• Enrollment recently begun
ACE-LY-003 (NCT02180711)	• Open label • ACP-196 100 mg BID and 200 mg QD • Follicular lymphoma	1	• Enrollment recently begun
15-H-0016 (NIH study)	• Open label • ACP-196 200 mg QD and 100 mg BID • CLL	0	• Enrollment recently begun
ACE-ST-003	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic pancreatic cancer	0	• Protocol in study start up

AE = adverse event; BID = twice per day; CLL = chronic lymphocytic leukemia; DLT = dose-limiting toxicity; ECGs = electrocardiograms; QD = once per day

Table 1-2. ACP-196 Clinical Studies as of January 2015 (continued)

Protocol	Design	Subjects Enrolled	Status
ACE-ST-005 (NCT02351739)	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic bladder cancer	0	• Protocol in study start up
ACE-LY-004 (NCT02213926)	• Open label • ACP-196 100 mg BID • Mantle cell lymphoma	0	• Enrollment recently begun
ACE-CL-002 (NCT02157324)	• Open label • ACP-196 50 mg BID and ACP-319 25 mg BID • CLL	8	• Enrollment recently begun
ACE-LY-001 (NCT02328014)	• Open label • ACP-196 100 mg BID and ACP-319 25 to 100 mg BID • B-cell malignancies	1	• Enrollment recently begun
ACE-CL-003 (NCT02296918)	• Open label • ACP-196 200 mg QD and Obinutuzumab per label • CLL	2	• Enrollment recently begun
ACE-HI-001	• Hepatic impairment study • ACP-196 50 mg QD	18	• Enrollment ongoing
ACE-LY-005	• Open label • ACP-196 100 mg BID and pembrolizumab 2 mg/kg IV Q3W • B-cell malignancies	None	• Protocol in study start up
ACE-ST-006	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic head & neck cancer	0	• Protocol in study start up
ACE-ST-007	• Open label • ACP-196 100 mg BID ± pembrolizumab 200 mg IV Q3W • Advanced or metastatic non-small cell lung cancer	0	• Protocol in study start up

AE = adverse event; BID = twice per day; CLL = chronic lymphocytic leukemia; DLT = dose-limiting toxicity; ECGs = electrocardiograms; IV = intravenous; Q3W = once every 3 weeks; QD = once per day

1.3.1 Pharmacokinetics and Pharmacodynamics of ACP-196 in Healthy Volunteers

ACE-HV-001 was a dose-ranging, food-effect, and drug-drug interaction study evaluating BID and QD dosing for 1 or 2 days in healthy volunteers. The starting dose for ACP-196 was 2.5 mg BID. This study has been completed and no adverse laboratory, vital signs, or ECG findings were observed (2.5 to 50 mg BID; 50 to 100 mg QD). Three AEs related to ACP-196 were reported. Each AE was Grade 1 and resolved

without treatment. The AEs were constipation (2.5 mg BID), feeling cold (75 mg QD), and somnolence (75 mg QD).

In Part 1, PK properties of ACP-196 were evaluated after oral administration of 2 daily doses of 2.5 to 50 mg and a single dose of 100 mg. Of the 30 subjects evaluated, all had measurable systemic concentrations of ACP-196. ACP-196 plasma time to maximum concentration (T_{max}) values were between 0.5 and 1.0 hour for all dose cohorts and independent of the dose level. The increase in mean maximum concentration (C_{max}) values was greater than dose proportion based on the increases of C_{max} from the first dose administered. When evaluating area under the concentration curve (AUC_{0-12}, AUC_{0-24} or AUC_{0-inf}), the mean values increased in a dose proportional manner based on the increases of the total dose administered. Mean half-life ($t_{1/2}$) values ranged from 0.97 to 2.1 hours, and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (Vz/F: 233 to 612 L) appeared to be independent of the dose administered.

ACP-196 was not detected in the urine of subjects who received the 2.5- or 5.0-mg BID doses of ACP-196. ACP-196 was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose dependent manner.

In Part 2, the effect of food on the PK of ACP-196 (75 mg) after a single oral administration was evaluated in 6 men and 6 women. Median ACP-196 plasma T_{max} values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma ACP-196 C_{max} values decreased to 27.3% of the values observed in the fasted state. In contrast, the relative exposure of ACP-196 (AUC) remained mostly unchanged in both states. Per FDA guidance on food-effect studies (FDA 2002), this decrease in exposure is not clinically significant, and therefore, ACP-196 can be taken with or without food.

In Part 3, after administration of a single dose of ACP-196 (50 mg), the effect of itraconazole on the PK was evaluated in 17 subjects. No difference in ACP-196 T_{max} values was observed in the presence or absence of itraconazole.

Mean ACP-196 exposures (as assessed by C_{max}, AUC_{0-last}, AUC_{0-24}, and AUC_{0-inf}) increased in the presence of itraconazole. The mean plasma ACP-196 C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma AUC_{0-last}, AUC_{0-24}, and AUC_{0-inf} values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and Vz/F values decreased in the presence of itraconazole

(CL/F: 217 vs 44 L/h; Vz/F: 1190 vs 184 L). No differences in half-life values were observed (3.3 vs 2.5 hours).

The pharmacodynamics (PD) profile of ACP-196 was evaluated using a Btk occupancy assay and correlated with a functional assay that determines the level of Btk inhibition by measuring expression of CD69 and CD86 on B-cells. A dose-dependent increase in Btk occupancy and corresponding decrease in CD69/86 expression was observed in this study. Full Btk occupancy (≥ 90%) and complete CD86 and CD69 inhibition (≥ 90%) occurred in the 75- and 100-mg single dose cohorts 1 to 3 hours after administration. However, only the 100 mg cohort maintained high Btk occupancy (91.5%) and high BCR functional inhibition (CD86: 86 ± 3% and CD69: 78 ± 8%) at 24 hours. For subjects who received a second dose of ACP-196 12 hours after the first administration, full Btk target occupancy was observed 3 hours after the second dose for the 50 mg dose cohort (Btk occupancy 97 ± 4%).

1.3.2 Clinical Experience of ACP-196 in CLL

ACE-CL-001 (NCT02029443), an ongoing Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL or Richter's syndrome, has a sequential, dose-escalation design. As of 22 January 2015, 125 subjects have received ACP-196 at dosages from 100 to 400 mg QD or 100 to 200 mg BID.

To date, ACP-196 has been well tolerated at all dose levels evaluated. No dose-limiting toxicities (DLTs) have occurred at any dose level. The MTD was not reached in this study; however, per the protocol, dose escalation was stopped once a plateau in PK was observed (ie, between 250 and 400 mg).

Preliminary data from ACE-CL-001 show that Btk occupancy with ACP-196, in peripheral blood cells, is > 95% at 4 hours but decreases to < 95% at 24 hours, while with BID dosing complete Btk occupancy (97% to 99%) is maintained over 24 hours at steady state (Table 1-3). These data suggest that synthesis of de novo Btk may occur within 24 hours.

Table 1-3. Btk Occupancy in Peripheral Blood of Subjects from ACE-CL-001 (December 2014)

	Subjects with Relapsed/Refractory CLL			
Timepoint*	**100 mg QD (n=8)**	**175 mg QD (n=8)**	**250 mg QD (n=6)**	**100 mg BID (n=17)**
Day 7: Median % Occupancy 24 h	89.0	86.9	93.5	**97.4**
Day 8: Median % Occupancy 4 h	98.6	98.7	100	**98.8**

Abbreviations: BID = twice per day; CLL = chronic lymphocytic leukemia; QD = once per day
*Note: 24-h timepoint on BID regimen represents 24 hours after first dose and 12 hours after second dose on Day 7. The 4-h timepoint on the BID regimen represents 4 hours after the first dose on Day 8.

Preliminary PK data from Day 8 show dose linearity from 100 to 250 mg and no accumulation with repeat dosing (Table 1-4).

Table 1-4. Preliminary Day 8 PK Results from ACE-CL-001 (October 2014)

Cohort	**Mean C_{max} ± SD (ng/mL)**	**Mean $AUC_{0\text{-}last}$ ± SD (ng•h/mL)**
100 mg QD (N=8)	529 ± 286	634 ± 197[a]
175 mg QD (N=7)	800 ± 692	1240 ± 789
250 mg QD (N=7)	1350 ± 933	2170 ± 1180
400 mg QD (N=6)	932 ± 576	1870 ± 1040
100 mg BID (N=22)	716 ± 658	837 ± 485[b]

Timepoints: Predose, 0.25, 0.50, 0.75, 1.0, 2.0, 4.0, and 6.0 postdose.
[a] N=7 for AUC calculations in 100 mg QD dose group.
[b] BID regimens were not sampled during the second daily dose interval; 0-24 h exposures are expected to be approximately 2-fold the $AUC_{0\text{-}6}$ values shown.
AUC = area under the curve; BID = twice per day; C_{max} = maximum concentration; SD = standard deviation

To date, 31 subjects have been evaluated for tumor response, by investigators, based on International Working Group response criteria (Hallek 2008) as recently updated (Cheson 2012) to include partial response with treatment-induced lymphocytosis. Based on preliminary, unaudited data an overall response rate (ORR) of 94% (71% PR + 23%

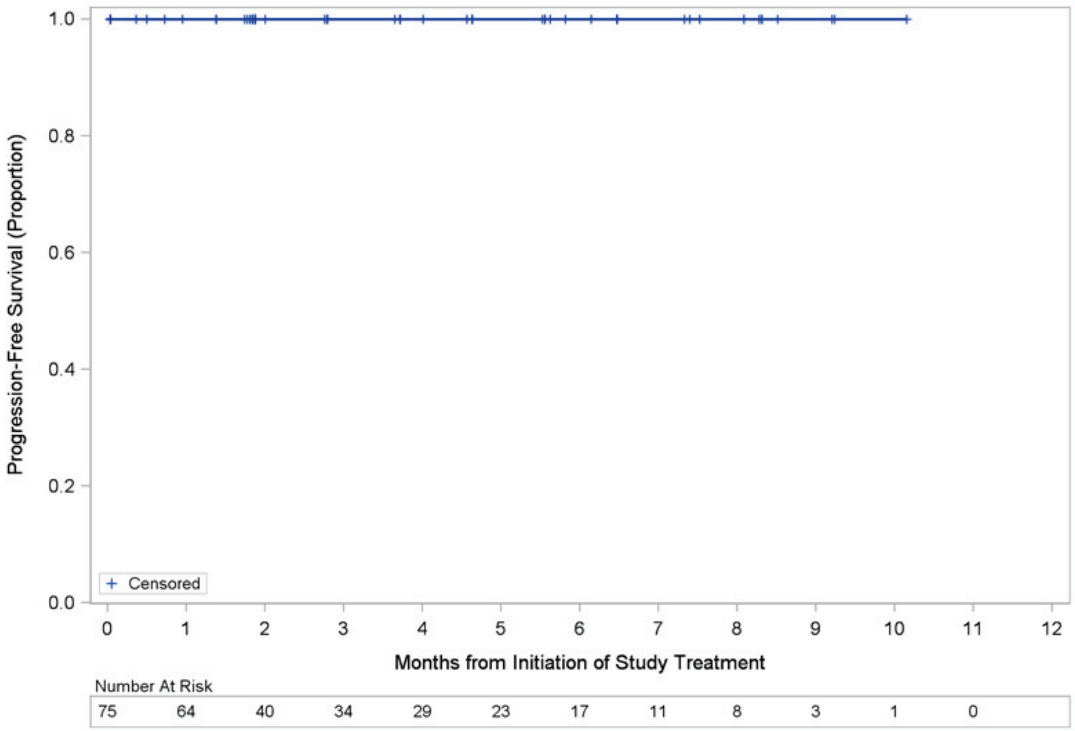
PR with lymphocytosis) has been observed (Table 1-5). Of the 31 subjects assessed, nearly half (15 of 31) have 17p del. Of the 15 subjects with 17p del, 80% (12/15) have PR and 20% (3/15) have PR with lymphocytosis. The median follow-up for the ACP-196 subjects evaluated for response is 7.3 cycles (range 3.0 to 10.8) and each cycle is 28 days. No primary disease progression has occurred on study (N = 75; Figure 1-2).

Table 1-5. Best Response by Cohort from ACE-CL-001 (23OCT2014)

n (%)	All Cohorts (N=31)	100 mg QD (N=8)	175 mg QD (N=8)	250 mg QD (N=7)	100 mg BID (N=3)	400 mg QD (N=5)
PR	22 (71)	7 (88)	5 (71)	4 (57)	3 (100)	2 (40)
PR+L	7 (23)	0 (0)	3 (38)	2 (29)	0 (0)	2 (40)
SD	2 (6)	1 (12)	1 (13)	0 (0)	0 (0)	1 (20)
PD	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Median (range) Cycles						
	7.3 (3.0-10.8)	10.0 (9.0-10.8)	8.6 (3.0-8.8)	7.0 (7.0-7.3)	5.2 (4.7-5.5)	5.0 (4.8-5.5)

BID = twice per day; PD = progressive disease; PR = partial response; PR+L = partial response with lymphocytosis; QD = once per day; SD = stable disease

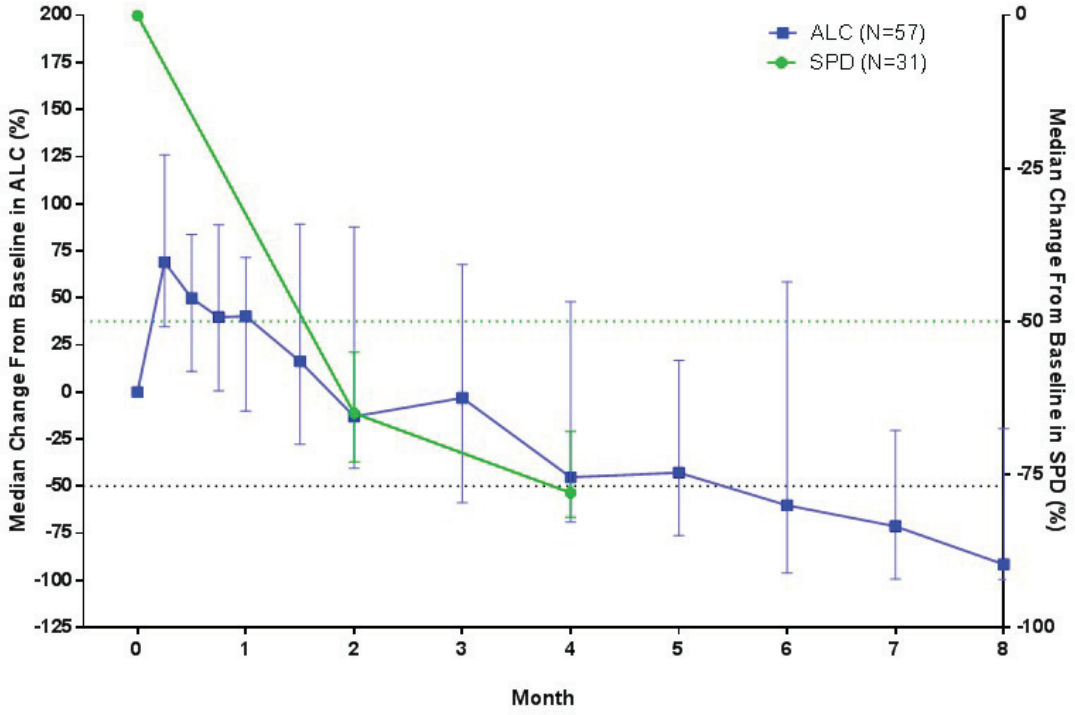
Figure 1-2. Kaplan-Meier Curves for Progression-free Survival by Investigator Assessment for ACE-CL-001 (N=75; excludes Richter's Syndrome Cohort and Ibrutinib R/R Cohort)



These results compare favorably with the Phase 3 results of ibrutinib, the first generation Btk inhibitor, when administered at dosages of 420 mg QD in subjects with relapsed/refractory CLL (N=195). In the ibrutinib study, Byrd and colleagues (2014) report a PR rate of 43%, a PR with lymphocytosis rate of 20%—for an ORR of 63%—an SD rate of 32%, and a progressive disease (PD) rate of 3% (Byrd 2014) based on independent review. The median follow-up time reported for the ibrutinib study was 9.5 months (range 0.1 to 16.6).

Figure 1-3 shows the change from baseline in sum of the product of the diameters (SPD) (N=31) and in absolute lymphocyte count (ALC) (N=57) over time. As shown in the figure, substantial reductions in lymphadenopathy have been observed despite the fact that three-quarters of the evaluable subjects have high-risk cytogenetics (17p del, 11q del, or both). As mentioned above, the observed reductions in lymphadenopathy are consistent with the clinical results for ibrutinib (Byrd 2013, Byrd 2014). However, the reduced drug-induced lymphocytosis and the rapid time to resolution of lymphocytosis with ACP-196 treatment varies greatly from that reported for ibrutinib. Per the IMBRUVICA package insert, 77% of patients with CLL treated with ibrutinib experienced lymphocytosis, which occurred during the first month of therapy and resolved by a median of 23 weeks (range 1 to 104+ weeks). With ACP-196 treatment, the onset of lymphocytosis, if it occurs, is within the first week of treatment and resolves by a median of 8 weeks (range 0 to 24+ weeks).

Figure 1-3. Median (95% CI) Change from Baseline in ALC/SPD Over Time



ALC = absolute lymphocyte count; CI = confidence interval; SPD = sum of the products of the perpendicular diameters (of lymph nodes).

1.4 BENEFIT/RISK

ACP-196 is a potent, orally available small-molecule inhibitor of Btk. A PK/PD study has been completed with ACP-196 in healthy volunteers (ACE-HV-001; Section1.3.1). The safety results showed no identified safety risks in healthy subjects receiving 1 or 2 days of ACP-196 ≤ 100 mg. In study ACE-CL-001, a study of ACP-196 in subjects with relapsed/refractory or previously untreated CLL or Richter's syndrome, no DLTs have been reported at dosages of ≤ 400 mg QD or 100 and 200 mg BID. The overall response rate in the evaluable subjects for this study is currently 94% with some subjects obtaining PRs after only 2 cycles of therapy. Based on these robust results in subjects with CLL, the evaluation of ACP-196 in subjects with relapsed or refractory MM is warranted.

1.5 SUMMARY AND CONCLUSIONS

This study comprises a pilot evaluation of the safety and activity of the potent, second-generation Btk inhibitor, ACP-196, in patients with relapsed or refractory MM. The design

and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with lymphoid cancers; knowledge of the efficacy and safety of the first-generation BCR inhibitor (eg, ibrutinib) in subjects with hematologic cancers; and the available nonclinical and clinical information regarding ACP-196. Preclinical studies are ongoing in parallel to identify biomarkers that may be evaluated in this clinical trial as correlates of response to Btk-directed therapy and that may permit selection of patients who are particularly likely to benefit from ACP-196 treatment for MM.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To characterize the safety profile of ACP-196 with and without dexamethasone in subjects with relapsed or refractory MM

2.2 SECONDARY OBJECTIVES:

- To characterize the PK profile of ACP-196 with and without dexamethasone and the PK profile of dexamethasone with concomitant ACP-196 administration
- To evaluate the PD effects of ACP-196 with and without dexamethasone
- To evaluate the activity of ACP-196 with and without dexamethasone as measured by overall response rate, duration of response, clinical benefit rate, disease control rate, and progression-free survival
- To explore the relationship between biological markers in MM cells and response to therapy

3.0 STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This study is a multicenter, open-label, randomized, parallel-group study to be conducted at approximately 20 sites in 2 countries (United Kingdom and United States). Forty subjects will be randomized 1:1 into the following 2 cohorts to receive ACP-196, with and without dexamethasone:

- Cohort 1: ACP-196 100 mg BID continuously
- Cohort 2: ACP-196 100 mg BID continuously and 40 mg dexamethasone once weekly

Twenty-eight days of study drug administration is 1 cycle. Treatment may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. For subjects in Cohort 1, if documented disease progression occurs, then dexamethasone can be added to the treatment regimen. Additional dose modification provisions are provided in Section 3.5.5. Note: temporary withholding of study drug for

as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe.

All subjects will have standard hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1 and Cycle 2. Tumor assessments will be done at 8- to 12-week intervals during the trial.

Refer to Appendix 5 for a comprehensive list of study assessments and their timing. The end of trial is defined as the point when the last subject on the study exits the study for any reason.

3.2 STUDY PARAMETERS

3.2.1 Safety Parameters

The safety of ACP-196 with and without dexamethasone will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug (ie, ACP-196, dexamethasone, or both) of any treatment-emergent AEs or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation or dose reduction of study treatment.

For consistency of interpretation, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Standard definitions for seriousness will be applied (see Section 6.1).

3.2.2 Efficacy Parameters

Standardized response and progression criteria have been established for MM (Rajkumar 2011); assessments of ACP-196 efficacy in this study will be based on these criteria. Efficacy endpoints will include:

- Overall response rate (ORR)
- Duration of response
- Clinical benefit rate
- Disease control rate

- Progression-free survival

3.2.3 Pharmacokinetic and Pharmacodynamic Parameters

Standard PK parameters for ACP-196 and dexamethasone in plasma will be evaluated in this study. A full description of the PK parameters is provided in Section 5.5.4.

The occupancy of Btk by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, when available, with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.

3.3 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.3, preliminary data from the ongoing Phase 1/2 study in subjects with relapsed/refractory or previously untreated CLL have shown that ACP-196 is well tolerated at dosages of 100 to 400 mg QD and 100 to 200 mg BID. In addition, preliminary PD data from ACE-CL-001 show that Btk occupancy with ACP-196, in peripheral blood, is > 95% at 4 hours after QD dosing but decreases to < 95% at 24 hours with QD dosing, while with BID dosing complete Btk occupancy (95% to 99%) is maintained over 24 hours at steady state (Table 1-3). These data suggest that de novo synthesis of Btk can occur within 24 hours in peripheral blood cells. BID dosing may ensure Btk inhibition for the entire 24 hours and thus may be beneficial in terms of increasing efficacy and/or decreasing development of resistance to ACP-196. In addition, having information regarding the safety and pharmacology of a BID schedule may support future combination studies with other drugs that are administered BID.

Evaluation of dexamethasone as a combination partner for ACP-196 builds on known antineoplastic activity of this drug in patients with MM. Dexamethasone therapy is commonly coadministered with targeted agents for MM (Ocio 2014). The dosing regimen of 40 mg weekly to be used in this study has been established based on randomized trial data showing the superiority of this method of administration (Rajkumar 2009). Combined use of ACP-196 and dexamethasone provides an all oral, non-cytotoxic regimen that may have increased efficacy relative to administration of the individual agents alone. While dexamethasone can increase CYP3A4 activity and thus might enhance ACP-196 metabolism, it is considered a weak inducer of this isoenzyme and has not substantially altered the disposition of other CYP3A4 substrates (eg, bortezomib) that are commonly used in the therapy of MM (Hellmann 2011). The

randomized design of this pilot study will allow the potential for drug-drug interactions between ACP-196 and dexamethasone to be assessed.

3.4 SELECTION OF STUDY POPULATION

3.4.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥ 18 years of age.
2. A confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥ 1 prior therapy for MM, and is progressing at the time of study entry.
3. Evaluable myeloma at screening, defined as the presence of at least one of the following:
   - Serum M-protein ≥ 0.5 g/dL
   - Urine M-protein ≥ 200 mg/24 hours
   - In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 100 mg/L (involved light chain) **and** an abnormal serum kappa/lambda ratio
   - For subjects whose disease can only be reliably measured by serum quantitative immunoglobulin A (IgA), IgA ≥ 750 mg/dL (0.75 g/dL)
4. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
5. Agreement to use acceptable methods of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children.
6. Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug.
7. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

3.4.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Plasma cell leukemia or circulating plasma cells ≥ 2 x 10^9/L
2. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor.
3. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with

the absorption or metabolism of ACP-196, or put the study outcomes at undue risk.

4. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or QTc > 480 msec.
5. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
6. Any immunotherapy within 4 weeks of first dose of study drug.
7. The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s).
8. Prior exposure to a B-cell receptor (BCR) inhibitor (eg, Btk, phosphoinositide-3 kinase [PI3K], or Syk inhibitors) or BCL-2 inhibitors (eg, ABT-199).
9. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MM or other conditions. Note: Subjects may use topical or inhaled corticosteroids as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids as needed for MM therapy or treatment-emergent comorbid conditions.
10. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
11. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.
12. Major surgery within 4 weeks before first dose of ACP-196.
13. Known history of a bleeding diathesis (eg, hemophilia, von Willebrand disease)
14. History of stroke or intracranial hemorrhage within 6 months before the first dose of ACP-196.
15. Requires or receiving anti-coagulation with warfarin or equivalent vitamin K antagonist (eg, phenprocoumon) within 28 days of first dose of study drug.
16. Requires treatment with long-acting proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
17. ANC < 0.75 x 10^9/L or platelet count < 50 x 10^9/L. For subjects with >50% marrow involvement with plasma cells, ANC < 0.50 x 10^9/L or platelet count < 30 x 10^9/L.
18. Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN; and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3.0 x ULN.
19. Breastfeeding or pregnant.
20. Concurrent participation in another therapeutic clinical trial.

3.4.3 Replacement of Subjects

Any subject who does not complete Cycle 2 may be replaced at the discretion of the study investigators and sponsor.

3.4.4 Enrollment and Randomization Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

- Notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled in the study.
- To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the form is faxed/emailed to the sponsor.
- An Enrollment Confirmation Form will be completed and faxed/emailed to the study center by the sponsor within 24 hours.
- The Enrollment Confirmation Form will contain cohort allocation per the randomization scheme generated by the sponsor.

Treatment must begin within the screening window (Section 4.1) and after the site has received the cohort allocation from the sponsor. Study treatment is not blinded on this study.

3.5 STUDY DRUG

3.5.1 Premedications

No specific premedications or supporting medications are required in conjunction with ACP-196 administration.

3.5.2 Formulation, Packaging, and Storage

3.5.2.1 ACP-196

ACP-196 is manufactured according to cGMP regulations and will be provided to the investigational site by Acerta Pharma or designee. ACP-196 should be stored according to the instructions on the label that is affixed to the package containing the drug product.

ACP-196 capsules is provided as hard gelatin capsules containing 100 mg drug substance. ACP-196 will be provided in white, high-density polyethylene bottles.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative.

Refer to the Investigator's Brochure for additional information regarding the drug product to be used in this trial.

3.5.2.2 Dexamethasone

This study will use commercially available dexamethasone tablets for oral administration. The Sponsor will either directly supply sites with dexamethasone or the sites will be reimbursed to prescribe dexamethasone; this will be detailed separately in each site's clinical trial agreement. Per the U.S. dexamethasone package insert (Appendix 4), tablets are to be stored at room temperature (20° to 25°C) and protected from moisture and light. Please refer to the appropriate dexamethasone package insert for further storage and handling instructions.

3.5.3 Administration of Study Drug

3.5.3.1 ACP-196

Investigators are prohibited from supplying ACP-196 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators on FDA Form 1572. The investigator must ensure that subjects receive ACP-196 only from personnel who fully understand the procedures for administering the drug.

ACP-196 is intended to be administered orally with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice and Seville orange juice due to CYP3A4 inhibition). ACP-196 may be taken with or without food. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. .

If a dose is missed, it can be taken up to 3 hours after the scheduled time with a return to the normal schedule with the following dose. If it has been greater than 3 hours, the dose should not be taken and the subject should take the next dose at the scheduled time. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.3.2 Dexamethasone

This study will use commercially available dexamethasone tablets for oral administration. At the time of weekly dexamethasone administration, the subject should take the dexamethasone tablets simultaneously with the ACP-196 capsules and with 8 ounces (approximately 240 mL) of water. The dexamethasone tablets should be swallowed intact and subjects should not attempt to chew them or dissolve them in water.

If a dexamethasone dose is missed, it can be taken up to 3.5 days (84 hours) days after the scheduled time with a return to the normal schedule the following week. If the interval of missed dosing has been > 3.5 days (84 hours), the dexamethasone dose should not be taken and the subject should take the next dose at the scheduled time in the following week. The missed dexamethasone dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.4 Assuring Subject Compliance

During cycle 1, subjects will receive their Day 1, 8, 15, 22, and 28 doses (for Cohort 2 this includes the dexamethasone dose) in the clinic. For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other treatments will be taken at home. Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining ACP-196 capsules and dexamethasone tablets to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules and tablets were administered. Any remaining or returned capsules and tablets will be counted and recorded as described in Section 7.7. Returned capsules or tablets must not be redispensed to another subject. The study staff will resupply the subject with the correct number of ACP-196 capsules and dexamethasone tablets needed for use until the next visit.

3.5.5 Study Treatment Regimen and Dose Modifications

3.5.5.1 ACP-196

Dose Delays

Treatment with ACP-196 should be held for any unmanageable, potentially study drug-related toxicity that is Grade ≥ 3 in severity. Any other clinically important events where

dose delays may be considered appropriate by the investigator must be discussed with the Medical Monitor. Study drug may be held for a maximum of 28 consecutive days from expected dose due to toxicity. Study treatment should be discontinued in the event of a toxicity lasting > 28 days, unless reviewed and approved by the Medical Monitor.

Note: temporary withholding of study drug for as little as 7 days can cause a transient worsening of disease and/or of constitutional symptoms. Refer to Section 3.8 for more information on assessing disease progression under these circumstances.

Dose Modification and Discontinuation

The actions in Table 3-1 should be taken for the following toxicities:

- Grade 4 ANC (< 500/μL) for > 7 days (Neutrophil growth factors are permitted per ASCO guidelines [Smith 2006] and use must be recorded on the electronic case report form [eCRF]).
- Grade 3 platelets in the presence of significant bleeding
- Grade 4 platelets
- Grade 3 or 4 nausea, vomiting, or diarrhea, if persistent despite optimal antiemetic and/or anti-diarrheal therapy
- Any other Grade 4 toxicity or unmanageable Grade 3 toxicity.

Table 3-1. Drug Discontinuation Actions for ACP-196

Occurrence	Action
1st - 2nd	Hold ACP-196 until recovery to Grade ≤ 1 or baseline; may restart at original dose level
3rd	Hold ACP-196 until recovery to Grade ≤ 1 or baseline; restart at 100 mg once daily
4th	Discontinue ACP-196

Subjects in Cohort 1 (ACP-196 monotherapy) who do not experience at least an minimal response (MR) after 2 cycles of study treatment may have dexamethasone (40 mg once weekly) added to their treatment.

Whenever possible, any dose adjustment of ACP-196, including adding dexamethasone to subjects in Cohort 1, should be discussed between the investigator and the Acerta Pharma medical monitor before implementation. The appropriate clinic staff should

dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level. Any changes to the dosing regimen must be recorded in the appropriate eCRF.

3.5.5.2 Dexamethasone

This study will use commercially available dexamethasone. Dosing of dexamethasone will be 40 mg once weekly. For subjects who experience intolerable dexamethasone-related adverse effects, dexamethasone may be reduced to 20 mg once weekly.

3.6 CONCOMITANT THERAPY

3.6.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

For subjects considered at risk for tumor lysis syndrome: Administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

3.6.2 Guideline for Use of CYP Inhibiting/Inducing Drugs

At the systemic exposure levels expected in this study, ACP-196 inhibition of CYP metabolism is not anticipated. However, as discussed in Section 1.3.1, concomitant administration of ACP-196 with a strong CYP3A4 inhibitor increased exposure by approximately 5-fold. Consequently, the concomitant use of strong inhibitors/inducers of CYP3A4 (Appendix 3) should be avoided when possible. If a subject requires a strong CYP3A4 inhibitor while on study, monitor the subject closely for potential toxicities.

3.6.3 Guideline for Use of Drugs that Affect Gastric pH

The effect of agents that reduce gastric acidity (eg, proton pump inhibitors, H2-receptor antagonists or antacids) on ACP-196 absorption is currently being evaluated in a healthy volunteer study (ACE-HV-004). Preliminary results from this study suggest subjects should avoid the use of calcium carbonate containing drugs or supplements (eg, antacids or calcium supplements) for a period of at least 2 hours before and after taking ACP-196.

Subjects should also avoid the use of H2-receptor antagonists for a period at least 2 hours before and after taking ACP-196. Use of omeprazole, esomeprazole, lansoprazole or any other long-acting proton pump inhibitors while taking ACP-196 is not

permitted due to a potential decrease in study drug exposure. However, if a subject requires treatment with a long-acting proton pump inhibitor while on study (eg, to treat an ulcer), discuss treatment options with the Medical Monitor.

3.6.4 Prohibited Concomitant Therapy

Any chemotherapy, immunotherapy, kinase inhibitors, bone marrow transplantation, experimental therapy, and radiotherapy are prohibited (see Section 3.4.2).

Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids, per the dexamethasone package insert (Appendix 4). Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.

3.7 PRECAUTIONS

3.7.1 Dietary Restrictions

Because ACP-196 may be metabolized by CYP3A4/3A5 (see Section 1.2.4), subjects should be strongly cautioned against excessive consumption of grapefruit, grapefruit juice, Seville oranges, or Seville orange juice (which contain potent CYP3A4 inhibitors) or using herbal remedies or dietary supplements (in particular, St. John's Wort, which is a potent CYP3A4 inducer).

ACP-196 may be taken with or without food.

3.7.2 Surgery

Susceptibility to bleeding has been observed with the first generation Btk inhibitor, ibrutinib [IMBRUVICA package insert]. As a precaution, it is suggested that ACP-196 be held for 3 days before and after any major surgical procedure.

3.7.3 Infections

Patients who are on corticosteroids are more susceptible to infections than are healthy individuals (dexamethasone package insert, Appendix 4). Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions.

3.7.4 Reproductive Toxicity

Definitive reproductive toxicity studies with ACP-196 are pending. Therefore, subjects with reproductive potential who are sexually active must use acceptable methods of

contraception during the study and for 30 days after the last dose of ACP-196. Examples of acceptable methods of contraception include condoms, implants, injectables, combined oral contraceptives, intrauterine devices, true sexual abstinence, or sterilized partner. Note that periodic abstinence, eg, calendar, ovulation, symptothermal, or postovulation methods, or withdrawal, are not acceptable methods of contraception.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue ACP-196 immediately. Pregnancy in a female subject or a male subject's partner must be reported (see Section 6.2.3). Male subjects must agree to refrain from sperm donation during the study and for 30 days after the last dose of study drug.

3.7.5 Overdose Instructions

For any subject experiencing an ACP-196 overdose (administration of a dose ≥ 1.5 times the highest intended dose level in the clinical study protocol), observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

The Acerta Pharma Medical Monitor should be contacted if a study drug overdose occurs.

3.8 STOPPING RULES

All study participants may receive ACP-196 indefinitely as long as they are safely benefitting. However:

- Any subject has the right to withdraw from the study at any time.
- Any subject who has objective evidence of definitive MM progression while receiving study treatment at the highest individual tolerable dose level allowed in the protocol (see Section 3.5.5) should be withdrawn from the study treatment. Note: If there is uncertainty regarding whether there is MM progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 4- to 8-week

intervals) pending confirmation of progression. In particular, transient worsening of disease during temporary interruption of study therapy (eg, for intercurrent illness, drug-related toxicity, or surgery) may not indicate definitive disease progression. In such circumstances, and if medically appropriate, subjects may resume therapy and relevant clinical, laboratory, and/or radiographic assessment should be done to document whether tumor control can be maintained or whether actual disease progression has occurred.

- Any subject who is unable to tolerate rechallenge at the lowest protocol-described, dose-modified levels (see Section 3.5.5) should be withdrawn from the study treatment unless continued therapy is permitted by the Acerta Pharma medical monitor.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the Acerta Pharma medical monitor. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.
- The investigator, in consultation with the Acerta Pharma medical monitor, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Subjects who discontinue study therapy will continue on study for safety (Section 4.3) unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate posttherapy period unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from study treatment or from the study and the reason for discontinuation will be recorded and also should be described on the appropriate eCRF.

3.9 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed internally on an

ongoing basis to identify safety concerns. Quarterly conference calls with the investigators will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs, and deaths).

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 5. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are required. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. Such unscheduled assessments will be captured in the protocol-specific database as appropriate.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand and sign the IRB/IEC approved ICF confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information.

4.1.2 Medical History

The subject's complete history should be collected and recorded through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1 All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

All concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug should be documented.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.4. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 1.

4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams, including tumor assessments by palpation, will be done during the treatment period and at the safety follow-up visits.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.

4.1.8 Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at screening or up to 30 days before the main screening procedures. Per the current response criteria (Rajkumar 2011), a bone marrow aspirate/biopsy will also be required at any time on study to confirm a complete response (CR). The baseline bone marrow aspirate/biopsy will used for immunohistochemistry and/or flow cytometry, cytogenetics, and FISH. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

When available, any unused bone marrow tissue will be used for PD testing. PD testing will be done by the sponsor.

4.1.9 Electrocardiogram

Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.

4.1.10 Urine Pregnancy Test

Pregnancy tests will be required only for women of childbearing potential. If positive, pregnancy must be ruled out by ultrasound. Testing will be done by the central laboratory.

4.1.11 Hematology

Hematology studies must include complete blood count (CBC) with differential and platelet and reticulocyte counts. Testing will be done by the central laboratory.

4.1.12 Serum Chemistry

Serum chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine, C-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by the central laboratory.

4.1.13 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, N-terminal telopeptide, and glucose. Testing will be done by the central laboratory.

4.1.14 T/B/NK Cell Count

Flow cytometry testing will include $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD16/56^+$ cells. Testing will be done by the central laboratory.

4.1.15 Disease Markers

Testing for serum M-protein levels (by serum protein electrophoresis [SPEP] and serum immunofixation electrophoresis [SIFE]), serum free light chains (SFLC), urine M-protein levels (by urine serum protein electrophoresis [UPEP] and urine immunofixation electrophoresis [UIFE]), and serum β2-microglobulin will be done by the central laboratory.

4.1.16 Skeletal Survey

Standard lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri are required at screening or baseline (ie, before the first dose of study drug). Radiographic imaging and analysis will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

4.1.17 Pharmacodynamics

Blood samples and bone marrow, when available, will be used for PD testing (eg, Btk occupancy and B-cell activation). Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be done by the sponsor.

4.1.18 Pharmacokinetics

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at the central clinical laboratory. Leftover plasma samples may be used for exploratory ACP-196 metabolite analyses. The PK sampling timepoints are provided in Table 4-1.

Table 4-1. Pharmacokinetic Sample Schedule

			HOURS POSTDOSE					
Cycle	Day	Predose	0.5 (±5 min)	0.75 (±5 min)	1 (±5 min)	2 (±10 min)	4 (±10 min)	6 (±10 min)
1	1	X	X	X	X	X	X	X
	8	X			X			
	15	X			X			
	22	X	X	X	X	X	X	X
	28	X			X			

Note: These timepoints are relative to the morning dose.

4.1.19 Tumor Assessment

Baseline myeloma assessments will consist of:

- M-protein determination using both of the following procedures:
  - serum protein electrophoresis (SPEP) and serum immunofixation electrophoresis (SIFE)

  - Urine protein electrophoresis (UPEP) and urine immunofixation electrophoresis (UIFE), all using the same 24-hour urine collection

- SFLC
- Plasmacytoma evaluation
- Bone marrow to quantify percent myeloma cell involvement (aspirate and biopsy required at baseline)
- Skeletal survey: lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri
- β2-microglobulin

On-study myeloma assessments will consist of:

- SPEP and/or UPEP (if results were measurable at baseline); quantitative immunoglobulins if used to follow disease; immunofixation to confirm a complete response
- SFLC
- Plasmacytoma evaluation (if only measurable disease at baseline)
- Bone marrow aspirate and/or trephine bone biopsy (to confirm a complete response or if clinically indicated).

4.1.20 Study Drug Accountability

See Section 7.7.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

Subjects will be evaluated by investigator review for disease response and progression according to the current guidelines proposed by the International Myeloma Workshop Consensus Panel 1 (Rajkumar 2011) and European Group for Blood and Marrow Transplant (EBMT; Bladé 1998)as listed below in . Response categories include sCR, CR, VGPR, PR, SD, and progressive disease. In addition, the number of subjects achieving the response category of MR will also be evaluated and reported. Subjects will be considered evaluable for response if they have a baseline and ≥1 adequate on-study myeloma assessment obtained ≥4 weeks from the start of therapy.

Table 4-2. Response Criteria (derived from Rajkumar 2011 and Bladé 1998)

Response Subcategory	Response Criteria[a]
Complete response (CR)	• Negative immunofixation of serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b].
Stringent complete response (sCR)	• CR as defined above plus • Normal FLC ratio and • Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry.
Very good partial response (VGPR)	• Serum and urine M-component detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 h.
Partial response (PR)	• ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h • If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥ 30% • In addition to the above criteria, if present at baseline, ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minimal response (MR)	• Requires all of the following: ○ ≥ 25% to ≤ 49% reduction of serum M-protein and ○ 50% to 89% reduction in 24-hour urine M-protein and ○ If present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas and ○ No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease (SD)	• Not meeting criteria for CR, VGPR, MR, PR or progressive disease
Progressive disease	Any of the following: • Increase of ≥ 25% from lowest response value[c] in: ○ Serum M-component (absolute increase must be ≥ 0.5 g/dL)[d] ○ Urine M-component (absolute increase must be ≥ 200 mg/24 h)

	○ Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL) ○ Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels bone marrow plasma cell percentage (absolute increase must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Abbreviations: FLC = (serum) free light chains
Note: in subjects in whom the only measurable disease is by serum FLC levels, CR requires a normal FLC ratio of 0.26-1.65 in addition to negative serum and urine immunofixation. VGPR in such subjects is defined as a > 90% decrease in the difference between involved and uninvolved free light chain FLC levels

a. All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at ≥4 weeks after the start of study therapy and any time before the institution of any new therapy after study therapy; CR, sCR, VGPR, PR, and SD 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.
b. Bone marrow assessments need not be confirmed.
c. Lowest response value does not need to be a confirmed value.
d. For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

4.3 EARLY TERMINATION/SAFETY FOLLOW-UP VISIT

An early termination visit is required for any subjects who permanently discontinue study drug early for any reason including disease progression. Each subject should be followed for 30 (±7) days after his or her last dose of study drug (ie, the "safety follow-up visit") to monitor for resolution or progression of AEs (see Section 6.2.5) and to document the occurrence of any new events; unless, the subject receives a new anticancer therapy within this timeframe. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Appendix 5) describes the procedures required for the safety follow-up.

4.4 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the

investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate. Analyses will be done by dosing regimen and overall.

5.2 SAMPLE SIZE CONSIDERATIONS

This study will assess safety, PK, PD, and antitumor activity of ACP-196 alone or in combination with dexamethasone. Subjects will be equally randomized into 1 of the 2 dosing regimens (ACP-196 monotherapy or ACP-196 + dexamethasone) as an efficient method for allocating patients into these regimens. The study is not formally designed to compare these regimens but rather to obtain descriptive information that can be used in support of further ACP-196 development.

While the primary objective of this study is to determine the safety in each of the 2 dosing cohorts, the sample size has been determine to independently evaluate the activity of each dosing regimen. The trial seeks to exclude an uninteresting ORR of $\leq 15\%$ (ie, the response rate that might be associated with single-agent dexamethasone therapy [Anderson 2013]) in favor a target response rate of $\geq 40\%$. Considering a sample size of 19 subjects per cohort, the power to detect the difference between a null-hypothesis response rate of 15% and an alternative-hypothesis response rate of 40% with a 0.025 one-sided significance level is 69% using a one-group, exact binomial test. A sample size of 19 subjects per cohort will also provide a 97.5% 1-sided confidence interval centered around an expected ORR of 40% that excludes an ORR of 18.6% as a lower bound.

5.3 DEFINITION OF ANALYSIS POPULATIONS

The following definitions will be used for the analysis populations:

- **Safety population:** All enrolled subjects who receive ≥ 1 dose of study drug.
- **Intent-to-treat (ITT) population**: All subjects who have been randomized.

The safety population will be used for evaluating the safety parameters in this study. The ITT population will be analyzed for efficacy parameters in this study.

5.4 MISSING DATA HANDLING

General Considerations: Subjects lost to follow-up (or who dropped out) will be included in statistical analyses up to the point of their last evaluation.

Duration of Response and Progression-free Survival: Data for subjects without disease progression or death will be censored at the date of the last tumor assessment and before the initiation of alternative anticancer therapy.

Safety: Missing or partial start and end dates for AEs and concomitant medications will be imputed according to prespecified, conservative imputation rules. No other imputation of values for missing data will be performed.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event (per CTCAE, v4.03) and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments and physical exams will be tabulated and summarized.

5.5.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

5.5.3 Analysis of Efficacy Parameters

5.5.3.1 Overall Response Rate

Tumor control will be documented at each assessment by response category (eg, CR, sCR, VGPR, PR, MR, SD, and disease progression) as defined for each response parameter, date that response is first documented, and date of MM disease progression.

The overall response rate (ORR) will be defined as the proportion of subjects who achieve a CR, sCR, VGPR, or PR. ORR will be calculated and the corresponding 95% two-sided confidence interval will be derived.

5.5.3.2 Duration of Response

The duration of response (DOR) defined as the interval from the first documentation of CR, sCR, VGPR, or PR to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quantiles (including the median). Data from surviving, nonprogressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of definitive MM progression was objectively documented. Data from subjects who have MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time before the missing assessments that lack of MM progression was objectively documented.

5.5.3.3 Clinical Benefit Rate

Clinical benefit rate (CBR) will be defined as the proportion of subjects who achieve a CR, sCR, VGPR, PR, or MR. CBR will be calculated and the corresponding 95% two-sided confidence interval will be derived.

5.5.3.4 Disease Control Rate

Disease control rate (DCR) will be defined as the proportion of subjects who achieve a CR, sCR, VGPR, PR, MR, or SD. DCR will be calculated and the corresponding 95% two-sided confidence interval will be derived.

5.5.3.5 Progression-free Survival

Progression-free survival (PFS) is defined as the interval from the date of randomization to the earlier of the first documentation of objective MM disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of anticancer treatment other than the study treatment or the last time that lack of MM progression was objectively documented. Data from subjects who have MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of MM progression was objectively documented.

5.5.4 Analysis of Pharmacokinetic/Pharmacodynamic Parameters

The plasma PK of ACP-196 and dexamethasone will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of ACP-196:

- AUC_{0-t} Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t).
- AUC_{0-12} Area under the plasma concentration-time curve from 0 to 12 hours, calculated using linear trapezoidal summation.
- $AUC_{0-\infty}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0-\infty} = AUC_{0-t} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.
- $AUC_{0-24calc}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated by doubling the value for AUC_{0-12}.
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- CL/F Oral clearance

Missing dates or times may be imputed for PK and PD samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. If PK and PD sampling for a given subject is not performed according to protocol instructions that subject may be excluded from the PK and PD analyses.

The PK parameters will be tabulated and summarized using descriptive statistics.

For each PD variable, the concentration at each assessment will be described. The change from baseline to each assessment will be summarized. The best change from baseline during the study will also be summarized. As appropriate, the on-treatment values will be compared with the pretreatment baseline values using paired t-tests.

5.5.5 Exploratory or Correlative Analyses

Additional PK or PD analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques. Such evaluations may assist in determining if baseline

parameters or early changes in PD biomarkers are predictive of response to Btk inhibition.

6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

6.1 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MM that were not present before the AE reporting period (see Section 6.2.1)
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values should not be reported as AEs; however, any clinically significant laboratory values (defined as requiring treatment, discontinuation from study, or dose modification) should be reported as AEs.

6.1.2 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).
- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on the SAE/Product Complaint form (see Section 6.2.4).

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study medication and ends with the safety follow-up visit (or last on-treatment visit if the safety follow-up visit is not done), or when the subject receives a new anticancer therapy. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. Fatal AEs occurring within 30 days after the last dose of ACP-196 ***AND*** assessed by the investigator as related to ACP-196 must be reported as a SAEs.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE/Product Complaint form.

Disease progression itself is not considered an adverse event; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (ie, ACP-196, dexamethasone, or both; see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' Answer Yes or No.

See Appendix 2 for more detail on assessing relationship.

6.2.3 Pregnancy

The investigator should report all pregnancies in study subjects and in the partners of subjects within 24 hours using the Pregnancy Report Form. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be

reported using the SAE report form, according to the usual timelines and directions for SAE reporting (Section 6.2.4).

Any uncomplicated pregnancy that occurs in a subject or a partner of a treated subject during this study will be reported for tracking purposes only, if agreed to by the subject or the partner of the subject in this study. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 30 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported, as long as the subject or partner is willing to participate in follow-up.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE/Product Complaint form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving ACP-196 who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

6.2.4 Expedited Reporting Requirements for Serious Adverse Events

All SAEs must be reported within 24 hours of discover. All initial SAE reports and follow-up information will be reported using the protocol-specific electronic data capture system. If electronic SAE reporting is not available, paper SAE/Product Complaint forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee. Acerta Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator's Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the SAE to all investigators. Each investigator must then notify his or her IRB/IEC of the SAE.

Drug Safety Contact Information	
Fax:	[redacted]
Email:	[redacted]

6.2.5 Type and Duration of Follow-up of Subjects After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the event as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination include:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failure to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 REGULATORY AND ETHICAL COMPLIANCE

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, applicable local regulations (including US Code of Federal Regulations Title 21 and

European Directive 2001/20/EC), and the ethical principles laid down in the Declaration of Helsinki.

7.2 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the ICF, Investigator's Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed FDA 1572 form (Statement of Investigator form) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agencies, as appropriate, before the implementation of changes in this study.

7.3 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved ICF must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.12), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance with individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study Sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected

health information from each subject, or if appropriate, the subject's legal guardian. If a subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.4 SUBJECT SCREENING LOG

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.5 CASE REPORT FORMS

Authorized study site personnel (see Section 7.12) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed within 5 days of each subject's visit (unless required earlier for SAE reporting). The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed, in accordance with the record retention policies in Section 7.8.

7.6 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits by the sponsor, regulatory authorities, or ethics committees.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology,

pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.7 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

ACP-196 capsules must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply ACP-196 capsules to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Acerta Pharma.

Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and regulatory authorities at any time.

Each shipment of study drug will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. If it is used, the Drug Re-order Form (provided in the pharmacy binder) must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of study drug capsules. Then the designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/emailing address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-MY-001)
2. subject identification number
3. lot number(s) of ACP-196 dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its representative, for return of unused investigational product. Before

disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.8 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, and all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or returned to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

7.9 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must

be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.10 PUBLICATION OF STUDY RESULTS

Acerta Pharma may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. The study is being conducted as part of a multicenter clinical trial. Data from all study centers shall be pooled and analyzed for publication in a final report (Primary Publication). The investigator agrees that the Primary Publication, which will be coordinated by Acerta Pharma, will be the first publication to present the pooled study results. After the Primary Publication, or if the Primary Publication is not published within 1 year of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement subject to providing Acerta Pharma with the opportunity to review the contents of any proposed presentation, abstract or publication about such work, including any results of this study, 90 days in advance of any presentation or submission for publication. Within that 90-day period, Acerta Pharma may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, Acerta Pharma may elect an additional review period not to exceed 60 days.

Authorship, in general, will follow the recommendations of the International Committee of Medical Journal Editors (International Committee of Medical Journal Editors 2014).

7.11 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been obtained according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.12 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. Electronic CRF pages are completed within 5 days of each subject's visit (unless required earlier for SAE reporting).
11. All IND Safety Reports/ Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge and to the IRB/IEC per their requirements.

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Vail DM, Michels GM, Khanna C, Selting KA, London CA; Veterinary Cooperative Oncology Group. Response evaluation criteria for peripheral nodal lymphoma in dogs (v1.0)—a Veterinary Cooperative Oncology Group (VCOG) consensus document. Vet Comp Oncol 2010;8:28-37.

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9.0 APPENDICES

Appendix 1. Performance Status Scores

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, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

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

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

Appendix 2. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug?

No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either "yes" or "no":

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject's clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix 3. Known Strong in Vivo Inhibitors of CYP3A4

Strong Inhibitors of CYP3A[a]	Strong Inducers of CYP3A[e]
boceprevir	carbamazepine[f]
clarithromycin[b]	phenytoin[f]
conivaptin[b]	rifampin[f]
grapefruit juice[c]	St John's wort[f]
indinavir	
itraconazole[b]	
ketoconazole[b]	
lopinavir/ritonavir[b] (combination drug)	
mibefradil[d]	
nefazodone	
nelfinavir	
posaconazole	
ritonavir[b]	
saquinavir	
telaprevir	
telithromycin	
voriconazole	

a. A strong inhibitor for CYP3A is defined as an inhibitor that increases the AUC of a substrate for CYP3A by ≥ 5-fold.
b. In vivo inhibitor of P-glycoprotein.
c. The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and preparation-dependent. Studies have shown that it can be classified as a "strong CYP3A inhibitor" when a certain preparation was used (eg, high dose, double strength) or as a "moderate CYP3A inhibitor" when another preparation was used (eg, low dose, single strength).
d. Withdrawn from the United States market because of safety reasons.
e. A strong inducer for CYP3A is defined as an inducer that results in ≥ 80% decrease in the AUC of a substrate for CYP3A.
f. In vivo inducer of P-glycoprotein.

Note: The list of drugs in these tables is not exhaustive. Any questions about drugs not on this list should be addressed to the Medical Monitor of the protocol.

Source:

FDA Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. Web link Accessed 21 January 2015:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#inVivo

Appendix 4. Dexamethasone Prescribing Information

The United States label for dexamethasone tablets (Roxane Laboratories 2007) is provided for reference. The United States label will also serve as the Reference Safety Information for dexamethasone for this study. Country-specific labels will be provided to investigative sites as appropriate.

4047401//04

Roxane Laboratories, Inc.
Columbus, Ohio 43216

DEXAMETHASONE Tablets USP, DEXAMETHASONE Oral Solution, and DEXAMETHASONE *Intensol*™ Oral Solution (Concentrate)

℞ only

DESCRIPTION

Dexamethasone Tablets 0.5, 0.75, 1, 1.5, 2, 4 and 6 mg USP, Dexamethasone Oral Solution, 0.5 mg per 5 mL and Dexamethasone *Intensol*™ Oral Solution (Concentrate), 1 mg per mL are for oral administration.

Each tablet contains:
Dexamethasone ..... 0.5, 0.75, 1, 1.5, 2, 4, or 6 mg
Each 5 mL of Oral Solution contains:
Dexamethasone ..... 0.5 mg
Each mL of *Intensol*™ Oral Solution (Concentrate) contains:
Dexamethasone ..... 1 mg
Alcohol 30%

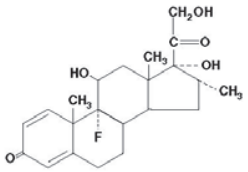
Inactive Ingredients

The tablets contain lactose monohydrate, magnesium stearate, starch, sucrose, cosmetic ochre (1 mg), D&C Yellow No. 10 (0.5, 4 mg), FD&C Blue No. 1 (0.75, 1.5 mg), FD&C Green No. 3 (4, 6 mg), FD&C Red No. 3 (1.5 mg), FD&C Red No. 40 (1.5 mg), and FD&C Yellow No. 6 (0.5, 4 mg).

The oral solution contains citric acid, disodium edetate, flavoring, glycerin, methylparaben, propylene glycol, propylparaben, sorbitol and water.

The *Intensol*™ oral solution contains alcohol, benzoic acid, citric acid, disodium edetate, propylene glycol, and water.

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water. The molecular formula is $C_{22}H_{29}FO_5$. The molecular weight is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene,3,20-dione and the structural formula is:



CLINICAL PHARMACOLOGY

Glucocorticoids, naturally occurring and synthetic, are adrenocortical steroids that are readily absorbed from the gastrointestinal tract. Glucocorticoids cause varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli. Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have sodium-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs including dexamethasone are primarily used for their anti-inflammatory effects in disorders of many organ systems.

At equipotent anti-inflammatory doses, dexamethasone almost completely lacks the sodium-retaining property of hydrocortisone and closely related derivatives of hydrocortisone.

INDICATIONS AND USAGE

Allergic States

Control of severe or incapacitating allergic conditions intractable to adequate trials of conventional treatment in asthma, atopic dermatitis, contact dermatitis, drug hypersensitivity reactions, perennial or seasonal allergic rhinitis, and serum sickness.

Dermatologic Diseases

Bullous dermatitis herpetiformis, exfoliative erythroderma, mycosis fungoides, pemphigus, and severe erythema multiforme (Stevens-Johnson syndrome).

Endocrine Disorders

Primary or secondary adrenocortical insufficiency (hydrocortisone or cortisone is the drug of choice; may be used in conjunction with synthetic mineralocorticoid analogs where applicable; in infancy mineralocorticoid supplementation is of particular importance), congenital adrenal hyperplasia, hypercalcemia associated with cancer, and nonsuppurative thyroiditis.

Gastrointestinal Diseases

To tide the patient over a critical period of the disease in regional enteritis and ulcerative colitis.

Hematologic Disorders

Acquired (autoimmune) hemolytic anemia, congenital (erythroid) hypoplastic anemia (Diamond-Blackfan anemia), idiopathic thrombocytopenic purpura in adults, pure red cell aplasia, and selected cases of secondary thrombocytopenia.

Miscellaneous

Diagnostic testing of adrenocortical hyperfunction, trichinosis with neurologic or myocardial involvement, tuberculous meningitis with subarachnoid block or impending block when used with appropriate antituberculous chemotherapy.

Neoplastic Diseases

For the palliative management of leukemias and lymphomas.

Nervous System
Acute exacerbations of multiple sclerosis, cerebral edema associated with primary or metastatic brain tumor, craniotomy, or head injury.
Ophthalmic Diseases
Sympathetic ophthalmia, temporal arteritis, uveitis, and ocular inflammatory conditions unresponsive to topical corticosteroids.
Renal Diseases
To induce a diuresis or remission of proteinuria in idiopathic nephrotic syndrome or that due to lupus erythematosus.
Respiratory Diseases
Berylliosis, fulminating or disseminated pulmonary tuberculosis when used concurrently with appropriate antituberculous chemotherapy, idiopathic eosinophilic pneumonias, symptomatic sarcoidosis.
Rheumatic Disorders
As adjunctive therapy for short-term administration (to tide the patient over an acute episode or exacerbation) in acute gouty arthritis, acute rheumatic carditis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, including juvenile rheumatoid arthritis (selected cases may require low-dose maintenance therapy). For the treatment of dermatomyositis, polymyositis, and systemic lupus erythematosus.

CONTRAINDICATIONS

Contraindicated in systemic fungal infections (see **WARNINGS**: **Infections**: *Fungal Infections*) and patients with known hypersensitivity to the product and its consituents.

WARNINGS

General
Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy (see **ADVERSE REACTIONS**).
Increased dosage of rapidly acting corticosteroids is indicated in patients on corticosteroid therapy subjected to any unusual stress before, during, and after the stressful situation.
Cardio-Renal
Average and large doses of corticosteroids can cause elevation of blood pressure, sodium and water retention, and increased excretion of potassium. These effects are less likely to occur with the synthetic derivatives except when used in large doses. Dietary salt restriction and potassium supplementation may be necessary. All corticosteroids increase calcium excretion.
Literature reports suggest an apparent association between use of corticosteroids and left ventricular free wall rupture after a recent myocardial infarction; therefore, therapy with corticosteroids should be used with great caution in these patients.
Endocrine
Corticosteroids can produce reversible hypothalamic-pituitary adrenal (HPA) axis suppression with the potential for corticosteroid insufficiency after withdrawal of treatment. Adrenocortical insufficiency may result from too rapid withdrawal of corticosteroids and may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. If the patient is receiving steroids already, dosage may have to be increased.
Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients. Changes in thyroid status of the patient may necessitate adjustment in dosage.
Infections
General: Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan or helminthic) in any location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection.
Fungal Infections: Corticosteroids may exacerbate systemic fungal infections and therefore should not be used in the presence of such infections unless they are needed to control life-threatening drug reactions. There have been cases reported in which concomitant use of amphotericin B and hydrocortisone was followed by cardiac enlargement and congestive heart failure (see **PRECAUTIONS**: **Drug Interactions**: *Amphotericin B injection and potassium-depleting agents*).
Special Pathogens: Latent disease may be activated or there may be an exacerbation of intercurrent infections due to pathogens, including those caused by *Amoeba, Candida, Cryptococcus, Mycobacterium, Nocardia, Pneumocystis, Toxoplasma.*
It is recommended that latent amebiasis or active amebiasis be ruled out before initiating corticosteroid therapy in any patient who has spent time in the tropics or any patient with unexplained diarrhea.
Similarly, corticosteroids should be used with great care in patients with known or suspected Strongyloides (threadworm) infestation. In such patients, corticosteroid-induced immunosuppression may lead to Strongyloides hyperinfection and dissemination with widespread larval migration, often accompanied by severe enterocolitis and potentially fatal gram-negative septicemia.
Corticosteroids should not be used in cerebral malaria.
Tuberculosis: The use of corticosteroids in active tuberculosis should be restricted to those cases of fulminating or disseminated tuberculosis in which the corticosteroid is used for the management of the disease in conjunction with an appropriate antituberculous regimen.
If corticosteroids are indicated in patients with latent tuberculosis or tuberculin reactivity, close observation is necessary as reactivation of the disease may occur. During prolonged corticosteroid therapy, these patients should receive chemoprophylaxis.
Vaccination: **Administration of live or live, attenuated vaccines is contraindicated in patients receiving immunosuppressive doses of corticosteroids. Killed or inactivated vaccines may be administered. However, the response to such vaccines cannot be predicted.** Immunization procedures may be undertaken in patients who are receiving corticosteroids as replacement therapy, e.g., for Addison's disease.
Viral infections: Chickenpox and measles can have a more serious or even fatal course in pediatric and adult patients on corticosteroids. In pediatric and adult patients who have not had these diseases, particular care should be taken to avoid exposure. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If exposed to chickenpox, prophylaxis with varicella zoster immune globulin (VZIG) may be indicated. If exposed to measles, prophylaxis with immune globulin (IG) may be indicated. (See the respective package inserts for VZIG and IG for complete prescribing information.) If chickenpox develops, treatment with antiviral agents should be considered.
Ophthalmic
Use of corticosteroids may produce posterior subcapsular cataracts, glaucoma with possible damage to the optic nerves, and may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. The use of oral corticosteroids is not recommended in the treatment of optic neuritis and may lead to an increase in the risk of new episodes. Corticosteroids should not be used in active ocular herpes simplex.

PRECAUTIONS

General

The lowest possible dose of corticosteroids should be used to control the condition under treatment. When reduction in dosage is possible, the reduction should be gradual.

Since complications of treatment with corticosteroids are dependent on the size of the dose and the duration of treatment, a risk/benefit decision must be made in each individual case as to dose and duration of treatment and as to whether daily or intermittent therapy should be used.

Kaposi's sarcoma has been reported to occur in patients receiving corticosteroid therapy, most often for chronic conditions. Discontinuation of corticosteroids may result in clinical improvement.

Cardio-Renal

As sodium retention with resultant edema and potassium loss may occur in patients receiving corticosteroids, these agents should be used with caution in patients with congestive heart failure, hypertension, or renal insufficiency.

Endocrine

Drug-induced secondary adrenocortical insufficiency may be minimized by gradual reduction of dosage. This type of relative insufficiency may persist for months after discontinuation of therapy; therefore, in any situation of stress occurring during that period, hormone therapy should be reinstituted. Since mineralocorticoid secretion may be impaired, salt and/or a mineralocorticoid should be administered concurrently.

Gastrointestinal

Steroids should be used with caution in active or latent peptic ulcers, diverticulitis, fresh intestinal anastomoses, and nonspecific ulcerative colitis, since they may increase the risk of a perforation.

Signs of peritoneal irritation following gastrointestinal perforation in patients receiving corticosteroids may be minimal or absent.

There is an enhanced effect due to decreased metabolism of corticosteroids in patients with cirrhosis.

Musculoskeletal

Corticosteroids decrease bone formation and increase bone resorption both through their effect on calcium regulation (i.e., decreasing absorption and increasing excretion) and inhibition of osteoblast function. This, together with a decrease in the protein matrix of the bone secondary to an increase in protein catabolism, and reduced sex hormone production, may lead to inhibition of bone growth in pediatric patients and the development of osteoporosis at any age. Special consideration should be given to patients at increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy.

Neuro-Psychiatric

Although controlled clinical trials have shown corticosteroids to be effective in speeding the resolution of acute exacerbations of multiple sclerosis, they do not show that they affect the ultimate outcome or natural history of the disease. The studies do show that relatively high doses of corticosteroids are necessary to demonstrate a significant effect. (See **DOSAGE AND ADMINISTRATION**.)

An acute myopathy has been observed with the use of high doses of corticosteroids, most often occurring in patients with disorders of neuromuscular transmission (e.g., myasthenia gravis), or in patients receiving concomitant therapy with neuromuscular blocking drugs (e.g., pancuronium). This acute myopathy is generalized, may involve ocular and respiratory muscles, and may result in quadriparesis. Elevation of creatinine kinase may occur. Clinical improvement or recovery after stopping corticosteroids may require weeks to years.

Psychic derangements may appear when corticosteroids are used, ranging from euphoria, insomnia, mood swings, personality changes, and severe depression, to frank psychotic manifestations. Also, existing emotional instability or psychotic tendencies may be aggravated by corticosteroids.

Ophthalmic

Intraocular pressure may become elevated in some individuals. If steroid therapy is continued for more than 6 weeks, intraocular pressure should be monitored.

Information for Patients

Patients should be warned not to discontinue the use of corticosteroids abruptly or without medical supervision. As prolonged use may cause adrenal insufficiency and make patients dependent on corticosteroids, they should advise any medical attendants that they are taking corticosteroids and they should seek medical advice at once should they develop an acute illness including fever or other signs of infection. Following prolonged therapy, withdrawal of corticosteroids may result in symptoms of the corticosteroid withdrawal syndrome including, myalgia, arthralgia, and malaise.

Persons who are on corticosteroids should be warned to avoid exposure to chickenpox or measles. Patients should also be advised that if they are exposed, medical advice should be sought without delay.

Drug Interactions

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 (see **Drug Interactions**: *Hepatic Enzyme Inducers, Inhibitors and Substrates*).

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 dexamethasone suppression test (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-adminstration 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 (NSAIDS): Concomitant use of aspirin (or other nonsteroidal antiinflammatory 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.

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 (see **WARNINGS: Infections***: Vaccination*).

Carcinogenesis, Mutagenesis, Impairment of Fertility

No adequate studies have been conducted in animals to determine whether corticosteroids have a potential for carcinogenesis or mutagenesis.

Steroids may increase or decrease motility and number of spermatozoa in some patients.

Pregnancy

Teratogenic Effects: Pregnancy Category C.: Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose. Animal studies in which corticosteroids have been given to pregnant mice, rats, and rabbits have yielded an increased incidence of cleft palate in the offspring. There are no adequate and well-controlled studies in pregnant women. Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who have received substantial doses of corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Because of the potential for serious adverse reactions in nursing infants from corticosteroids, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids, which is similar in pediatric and adult populations. Published studies provide evidence of efficacy and safety in pediatric patients for the treatment of nephrotic syndrome (patients >2 years of age), and aggressive lymphomas and leukemias (patients >1 month of age). Other indications for pediatric use of corticosteroids, e.g., severe asthma and wheezing, are based on adequate and well-controlled trials conducted in adults, on the premises that the course of the diseases and their pathophysiology are considered to be substantially similar in both populations.

The adverse effects of corticosteroids in pediatric patients are similar to those in adults (see **ADVERSE REACTIONS**). Like adults, pediatric patients should be carefully observed with frequent measurements of blood pressure, weight, height, intraocular pressure, and clinical evaluation for the presence of infection, psychosocial disturbances, thromboembolism, peptic ulcers, cataracts, and osteoporosis. Pediatric patients who are treated with corticosteroids by any route, including systemically administered corticosteroids, may experience a decrease in their growth velocity. This negative impact of corticosteroids on growth has been observed at low systemic doses and in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA) axis suppression (i.e., cosyntropin stimulation and basal cortisol plasma levels). Growth velocity may therefore be a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA axis function. The linear growth of pediatric patients treated with corticosteroids should be monitored, and the potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the availability of treatment alternatives. In order to minimize the potential growth effects of corticosteroids, pediatric patients should be *titrated* to the lowest effective dose.

Geriatric Use

Clinical studies did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. In particular, the increased risk of diabetes mellitus, fluid retention and hypertension in elderly patients treated with corticosteroids should be considered.

ADVERSE REACTIONS
(listed alphabetically, under each subsection)

The following adverse reactions have been reported with dexamethasone or other corticosteroids:

Allergic Reactions

Anaphylactoid reaction, anaphylaxis, angioedema.

Cardiovascular

Bradycardia, cardiac arrest, cardiac arrhythmias, cardiac enlargement, circulatory collapse, congestive heart failure, fat embolism, hypertension, hypertrophic cardiomyopathy in premature infants, myocardial rupture following recent myocardial infarction (see **WARNINGS: Cardio-Renal**), edema, pulmonary edema, syncope, tachycardia, thromboembolism, thrombophlebitis, vasculitis.

Dermatologic

Acne, allergic dermatitis, dry scaly skin, ecchymoses and petechiae, erythema, impaired wound healing, increased sweating, rash, striae, suppression of reactions to skin tests, thin fragile skin, thinning scalp hair, urticaria.

Endocrine

Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness), suppression of growth in pediatric patients.

Fluid and Electrolyte Disturbances

Congestive heart failure in susceptible patients, fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal

Abdominal distention, elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic

Negative nitrogen balance due to protein catabolism.

Musculoskeletal
Aseptic necrosis of femoral and humeral heads, loss of muscle mass, muscle weakness, osteoporosis, pathologic fracture of long bones, steroid myopathy, tendon rupture, vertebral compression fractures.
Neurological/Psychiatric
Convulsions, depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.
Ophthalmic
Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.
Other
Abnormal fat deposits, decreased resistance to infection, hiccups, increased or decreased motility and number of spermatozoa, malaise, moon face, weight gain.

OVERDOSAGE

Treatment of overdosage is by supportive and symptomatic therapy. In the case of acute overdosage, according to the patient's condition, supportive therapy may include gastric lavage or emesis.

DOSAGE AND ADMINISTRATION

For Oral Administration
The initial dosage varies from 0.75 to 9 mg a day depending on the disease being treated.
It Should Be Emphasized That Dosage Requirements Are Variable And Must Be Individualized On The Basis Of The Disease Under Treatment And The Response Of The Patient.
After a favorable response is noted, the proper maintenance dosage should be determined by decreasing the initial drug dosage in small decrements at appropriate time intervals until the lowest dosage that maintains an adequate clinical response is reached.
Situations which may make dosage adjustments necessary are changes in clinical status secondary to remissions or exacerbations in the disease process, the patient's individual drug responsiveness, and the effect of patient exposure to stressful situations not directly related to the disease entity under treatment. In this latter situation it may be necessary to increase the dosage of the corticosteroid for a period of time consistent with the patient's condition. If after long-term therapy the drug is to be stopped, it is recommended that it be withdrawn gradually rather than abruptly.
In the treatment of acute exacerbations of multiple sclerosis, daily doses of 30 mg of dexamethasone for a week followed by 4 to 12 mg every other day for one month have been shown to be effective (see **PRECAUTIONS: Neuro-Psychiatric**).
In pediatric patients, the initial dose of dexamethasone may vary depending on the specific disease entity being treated. The range of initial doses is 0.02 to 0.3 mg/kg/day in three or four divided doses (0.6 to 9 mg/m^2bsa/day).
For the purpose of comparison, the following is the equivalent milligram dosage of the various corticosteroids:

Cortisone, 25	Triamcinolone, 4
Hydrocortisone, 20	Paramethasone, 2
Prednisolone, 5	Betamethasone, 0.75
Prednisone, 5	Dexamethasone, 0.75
Methylprednisolone, 4	

These dose relationships apply only to oral or intravenous administration of these compounds. When these substances or their derivatives are injected intramuscularly or into joint spaces, their relative properties may be greatly altered.
In acute, self-limited allergic disorders or acute exacerbations of chronic allergic disorders, the following dosage schedule combining parenteral and oral therapy is suggested:
Dexamethasone sodium phosphate injection, 4 mg per mL
First Day: 1 or 2 mL, intramuscularly
Dexamethasone tablets, 0.75 mg
Second Day: 4 tablets in two divided doses
Third Day: 4 tablets in two divided doses
Fourth Day: 2 tablets in two divided doses
Fifth Day: 1 tablet
Sixth Day: 1 tablet
Seventh Day: No treatment
Eighth Day: Follow-up visit
This schedule is designed to ensure adequate therapy during acute episodes, while minimizing the risk of overdosage in chronic cases.
In *cerebral edema*, dexamethasone sodium phosphate injection is generally administered initially in a dosage of 10 mg intravenously followed by 4 mg every six hours intramuscularly until the symptoms of cerebral edema subside. Response is usually noted within 12 to 24 hours and dosage may be reduced after two to four days and gradually discontinued over a period of five to seven days. For palliative management of patients with recurrent or inoperable brain tumors, maintenance therapy with either dexamethasone sodium phosphate injection or dexamethasone tablets in a dosage of 2 mg two or three times daily may be effective.
Dexamethasone Suppression Tests
1. Tests for Cushing's syndrome
   Give 1.0 mg of dexamethasone orally at 11:00 p.m. Blood is drawn for plasma cortisol determination at 8:00 a.m. the following morning.
   For greater accuracy, give 0.5 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.
2. Test to distinguish Cushing's syndrome due to pituitary ACTH excess from Cushing's syndrome due to other causes.
   Give 2.0 mg of dexamethasone orally every 6 hours for 48 hours. Twenty-four hour urine collections are made for determination of 17-hydroxycorticosteroid excretion.

Proper Use of an Intensol™
An Intensol is a concentrated oral solution as compared to standard oral liquid medications. It is recommended that an Intensol be mixed with liquid or semi-solid food such as water, juices, soda or soda-like beverages, applesauce and puddings.
Use only the calibrated dropper provided with this product. Draw into the dropper the amount prescribed for a single dose. Then squeeze the dropper contents into a liquid or semi-solid food. Stir the liquid or food gently for a few seconds. The Intensol formulation blends quickly and completely. The entire amount of the mixture, of drug and liquid or drug and food, should be consumed immediately. Do not store for future use.

HOW SUPPLIED

Dexamethasone Tablets USP:
0.5 mg yellow, scored tablets (Identified 54 299).
NDC 0054-8179-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4179-25: Bottles of 100 tablets.
0.75 mg pale blue, scored tablet (Identified 54 960).
NDC 0054-8180-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4180-25: Bottles of 100 tablets.
1 mg yellow, scored tablets (Identified 54 489).
NDC 0054-8174-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4181-25: Bottles of 100 tablets.
1.5 mg pink, scored tablets (Identified 54 943).
NDC 0054-8181-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4182-25: Bottles of 100 tablets.
NDC 0054-4182-31: Bottles of 1000 tablets.
2 mg white, scored tablets (Identified 54 662).
NDC 0054-8176-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4183-25 Bottles of 100 tablets.
4 mg green, scored tablets (Identified 54 892).
NDC 0054-8175-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4184-25: Bottles of 100 tablets.
6 mg aqua, scored tablets (Identified 54 769).
NDC 0054-8183-25: Unit dose, 10 tablets per strip, 10 strips per shelf pack, 10 shelf packs per shipper.
NDC 0054-4186-25: Bottles of 100 tablets.

Store and Dispense
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF.

Dexamethasone Oral Solution, 0.5 mg per 5 mL:
NDC 0054-3177-57: Bottles of 240 mL.
NDC 0054-3177-63: Bottles of 500 mL.

Store and Dispense
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Dispense in a tight, light-resistant container as defined in the USP/NF.

Dexamethasone *Intensol*™ Oral Solution (Con-centrate), 1 mg per mL:
NDC 0054-3176-44: Bottles of 30 mL with calibrated dropper [graduations of 0.25 mL (0.25 mg), 0.5 mL (0.5 mg), 0.75 mL (0.75 mg), and 1 mL (1 mg), on the dropper].

Store and Dispense
Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. Do not freeze. Do not use if solution contains a precipitate. Dispense only in this bottle and only with the calibrated dropper provided. Discard opened bottle after 90 days.

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Revised September 2007

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Roxane Laboratories

Appendix 5. Schedule of Assessments

	Screening[a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12[b]	ET/Safety Follow Up[c]
		Days (± 2)					Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	
		1	8	15	22	28	15	28	28	28	28	
Informed consent	x											
Confirm eligibility	x											
Medical history	x											
PE[d]/Vital signs[e]/Weight	x	x	x	x	x	x	x	x	x	x	x	x
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x
ECG[f]	x	x										x
Lab assessments:												
Urine pregnancy test[g]	x											x
Hematology[h]	x	x[q]	x	x	x	x	x	x	x	x	x	x
Serum chemistry[i]	x	x[q]	x	x	x	x	x	x	x	x	x	x
Urinalysis[j]	x					x		x	x	x	Every 2 mos	
T/B/NK cell count[k]		x[q]	x	x		x		x			Every 6 mos	
Disease markers[l]	x			x		x		x	x	x	Every 2 mos	x
Bone marrow (aspirate/biopsy) /Skeletal survey[p]	x								As clinically indicated or to confirm a CR	As clinically indicated or to confirm a CR	As clinically indicated or to confirm a CR	
Pharmacodynamics		x[m]	x[m]			x[n]		x[n]				x
Pharmacokinetics[o]		x	x	x	x	x						
ACP-196/ dexamethasone dispensed		x	x	x	x	x	x	x	x	x	x	
Study drug compliance		x	x	x	x	x	x	x	x	x	x	
Tumor assessment[p]	x					x		x	x	x	x	
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x	x	x	x

Abbreviations: CR = complete remission; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ET + early termination; Ig = immunoglobulin; mos = months; PE = physical exam;

Footnotes for ACE-MY-001 Schedule of Study Activities:

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. Any subjects who have not progressed while receiving study drug treatment, may be eligible to enroll into a long-term follow up study and continue to receive ACP-196.
c. An early termination visit is required for any subjects who permanently discontinue study drug early for any reason including disease progression. A 30-day (± 7 days) safety follow-up visit is required when subjects discontinue study drug unless they start another anticancer therapy within that timeframe.
d. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter.
e. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
f. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs.
g. Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
h. Hematology includes complete blood count with differential and platelet and reticulocyte counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days.
i. Serum chemistry: albumin, alkaline phosphatase, bone-specific alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, C-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening serum chemistry was within 5 days.
j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, N-terminal telopeptide, and glucose.
k. T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD16/56). During Cycle 5-12, only done at end of Cycle 6 and 12.
l. Refer to Section 4.1 for a list of myeloma disease markers.
m. Pharmacodynamic samples are drawn predose and 4 hours (±10 minutes) postdose on the days indicated. Note: These timepoints are relative to the morning dose.
n. Pharmacodynamic samples are drawn predose on the days indicated.
o. Pharmacokinetic samples are drawn per Table 4-1.
p Refer to Section 4-2. Bone marrow aspirate/biopsy and skeletal survey are required at baseline (ie, before the first dose of study drug). Thereafter they are required as indicated in the table above.
q. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.

PROTOCOL

TITLE:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma
PROTOCOL NUMBER:	ACE-MY-001
STUDY DRUG:	ACP-196
IND NUMBER:	118717
SPONSOR MEDICAL MONITOR:	[redacted] Acerta Pharma BV [redacted] [redacted]
SPONSOR:	Acerta Pharma BV Molenstraat 110 5342 CC Oss The Netherlands
PROTOCOL DATE:	11 July 2014

Confidentiality Statement

PROTOCOL APPROVAL PAGE

I have carefully read Protocol ACE-MY-001 entitled "An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma". I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Acerta Pharma, and the IRB/IEC must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Acerta Pharma. All data pertaining to this study will be provided to Acerta Pharma. The policy of Acerta Pharma BV requires that any presentation or publication of study data by clinical investigators be reviewed by Acerta Pharma, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

The following Acerta Pharma BV representative is authorized to sign the protocol and any amendments:

[redacted]

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ABBREVIATIONS

AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BID	twice a day (dosing)
Btk	Bruton tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
C_{max}	maximum concentration
CLL	chronic lymphocytic leukemia
CR	complete remission (response)
CSSF	Clinical Supplies Shipping Receipt Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
FDA	Food and Drug Administration
FIH	first-in-human (trial)
FLC	(serum) free light chains
GCP	Good Clinical Practice
GLP	Good Laboratory Practices

HBV	hepatitis B virus
HCV	hepatitis C virus
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
HNSTD	highest nonseverely toxic dose
ICF	informed consent form
IEC	Independent Ethics Committee
IFE	immunofixation electrophoresis
Ig	immunoglobulin
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LTFU	long-term follow up
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MR	minor response
NHL	non-Hodgkin lymphoma
NK	natural killer (cells)
ORR	overall response rate
PBMC(s)	peripheral blood mononuclear cells
PD	pharmacodynamics
PK	pharmacokinetics
PR	partial remission (response)
QD	once a day (dosing)
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SD	stable disease
SFLC	serum free light chains
SIFE	serum immunofixation electrophoresis
SPD	sum of the products of the perpendicular diameters (of lymph nodes)
SPEP	serum protein electrophoresis
SUSAR	Suspected Unexpected Serious Adverse Reaction (report)
T_{max}	time to maximum drug concentration

UIFE	urine immunofixation electrophoresis
ULN	upper limit of normal
UPEP	urine serum protein electrophoresis
VGPR	very good partial response
WHO	World Health Organization

STUDY SYNOPSIS

Protocol Number:	ACE-MY-001
Study Drug:	ACP-196
Protocol Title:	An Open-label, Phase 1b Study of ACP-196 in Subjects with Multiple Myeloma
Phase:	Phase 1b
Comparator:	None
Background and Rationale for Study	Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton tyrosine kinase (Btk) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL). Preclinical studies have shown that Btk inhibition significantly reduces in vivo multiple myeloma (MM) cell growth and MM cell-induced osteolysis in a murine model (Tai 2012). Data on the utility of Btk targeted therapy in patients with MM is very preliminary, but suggests there are subsets of patients with malignant plasma cell clones in which Btk is active as evidenced by expression of phosphorylated Btk (p-Btk), and that these cancers may be particularly responsive to Btk inhibitor therapy. Acerta Pharma BV (Acerta Pharma) has developed a novel second generation Btk inhibitor, ACP-196, that achieves significant oral bioavailability and potency in preclinical models. ACP-196 monotherapy is currently in Phase 1 studies in subjects with chronic lymphocytic leukemia (CLL) and in healthy volunteers. The purpose of this study is to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and activity of 2 different schedules of ACP-196 administration in subjects with relapsed MM. The study will explore the concept of whether biomarkers may help identify patients with MM that be particularly benefit from Btk inhibitor therapy.
Study Design:	This study is a multicenter, open-label, randomized, parallel-group study. Forty subjects will be equally randomized (1:1 ratio) into 2 cohorts to receive ACP-196, without or without dexamethasone: • Cohort 1: ACP-196 100 mg twice per day (BID) continuously • Cohort 2: ACP-196 100 mg BID continuously and dexamethasone 40 mg once weekly Twenty-eight days of study drug administration is 1 cycle. Treatment may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. For subjects in Cohort 1, if documented disease progression occurs,

	then dexamethasone can be added to the treatment regimen. Additional dose modification provisions are provided in the study protocol. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. All subjects will have hematology, chemistry, and urinalysis safety panels done at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1. Tumor assessments will be done at 8- to 12-week intervals during the trial. Refer to Appendix 4 for a comprehensive list of study assessments and their timing.
Study Objectives:	**Primary Objective:** • To characterize the safety profile of ACP-196 with and without dexamethasone in subjects with relapsed or refractory MM **Secondary Objectives:** • To characterize the PK profile of ACP-196 with and without dexamethasone and the PK profile of dexamethasone with concomitant ACP-196 administration • To evaluate the PD effects of ACP-196 with and without dexamethasone • To evaluate the activity of ACP-196 with and without dexamethasone as measured by response rate, duration of response, time-to-next treatment, and progression-free survival • To explore the relationship between biological markers in MM cells and response to therapy
Safety Parameters:	Type, frequency, severity, timing of onset, duration, and relationship to study drug (ie, ACP-196, dexamethasone, or both) of any adverse events (AEs) or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of study treatment.
Efficacy Parameters:	• Overall response rate (ORR) • Duration of response • Progression-free survival • Time-to-next treatment

Pharmacokinetic Parameters:	The plasma PK of ACP-196 will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of analytes: • $AUC_{(0-t)}$: Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t). • $AUC_{(0-24)}$: Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation. • $AUC_{(0-\infty)}$: Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant. • C_{max}: Maximum observed plasma concentration • T_{max}: Time of the maximum plasma concentration (obtained without interpolation) • $t_{½}$: Terminal elimination half-life (whenever possible) • λ_z: Terminal elimination rate constant (whenever possible) • Cl/F: Oral clearance
Pharmacodynamic Parameters:	The occupancy of Btk by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) and in bone marrow, when available, with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.
Sample Size:	Forty subjects with 20 subjects in each cohort.
Inclusion Criteria:	• Men and women ≥ 18 years of age. • A confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥ 1 prior therapy for MM, and is progressing at the time of study entry. • Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2. • Agreement to use acceptable methods of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children. • Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug. • Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty. • Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with

	national and local subject privacy regulations).
Exclusion Criteria:	• Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor. • A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ACP-196, or put the study outcomes at undue risk. • Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification • Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. • Any immunotherapy within 4 weeks of first dose of study drug. • The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s). • Relapsed or refractory to prior Btk inhibitor therapy. • Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MM or other conditions. Note: Subjects may use topical or inhaled corticosteroids as therapy for comorbid conditions. During study participation, subjects may receive systemic or enteric corticosteroids as needed for MM therapy or treatment-emergent comorbid conditions. • Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation. • Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection. • Major surgery within 4 weeks before first dose of study drug. • History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug. • Requires anti-coagulation with warfarin or a vitamin K antagonist. • ANC < 0.75 x 10^9/L or platelet count < 50 x 10^9/L unless associated with >50% plasma cells in the marrow. • Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase

	(ALT) > 2.5 x ULN unless disease related. • Significant screening electrocardiogram (ECG) abnormalities including left bundle-branch block, 2nd-degree AV block type II, 3rd-degree block, Grade ≥ 2 bradycardia, or QTc > 480 msec. • Breastfeeding or pregnant. • Concurrent participation in another therapeutic clinical trial.
Dosage Form and Strength:	ACP-196 is provided as 25- and 100-mg hard gelatin capsules prepared using standard pharmaceutical grade excipients.
Dose Regimen/Route of Administration:	ACP-196 is an orally administered product. ACP-196 will be administered on an empty stomach defined as no food 2 hours before and 1 hour after dosing. <u>Regimens:</u> • Cohort 1 (BID): 100 mg ACP-196 (1 x 100-mg capsule) administered 12 hours apart (BID dosing = 200-mg total daily dose) • Cohort 2 (BID + dexamethasone): 100 mg ACP-196 (1 x 100-mg capsule) administered 12 hours apart (BID dosing = 200-mg total daily dose) plus 40 mg dexamethasone (1 x 40-mg capsule) administered once weekly (weekly dosing = 40-mg total weekly dose)
Statistics:	Subjects meeting the stated eligibility requirements will be enrolled onto the study. Subjects will be equally randomized into 1 of 2 regimens (ACP-196 with or without dexamethasone). With a sample size of 19 subjects per cohort, the power to detect the difference between a null-hypothesis response rate of 15% and an alternative response rate of 40% with a 0.025 one-sided significance level is 0.84 using a one-group, chi-square test and 0.69 using a one-group, exact binomial test. A sample size of 19 subjects per cohort will also provide a 97.5% one-sided confidence interval centered around an expected ORR of 40% that excludes an ORR of 18.6% as a lower bound. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data, as appropriate.

1.0 BACKGROUND INFORMATION

1.1 ROLE OF BTK IN LYMPHOID CANCERS

Bruton tyrosine kinase (Btk) is a non-receptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration (Mohamed 2009, Bradshaw 2010). Functional null mutations of Btk in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells (Vihinen 2000). Conversely, Btk activation is implicated in the pathogenesis of several B-cell malignancies (Buggy 2012). Taken together, these findings have suggested that inhibition of Btk may offer an attractive strategy for treating B-cell neoplasms. Ibrutinib (IMBRUVICA™), a first-generation oral, small-molecule Btk inhibitor has been approved for the treatment for chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) and is being evaluated for activity in other B-cell neoplasms including multiple myeloma (MM). Preclinical studies have shown that Btk inhibition with ibrutinib significantly reduces in vivo multiple myeloma (MM) cell growth and MM cell-induced osteolysis in a murine model (Tai 2012). While current therapies have provided substantial benefit to patients, MM remains incurable; for patients who experience disease relapse after application of existing therapies, the prognosis is dismal and new drugs and therapeutic strategies are required for continued disease control (Romano 2014). Inhibition of Btk may simultaneously address the MM-related bone complications as well improve patient outcome in MM (Edwards 2012).

1.2 PRECLINICAL STUDIES

Knowledge of the critical importance of Btk in tumor biology and the clinical profile observed with ibrutinib has encouraged the development of second-generation Btk inhibitors as a therapy for lymphoid cancers. Acerta Pharma, a pharmaceutical company with sites in San Carlos, CA, USA and in Oss, The Netherlands, has identified novel compounds that selectively inhibit Btk. Chemical optimization, pharmacologic characterization, and toxicologic evaluation have led to identification of ACP-196, an orally bioavailable, new chemical entity that covalently inhibits Btk and shows encouraging activity and acceptable safety in nonclinical studies. ACP-196 may offer an improved therapeutic index relative to ibrutinib and may be more readily combined with other agents active in the therapy of lymphoid cancers. Summaries of preclinical studies

are provided below. For more detailed information please refer to the Investigator's Brochure.

1.2.1 Chemistry

[redacted] ACP-196 is orally bioavailable in animals and is suitable for formulating in capsules. For clinical testing, ACP-196 has been manufactured and formulated according to current Good Manufacturing Practices (cGMP).

1.2.2 Efficacy Pharmacology

Spontaneous canine B-cell lymphoma shares many characteristics with human NHL, including diagnostic classifications and response to Btk inhibition (Honigberg 2010). The life expectancy in untreated animals with aggressive disease is ~6 weeks, thus enabling rapid assessment of drug efficacy (Vail and Thamm, 2004). ACP-196 is currently being evaluated in an ongoing dose-escalation study in canine spontaneous B-cell lymphoma. Fourteen dogs, all of which had diffuse large B-cell lymphoma (DLBCL) confirmed by histology, have been treated with ACP-196 for at least 2 weeks. The dosages have ranged from 2.5 to 20 mg/kg once (QD) or twice (BID) per day. To date, per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma (Vail 2010), partial responses (PRs) been observed in 4 of 14 dogs (29%) and stable disease has been observed in 8 of 14 dogs (57%). No ACP-196-related adverse events (AEs) have been reported to date in this study. These findings are preliminary and similar to the clinical responses (ie, 1 dog with PR out of 5 dogs treated with suspected or confirmed DLBCL) observed with ibrutinib in dogs with spontaneous B-cell lymphoma (Honigberg 2010).

Preliminary results assessing Btk occupancy using a biotin-tagged analogue of ACP-196 show near complete Btk occupancy over 24 hours with both BID and QD dosing in canine tumor tissue (Table 1-1).

Table 1-1. Assessment of ACP-196 Active-site Occupancy in Fine Needle Aspirates of Canine Lymph Node Tumors (N=4)

Timing	Dog Identification and ACP-196 Dosing Regimen			
	DL-12	DL-14	DL-15	DL-16
	10 mg/kg BID	20 mg/kg QD	20 mg/kg QD	20 mg/kg QD
	Btk Occupancy (% versus predose)			
Day 1 (3 hours after morning dose)	99%	98%	87%	99%
Day 7 (before morning dose)	98%	77%	ND	93%

BID = twice per day; Btk = Bruton tyrosine kinase; ND = not determined; QD = once per day

These canine data provide nonclinical support for the ability of ACP-196 to target Btk in vivo. The role of Btk expression in driving the proliferation and survival of malignant plasma cells in multiple myeloma (MM) has been less clear than among other lymphoid cancers. However, emerging, unpublished, preclinical data from the laboratory of Sagar Lonial (Emory University) suggest that Btk and phosphorylated Btk (p-Btk) expression is present to varying levels in a standard panel of 12 myeloma cell lines, thus providing a basis for evaluating Btk inhibition as a therapy for MM.

1.2.3 Safety Pharmacology

In vitro and in vivo safety pharmacology studies with ACP-196 have demonstrated a favorable nonclinical safety profile.

When screened at 10 μM in binding assays evaluating interactions with 80 known pharmacologic targets such as G-protein-coupled receptors, nuclear receptors, proteases, and ion channels, ACP-196 shows significant activity only against the A3 adenosine receptor; follow-up dose-response experiments indicated a IC_{50} of 2.7 μM, suggesting a low clinical risk of off-target effects. ACP-196 at 10 μM showed no inhibition of in vitro epidermal growth factor receptor (EGFR) phosphorylation in an A431 human epidermoid cancer cell line, whereas ibrutinib had an IC_{50} of 66 nM.

The in vitro effect of ACP-196 on human ether-à-go-go-related gene (hERG) channel activity was investigated in vitro in human embryonic kidney cells stably transfected with hERG. ACP-196 inhibited hERG channel activity by 25% at 10 μM, suggesting a low clinical risk that ACP-196 would induce clinical QT prolongation as predicted by this assay.

ACP-196 was well tolerated in standard in vivo Good Laboratory Practices (GLP) studies of pharmacologic safety. A functional observation battery in rats at doses of through 300 mg/kg (the highest dose level) revealed no adverse effects on neurobehavioral effects or body temperature at any dose level. A study of respiratory function in rats also indicated no treatment-related adverse effects at doses through 300 mg/kg (the highest dose level). In a cardiovascular function study in awake telemeterized male beagle dogs, single doses of ACP-196 at dose levels through 30 mg/kg (the highest dose level) induced no meaningful changes in body temperature, cardiovascular, or electrocardiographic (ECG) (including QT interval) parameters. The results suggest that ACP-196 is unlikely to cause serious off-target effects or adverse effects on critical organ systems.

1.2.4 Drug-drug Interaction Potential

In vitro metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with ^{14}C-labelled ACP-196 indicated 2 mono-oxidized metabolites and a glutathione conjugate. No unique human metabolite was identified. Preliminary evaluations of metabolism in the plasma, bile, and urine of rats, dogs, and monkeys indicated metabolic processes of oxidation, glutathione binding, and hydrolysis. It was shown that ACP-196 binds to glutathione but does not deplete glutathione in vitro.

In vitro experiments evaluating loss of parent drug as catalyzed by cytochrome P450 enzymes (CYPs) indicated that ACP-196 is metabolized by CYP3A4. Drugs potentially altering activity of this isoenzyme may alter ACP-196 disposition (see Section 1.3).

Nonclinical CYP interaction studies data indicate that ACP-196 is very unlikely to cause clinical drug-drug interactions through alteration of the metabolism of drugs that are substrates for CYPs.

1.2.5 In Vivo General Toxicology

To date, the toxicology program has included 28-day GLP evaluations in rats and dogs. In the 28-day study in male and female Sprague-Dawley rats, animals received oral gavage ACP-196 dosages of 30, 100, and 300 mg/kg/day. In the 28-day study in male and female beagle dogs, animals received oral ACP-196 dosages of 3, 10, and 30 mg/kg/day. Both studies had 28-day recovery periods.

The no observable adverse effect level in the dog was 30 mg/kg/day, which was the highest dose evaluated. In rats, 30 mg/kg/day resulted in minimal inflammation of the

pancreas in some animals, with reversal, indicating the rat to be the more sensitive preclinical species. The pancreatic effects were minimally increased at 100 mg/kg/day in the rat though there was no clinical evidence of toxicity. Hence, 100 mg/kg/day was selected to conservatively represent the highest nonseverely toxic dose (HNSTD). In dogs at 30 mg/kg/day, no adverse effects on the pancreas were observed. In rats and dogs, no adverse ECG or histopathologic cardiovascular effects were noted at the planned conclusion of the 28-day toxicology studies. However, in 5 of 6 rats from the 300-mg/kg dose group that died early in the study, slight to moderate necrosis of the myocardium and/or white blood cell infiltration/inflammation of the myocardium were noted on microscopic examination of the hearts. These findings were most likely incidental postmortem changes.

1.3 CLINICAL EXPERIENCE

Table 1-2 lists the studies currently being conducted with ACP-196 monotherapy.

Table 1-2. ACP-196 Clinical Studies

Protocol	Design	Subjects Enrolled	Status
ACE-CL-001 (NCT02029443)	• First-in-human • Open label • Dose escalation (100-450 mg QD) • Subjects with relapsed/refractory CLL	24	• 1st cohort (100 mg QD) enrolled and no DLTs observed. • 2nd cohort (175 mg QD) enrolled and no DLTs observed. • 3rd cohort (250 mg QD) enrolled and no DLTs observed.
ACE-HV-001	• Open label • Single-dose escalation (2.5-50 mg BID and 100 mg QD) • Food effect (75 mg QD) • Drug-drug interaction (50 mg QD) • Healthy volunteers	59	• Enrollment completed. • No adverse laboratory, vital signs, or ECGs findings observed. • 1 event each of constipation, feeling cold, somnolence (each Grade 1) was reported as related to study drug.

AE = adverse event; BID = twice per day; CLL = chronic lymphocytic leukemia; DLT = dose-limiting toxicity; QD = once per day

ACE-CL-001 (NCT02029443), an ongoing FIH study in subjects with relapsed/refractory CLL, has a sequential, dose-escalation design. The starting dosage for ACP-196 is 100 mg QD and the DLT observation period is 28 days (ie, 1 cycle of treatment). To

date, ACP-196 has been well tolerated with no DLTs observed from 100 to 250 mg QD. PD data from the first 2 cohorts in this study show that Btk occupancy with ACP-196, in peripheral blood cells, is > 95% at 4 hours after dosing but decreases to < 90% 24 hours after QD dosing (Table 1-3).

Table 1-3. Btk Occupancy in Peripheral Blood of Subjects from ACE-CL-001

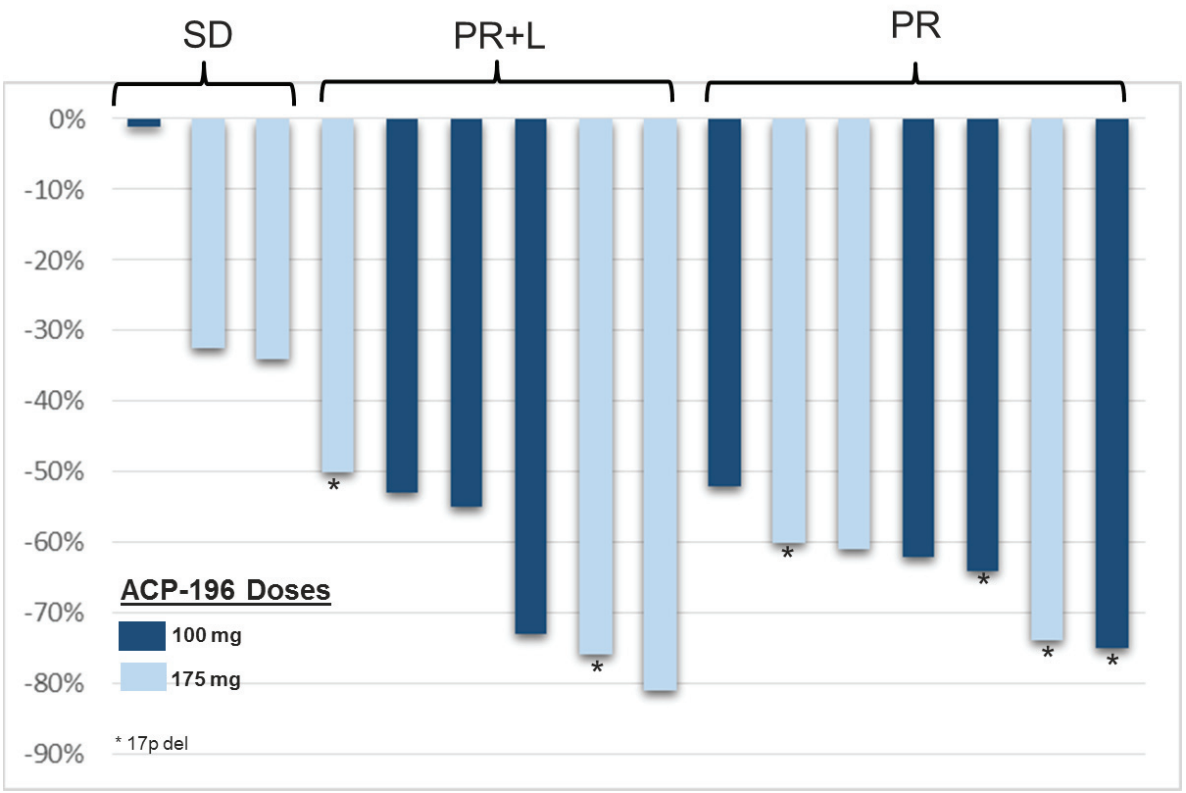
	Percent Btk Occupancy Versus Day 1 Predose					
	100 mg QD			175 mg QD		
Timing	Mean	Std Dev	N	Mean	Std Dev	N
Day 1: 4 h postdose	96.0	3.2	8	97.4	2.4	8
Day 1: 24 h postdose	84.4	9.8	8	80.2	10.7	8
Day 8: predose	87.6	5.0	8	87.0	10.5	7
Day 8: 4 h postdose	98.0	1.8	8	96.6	5.1	7

Btk = Bruton tyrosine kinase; std dev = standard deviation; QD = once per day

To date, 16 subjects have been evaluated for tumor response in the 100- and 175-mg cohorts after 56 days of treatment; a response rate of 81% (13 of 16 subjects) has been observed based on International Working Group response criteria (Halleck 2008) as recently updated (Cheson 2012). Of the 16 evaluable subjects, 15 (94%) have experienced reductions in lymphadenopathy, with 7 subjects achieving PRs, 6 subjects experiencing a ≥ 50% decrease in lymphadenopathy with lymphocytosis (ie, PR with lymphocytosis), and 3 subjects having stable disease (SD) (Figure 1-1). As shown in the figure, substantial response has been observed even among subjects with the adverse prognostic indicator of del17p in CLL cells. ACP-196 has been well tolerated in all subjects.

Figure 1-1. Changes in the SPDs of Lymph Nodes at Week 8 of ACP-196 Therapy as Documented by CT Scans

(Evaluable CLL Subjects, N=16)



CLL = chronic lymphocytic leukemia; CT= computed tomography; PR = partial response; PR+L = partial response with lymphocytosis; SD = stable disease; SPD = sum of the products of the perpendicular diameters (of lymph nodes).

ACE-HV-001 is a dose-ranging, food-effect, and drug-drug interaction study evaluating BID and QD dosing for 1 day in healthy volunteers. The starting dose for ACP-196 was 2.5 mg BID. The healthy volunteer study has completed and no adverse laboratory, vital signs, or ECG findings were observed (2.5 to 50 mg BID; 50 to 100 mg QD). Three AEs related to study drug were reported. Each AE was Grade 1 and resolved without treatment. The AEs were constipation (2.5 mg BID), feeling cold (75 mg QD), and somnolence (75 mg QD).

The food-effect evaluation indicated that there was no difference in area under the curve (AUC) between the fed and fasted states; however, there was an approximately 3-fold decrease in the mean maximum concentration (C_{max}) in the fed state. Therefore, ACP-196 should be administered on an empty stomach as outlined in Section 3.5.3.

The effect of coadministration of a potent CYP3A4 inhibitor, itraconazole, on the plasma levels of ACP-196 was also evaluated. The mean plasma ACP-196 C_{max} and AUC_{last} values increased 4.1- and 5.3-fold, respectively, in the presence of itraconazole relative to no pretreatment. Please refer to Section 3.7.2 for more information on drug-drug interactions.

1.4 SUMMARY AND CONCLUSIONS

This study comprises a pilot evaluation of the safety and activity of the potent, second-generation Btk inhibitor, ACP-196, in patients with relapse or refractory MM. The design and conduct of this study is supported by an understanding of the natural history and current therapies for subjects with lymphoid cancers; knowledge of the activity and safety of the first-generation BCR inhibitor (eg, ibrutinib) in subjects with hematologic cancers; and the available nonclinical and clinical information regarding ACP-196. Preclinical studies are ongoing in parallel to identify biomarkers that may be evaluated in this clinical trial as correlates of response to Btk-directed therapy and that may permit selection of patients who are particularly likely to benefit from ACP-196 treatment for MM.

2.0 STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To characterize the safety profile of ACP-196 with and without dexamethasone in subjects with relapsed or refractory MM

2.2 SECONDARY OBJECTIVES:

- To characterize the PK profile of ACP-196 with and without dexamethasone and the PK profile of dexamethasone with concomitant ACP-196 administration
- To evaluate the PD effects of ACP-196 with and without dexamethasone
- To evaluate the activity of ACP-196 with and without dexamethasone as measured by response rate, duration of response, time-to-next treatment, and progression-free survival
- To explore the relationship between biological markers in MM cells and response to therapy

3.0 STUDY DESIGN

3.1 DESCRIPTION OF STUDY

This study is a multicenter, open-label, randomized, parallel-group study. Forty subjects will be randomized 1:1 into the following 2 cohorts to receive ACP-196, with or without dexamethasone:

- Cohort 1: ACP-196 100 mg BID continuously
- Cohort 2: ACP-196 100 mg BID continuously and 40 mg dexamethasone once weekly

Twenty-eight days of study drug administration is 1 cycle. Treatment may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. For subjects in Cohort 1, if documented disease progression occurs, then dexamethasone can be added to the treatment regimen. Additional modification provisions are provided in Section 3.5.5. All subjects who discontinue study drug will have a safety follow-up visit 30 (±7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe.

All subjects will have standard hematology, chemistry, and urinalysis safety panels performed at screening. Once dosing commences (Day 1), all subjects will be evaluated for safety, including serum chemistry and hematology, once weekly for the first 4 weeks, every 2 weeks in Cycle 2 and monthly thereafter. PK/PD testing will be done in Cycle 1. Tumor assessments will be done at 8- to 12-week intervals during the trial.

Refer to Appendix 4 for a comprehensive list of study assessments and their timing.

3.2 STUDY PARAMETERS

3.2.1 Safety Parameters

The safety of ACP-196 with and without dexamethasone will be characterized by the type, frequency, severity, timing of onset, duration, and relationship to study drug (ie, ACP-196, dexamethasone, or both) of any treatment-emergent AEs or abnormalities of laboratory tests; serious adverse events (SAEs); or AEs leading to discontinuation of study treatment.

For consistency of interpretation, AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and the severity of AEs and laboratory abnormalities will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. Standard definitions for seriousness will be applied (see Section 6.1).

3.2.2 Efficacy Parameters

Standardized response and progression criteria have been established for MM (Durie 2006); assessments of ACP-196 efficacy in this study will be based on these criteria. Efficacy endpoints will include:

- Overall response rate (ORR)
- Duration of response
- Progression-free survival
- Time-to-next treatment

3.2.3 Pharmacokinetic and Pharmacodynamic Parameters

Standard PK parameters for ACP-196 and dexamethasone in plasma will be evaluated in this study. A full description of the PK parameters is provided in Section 5.5.4.

The occupancy of Btk by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) and bone marrow, when available, with the aid of a biotin-tagged ACP-196 analogue probe. The effect of ACP-196 on biologic markers of B-cell function will also be evaluated.

3.3 RATIONALE FOR STUDY DESIGN AND DOSING REGIMEN

As described in Section 1.3, preliminary data from the ongoing FIH study in subjects with relapsed/refractory CLL have shown that ACP-196 is well tolerated at dosages of 100 and 250 mg QD. In addition, preliminary PD data from the first 2 cohorts in the FIH study suggest full Btk occupancy (96% to 98%) in peripheral blood is observed 4 hours after dosing but decreases to < 90% occupancy at 24 hours (Table 1-3). These data suggest that de novo synthesis of Btk can occur within 24 hours in peripheral blood cells. BID dosing may ensure Btk inhibition for the entire 24 hours and thus may be beneficial in terms of increasing efficacy and/or decreasing development of resistance to ACP-196. In addition, having information regarding the safety and pharmacology of a BID schedule may support future combination studies with other drugs that are administered BID.

Evaluation of dexamethasone as a combination partner for ACP-196 builds on known antineoplastic activity of this drug in patients with MM. Dexamethasone therapy is commonly coadministered with targeted agents for MM (Ocio 2014). The dosing regimen of 40 mg weekly to be used in this study has been established based on randomized trial data showing the superiority of this method of administration (Rajkumar 2009). Combined use of ACP-196 and dexamethasone provides an all oral, non-cytotoxic regimen that may have increased efficacy relative to administration of the

individual agents alone. While dexamethasone can increase CYP3A4 activity and thus might enhance ACP-196 metabolism, it is considered a weak inducer of this isoenzyme and has not substantially altered the disposition of other CYP3A4 substrates (eg, bortezomib) that are commonly used in the therapy of MM (Hellmann 2011). The randomized design of this pilot study will allow the potential for drug-drug interactions between ACP-196 and dexamethasone to be assessed.

3.4 SELECTION OF STUDY POPULATION

3.4.1 Inclusion Criteria

Eligible subjects will be considered for inclusion in this study if they meet **all** of the following criteria:

1. Men and women ≥ 18 years of age.
2. A confirmed diagnosis of MM, which has relapsed after, or been refractory to ≥ 1 prior therapy for MM, and is progressing at the time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
4. Agreement to use acceptable methods of contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear or beget children.
5. Agreement to refrain from sperm donation during the study and for 30 days after the last dose of study drug.
6. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
7. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (in accordance with national and local subject privacy regulations).

3.4.2 Exclusion Criteria

Subjects will be ineligible for this study if they meet **any** of the following criteria:

1. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with the Medical Monitor.
2. A life-threatening illness, medical condition or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ACP-196, or put the study outcomes at undue risk.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.

4. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
5. Any immunotherapy within 4 weeks of first dose of study drug.
6. The time from the last dose of the most recent chemotherapy or experimental therapy to the first dose of study drug is < 5 times the half-life of the previously administered agent(s).
7. Relapsed after or refractory to prior Btk inhibitor therapy.
8. Ongoing immunosuppressive therapy, including systemic or enteric corticosteroids for treatment of MM or other conditions. Note: Subjects may use topical or inhaled corticosteroids as therapy for comorbid conditions. During study participation, subjects may also receive systemic or enteric corticosteroids as needed for MM therapy or treatment-emergent comorbid conditions.
9. Grade ≥ 2 toxicity (other than alopecia) continuing from prior anticancer therapy including radiation.
10. Known history of human immunodeficiency virus (HIV) or active infection with hepatitis C virus (HCV) or hepatitis B virus (HBV) or any uncontrolled active systemic infection.
11. Major surgery within 4 weeks before first dose of study drug.
12. History of stroke or intracranial hemorrhage within 6 months before the first dose of study drug.
13. Requires anti-coagulation with warfarin or a vitamin K antagonist.
14. ANC < 0.75 x 109/L or platelet count < 50 x 109/L unless >50% marrow involvement with plasma cells are present.
15. Creatinine > 2.5 x institutional upper limit of normal (ULN); total bilirubin > 2.5 x ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN unless disease related.
16. Significant screening ECG abnormalities including left bundle-branch block, 2nd-degree AV block type II, 3rd-degree block, Grade ≥ 2 bradycardia, or QTc > 480 msec.
17. Breastfeeding or pregnant.
18. Concurrent participation in another therapeutic clinical trial.

3.4.3 Replacement of Subjects

Any subjects who do not complete Cycle 2 may be replaced at the discretion of the study investigators and sponsor.

3.4.4 Enrollment and Randomization Procedures

Enrollment of a subject into the study will be performed according to the following procedure:

- Notify the sponsor when a clinically eligible subject is identified and is ready to screen, to ensure enrollment availability on the study.
- After the subject has signed and dated the Informed Consent Form (ICF), all screening procedures have been completed, and eligibility has been confirmed, the subject can be officially enrolled in the study.
- To enroll a subject, the study center will fax/email a completed Enrollment Confirmation Form to the sponsor. The enrollment date will be the date that the form is faxed/emailed to the sponsor.
- An Enrollment Confirmation Form will be completed and faxed/emailed to the study center by the sponsor within 24 hours.
- The Enrollment Confirmation Form will contain cohort allocation per the randomization scheme generated by the sponsor.

Treatment must begin within the screening window (Section 4.1) and after the site has received the cohort allocation from the sponsor. Study treatment is not blinded on this study.

3.5 STUDY DRUG

3.5.1 Premedications

No specific premedications or supporting medications are required in conjunction with ACP-196 administration.

3.5.2 Formulation, Packaging, and Storage

3.5.2.1 ACP-196

ACP-196 should be stored according to the instructions on the label that is affixed to the package containing the drug product.

ACP-196 capsules are available in 2 dose strengths: 25 and 100 mg. The 25-mg capsules are Swedish orange in color; the 100-mg capsules are grey in color. Capsules also include the following inactive excipients: microcrystalline cellulose, gelatin, and globally acceptable colorant. ACP-196 will be provided in white, high-density polyethylene bottles; each bottle contains 30 capsules.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and emailed or faxed to the sponsor or the sponsor's representative.

Refer to the Investigator's Brochure for additional information.

3.5.2.2 Dexamethasone

This study will use commercially available dexamethasone. Please refer to the appropriate dexamethasone package insert for storage and handling instructions.

3.5.3 Administration of Study Drug

3.5.3.1 ACP-196

Investigators are prohibited from supplying ACP-196 to any subjects not properly enrolled in this study or to any physicians or scientists except those designated as subinvestigators on FDA Form 1572. The investigator must ensure that subjects receive ACP-196 only from personnel who fully understand the procedures for administering the drug.

ACP-196 is intended to be administered orally with 8 ounces (approximately 240 mL) of water. Subjects should be instructed to take each dose of study drug on an empty stomach defined as no food 2 hours before and 1 hour after dosing. The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water. Dietary restrictions are provided in Section 3.7.1.

If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been greater than 6 hours, the dose should not be taken and the subject should take the next dose at the scheduled time the next day. The missed dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.3.2 Dexamethasone

This study will use commercially available dexamethasone tablets for oral administration. At the time of weekly dexamethasone administration, the subject should take the dexamethasone tablets simultaneously with the ACP-196 capsules and with 8 ounces (approximately 240 mL) of water. The dexamethasone tablets should be swallowed intact and subjects should not attempt to chew them or dissolve them in water.

If a dexamethasone dose is missed, it can be taken up to 3.5 days (84 hours) days after the scheduled time with a return to the normal schedule the following week. If the interval of missed dosing has been > 3.5 days (84 hours), the dexamethasone dose should not be taken and the subject should take the next dose at the scheduled time in

the following week. The missed dexamethasone dose will not be made up and must be returned to the site at the next scheduled visit.

3.5.4 Assuring Subject Compliance

During cycle 1, subjects will receive their Day 1, 8, 15, 22, and 28 doses (for Cohort 2 this includes the dexamethasone dose) in the clinic because predose PK/PD measurements are required. For treatments that are taken in the clinic, subjects should take the dose from the drug dispensed for them for that particular time period. All other treatments will be taken at home. Subjects will receive a diary to record the specific time each dose was taken and to record reasons for any missed doses.

Subject compliance will be assessed at every visit. The subject will be instructed to bring the diary and any remaining ACP-196 capsules and dexamethasone tablets to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules and tablets were administered. Any remaining or returned capsules and tablets will be counted and recorded as described in Section 7.6. Returned capsules or tablets must not be redispensed to another subject. The study staff will resupply the subject with the correct number of ACP-196 capsules and dexamethasone tablets needed for use until the next visit.

3.5.5 Study Treatment Regimen and Dose Modifications

3.5.5.1 ACP-196

ACP-196 dose levels and capsule numbers are shown in Table 3-1. Lower dose levels are provided should individual subjects require an ACP-196 dose reduction for drug-related toxicity. A higher dose level is provided should an individual subject warrant a dose escalation for lack of response or for disease progression.

Table 3-1. ACP-196 Dose Levels for Cohort 1 and Cohort 2

Dose Level	Dosage Twice per Day (mg)	Capsule Strength (mg)	Capsule Number per Dose	Total Daily Dosage (mg)
+1	200	100	2	400
Starting	**100**	**100**	**1**	**200**
-1	50	25	2	100
-2	25	25	1	50

Subjects should be followed closely for AEs or laboratory abnormalities that might indicate ACP-196-related toxicity and for disease response to ACP-196 therapy. If a subject experiences an ACP-196-related adverse event requiring dose modification

during the course of ACP-196 therapy, then study drug administration should be held, as necessary, until the AE resolves or stabilizes to an acceptable degree. As appropriate, certain laboratory abnormalities may warrant more frequent monitoring (eg, once per week) until abnormalities have recovered to Grade ≤ 1. Thereafter, ACP-196 may be reinstituted at the current dose or at a lower dose, based on the judgment of the investigator. Successive adjustments to progressively lower dose levels can be done as outlined in Table 3-1.

After a dose is reduced for apparent drug-related toxicity, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of ACP-196 for ≥ 4 weeks then the ACP-196 dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the AE that led to the dose reduction was not study drug-related. Successive adjustments to progressively higher dose levels, as outlined in the tables above, can be made at 4-week intervals.

Individual subjects who are tolerating the current dose level of ACP-196 therapy may have the dose escalated, as outlined in the tables above, if the investigator feels that a dose escalation is medically warranted to maximize therapeutic benefit (eg, for lack of response or for disease progression in a subject who is tolerating the current dose level of ACP-196 therapy). In addition, subjects in Cohort 1 who have reached the highest dose level allowed by the protocol and show lack of response or disease progression may have dexamethasone (40 mg once weekly) added to their treatment.

Whenever possible, any dose adjustment of ACP-196, including adding dexamethasone to subjects in Cohort 1, should be discussed between the investigator and the Acerta Pharma medical monitor before implementation. The appropriate clinic staff should dispense the study drug for the new dose level and instruct the subject/caregiver about the change in dose level.

3.5.5.2 Dexamethasone

This study will use commercially available dexamethasone. Dosing of dexamethasone will be 40 mg once weekly. For subjects who experience intolerable dexamethasone-related adverse effects, dexamethasone may be reduced to 20 mg once weekly.

3.6 CONCOMITANT THERAPY

3.6.1 Permitted Concomitant Therapy

Antiemetics are permitted if clinically indicated. Standard supportive care medications are permitted as per institutional standards.

For subjects considered at risk for tumor lysis syndrome: Administer appropriate hydration and allopurinol or rasburicase per institutional standards before initiating treatment.

3.6.2 Prohibited Concomitant Therapy

Any chemotherapy, immunotherapy, kinase inhibitors, bone marrow transplantation, experimental therapy, and radiotherapy are prohibited (see Section 3.4.2).

3.7 PRECAUTIONS

3.7.1 Dietary Restrictions

There are no dietary restrictions on this protocol.

Subjects should be encouraged to follow instructions relating to eating relative to study drug administration (Section 3.5.3).

3.7.2 Drug-drug Interactions

At the systemic exposure levels expected in this study, ACP-196 inhibition of CYP-mediated metabolism of other drugs is not anticipated. However, ACP-196 is metabolized in part by CYP3A4. In a clinical drug-drug interaction study, coadministration of the potent CYP3A4 inhibitor, itraconazole, increased the mean plasma exposures of ACP-196 by > 4-fold (see Section 1.3). Dexamethasone is also metabolized by CYP3A4 (Gentile 1996). These data indicate that coadministration of inhibitors of CYP3A4 could increase ACP-196 and dexamethasone exposure while coadministration of inducers of these enzymes could decrease ACP-196 or dexamethasone exposure. Thus, there is the potential that subjects receiving inhibitors of these enzymes might have exaggerated pharmacological or toxic responses to ACP-196 or dexamethasone or that those receiving inducers of these enzymes might have reduced ACP-196 or dexamethasone activity. A list of inhibitors or inducers of CYP3A4 is provided in Appendix 3. Subjects receiving concomitant medications that are inhibitors or inducers of these isoenzymes should have therapeutically equivalent drugs that do not inhibit these enzymes substituted if possible (particularly if the

coadministered agents are strong inhibitors or inducers). If substitution is not possible, investigators should carefully monitor for toxicity or loss of ACP-196 activity and appropriately alter ACP-196 administration consistent with protocol recommendations for dose modification in response to ACP-196-related adverse events (see Section 3.5.3).

The study medical monitor should be consulted if there are questions regarding the potential for drug-drug interactions with ACP-196.

3.7.3 Reproductive Toxicity

Reproductive toxicity studies have not been done with ACP-196. Therefore, subjects with reproductive potential who are sexually active must use acceptable methods of contraception during the study and for 30 days after the last dose of ACP-196. Examples of acceptable methods of contraception include condoms, implants, injectables, combined oral contraceptives, intrauterine devices, true sexual abstinence, or sterilized partner. Note that periodic abstinence, eg, calendar, ovulation, symptothermal, postovulation methods or withdrawal, are not acceptable methods of contraception.

Subjects should promptly notify the investigator if they, or their partner, become pregnant during this period. If a female subject becomes pregnant during the treatment period, she must discontinue ACP-196 immediately. Pregnancy in a female subject or a male subject's partner must be reported (see Section 6.2.3). Male subjects must agree to refrain from sperm donation during the study and for 30 days after the last dose of study drug.

3.7.4 Overdose Instructions

For any subject experiencing an ACP-196 overdose (administration of a dose ≥ 1.5 times the highest intended dose level in the clinical study protocol), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered.

The Acerta Pharma Medical Monitor should be contacted if a study drug overdose occurs.

3.8 STOPPING RULES

All study participants may receive ACP-196 indefinitely as long as they are safely benefitting. However:

- Any subject has the right to withdraw from the study at any time.
- Any subject who has objective evidence of definitive MM progression while receiving study treatment at the highest individual tolerable dose level allowed in the protocol (total dose = 400 mg of ACP-196 plus dexamethasone) (see Section 3.5.5) should be withdrawn from the study treatment. Note: If there is uncertainty regarding whether there is MM progression, the subject should continue study treatment and remain under close observation (eg, evaluated at 4- to 8-week intervals) pending confirmation of progression. In particular, worsening of constitutional symptoms in the absence of objective evidence of worsening MM will not be considered definitive disease progression; in such subjects, both MM-related and non-MM-related causes for the constitutional symptoms should be considered. Transient worsening of disease during temporary interruption of study therapy (eg, for intercurrent illness) may also not indicate definitive disease progression. In these instances, relevant clinical, laboratory, and/or radiographic assessment should be attempted to document whether definitive disease progression has occurred. If subsequent evaluations suggest that the subject has experienced persistent definitive disease progression, then the date of progression will be the timepoint at which progression was first objectively documented.
- Any subject is unable to tolerate a second rechallenge with protocol-described, dose-modified levels (see Section 3.5.5) should be withdrawn from the study treatment unless continued therapy is permitted by the Acerta Pharma medical monitor.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the Acerta Pharma medical monitor. Such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be removed from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment

in circumstances that increase risk or substantially compromise the interpretation of study results.

- The investigator, in consultation with the Acerta Pharma medical monitor, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

Subjects who discontinue study therapy will continue on study for follow-up of safety (Section 4.3) and time-to-next therapy for MM unless they withdraw consent for further follow-up. Thus, all subjects receiving ≥ 1 dose of study drug will be followed during the immediate posttherapy and long-term follow-up assessments unless the subject withdraws consent for such follow-up to be conducted. The date the subject is withdrawn from study treatment or from the study (including long-term follow-up) and the reason for discontinuation will be recorded and also should be described on the appropriate electronic case report form (eCRF).

3.9 DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the sponsor's Pharmacovigilance Committee procedures. Adverse events and SAEs will be reviewed internally on an ongoing basis to identify safety concerns. Quarterly conference calls with the investigators will be conducted to discuss study progress, obtain investigator feedback and exchange, and discuss "significant safety events" (ie, AEs leading to dose reductions, related SAEs, and deaths).

4.0 STUDY ACTIVITIES AND ASSESSMENTS

The schedule of events is provided in Appendix 4. Descriptions of the scheduled evaluations are outlined below and complete information on study drug and dosing is provided in Section 3.5.

Before study entry, throughout the study, and at the follow-up evaluation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated.

4.1 DESCRIPTION OF PROCEDURES

4.1.1 Informed Consent

The subject must read, understand and sign the IRB/IEC approved ICF confirming his or her willingness to participate in this study before initiating any screening activity that is not standard of care. Subjects must also grant permission to use protected health information.

4.1.2 Medical History

The subject's complete history should be collected and recorded through review of medical records and by interview. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer treatments, and responses and duration of response to these treatments, also will be recorded.

4.1.3 Adverse Events

The accepted regulatory definition for an AE is provided in Section 6.1 All medical occurrences from the time of first dose that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 6.2.

4.1.4 Concomitant Medications and Therapy

All concomitant medications and procedures from within 21 days before the start of study drug administration through 30 days after the last dose of study drug should be documented.

4.1.5 Confirmation of Eligibility

Subject eligibility for enrollment will be assessed per Section 3.4. All screening procedures, unless otherwise indicated, should be completed within 21 days of the first dose of study drug.

4.1.6 ECOG Performance Status

The ECOG performance index is provided in Appendix 1.

4.1.7 Physical Examination, Vital Signs, Height & Weight

The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes,

ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams, including tumor assessments by palpation, will be done during the treatment period and at the safety follow-up visits.

Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) will be assessed after the subject has rested in the sitting position.

4.1.8 Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at screening or up to 30 days before the main screening procedures. Per the current response criteria (Durie 2006), a bone marrow aspirate/biopsy will also be required at any time on study to confirm a complete response (CR). The baseline bone marrow aspirate/biopsy will used for immunohistochemistry and/or flow cytometry, cytogenetics, and FISH. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572. De-identified copies of all bone marrow biopsy/aspirate results may be requested by the sponsor.

When available, any unused bone marrow tissue will be used for PD testing. PD testing will be done by the sponsor.

4.1.9 Electrocardiogram

Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs. At screening, results from the sites ECG machine (12-lead; triplicates taken ≥ 1 minute apart) will be averaged to determine eligibility and must meet the eligibility criteria of QTc ≤ 480 msec.

4.1.10 Urine Pregnancy Test

Pregnancy tests will be required only for women with childbearing potential. If positive, pregnancy must be ruled out by ultrasound. Testing will be done by a central laboratory as listed on the investigator's form FDA 1572.

4.1.11 Hematology

Hematology studies must include complete blood count (CBC) with differential and platelet and reticulocyte counts. Testing will be done by a central laboratory as listed on the investigator's form FDA 1572.

4.1.12 Serum Chemistry

Serum chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), bone-specific alkaline phosphatase, calcium, chloride, creatinine, C-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time, then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be done by a central laboratory as listed on the investigator's form FDA 1572.

4.1.13 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, N-terminal telopeptide, and glucose. Testing will be done by a central laboratory as listed on the investigator's form FDA 1572.

4.1.14 T/B/NK Cell Count

Flow cytometry testing for $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD16/56^+$ cells. Testing will be done by a central laboratory as listed on the investigator's form FDA 1572.

4.1.15 Disease Markers

Testing for serum M-protein levels (by serum protein electrophoresis [SPEP] and serum immunofixation electrophoresis [SIFE]), serum-free light chains (SFLC), urine M-protein levels (by urine serum protein electrophoresis [UPEP] and urine immunofixation electrophoresis [UIFE]), and serum β2-microglobulin will be done by a central laboratory as listed on the investigator's form FDA 1572.

4.1.16 Skeletal Survey

Standard lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri are required at screening or baseline (ie, before the first dose of study drug). Radiographic imaging and analysis will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

4.1.17 Pharmacodynamics

Blood samples and bone marrow, when available, will be used for PD testing (eg, Btk occupancy and B-cell activation). Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be done by the sponsor.

4.1.18 Pharmacokinetics

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory. The PK sampling timepoints are provided in Table 4-1.

Table 4-1. Pharmacokinetic Sample Schedule

			HOURS POSTDOSE					
Cycle	**Day**	**Predose**	**0.5 (±5 min)**	**0.75 (±5 min)**	**1 (±5 min)**	**2 (±10 min)**	**4 (±10 min)**	**6 (±10 min)**
1	**1**	X	X	X	X	X	X	X
	8	X			X			
	15	X			X			
	22	X	X	X	X	X	X	X
	28	X			X			

Note: These timepoints are relative to the morning dose.

4.1.19 Tumor Assessment

Baseline myeloma assessments will consist of:

- M-protein determination using both of the following procedures:
  - SPEP and SIFE
  - UPEP and UIFE (all using the same 24-hour urine collection)
- SFLC
- Plasmacytoma evaluation
- Bone marrow to quantify percent myeloma cell involvement (aspirate and biopsy required at baseline)
- Skeletal survey: lateral radiograph of the skull, anterioposterior and lateral views of the spine, and anterioposterior views of the pelvis, ribs, femora, and humeri
- β2-microglobulin

On-study myeloma assessments will consist of:

- SPEP and/or UPEP (if results were measurable at baseline); quantitative immunoglobulins if used to follow disease; immunofixation to confirm a complete response
- SFLC
- Plasmacytoma evaluation (if only measurable disease at baseline)
- Bone marrow aspirate and/or trephine bone biopsy (to confirm a complete response or if clinically indicated).

4.1.20 Study Drug Accountability

See Section 7.6.

4.2 INVESTIGATOR'S ASSESSMENT OF RESPONSE TO TREATMENT

Subjects will be evaluated by investigator review for disease response and progression according to the International Myeloma Working Group (IMWG; Durie 2006) and European Group for Blood and Marrow Transplant (EBMT; Bladé 1998) criteria as listed below. Response categories include sCR, CR, nCR, VGPR, PR, SD, and progressive disease. In addition, the number of subjects achieving the response category of MR will also be evaluated and reported. Subjects will be considered evaluable for response if they have a baseline and ≥1 adequate on-study anti-myeloma assessment obtained ≥4 weeks from the start of therapy.

Table 4-1. Response Criteria (incorporating EBMT [Bladé 1998] and IMWG [Durie 2006])

Response Subcategory	Response Criteria [a]
Complete response (CR)	• Negative immunofixation on the serum and urine and • Disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow[b].
Stringent complete response (sCR)	• CR as defined above plus • Normal FLC ratio and • Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c].
Near complete response (nCR)	• Meeting the criteria for CR, except that the persistence of original monoclonal protein by immunofixation while absence of monoclonal protein on serum or urine protein electrophoresis.

Very good partial response (VGPR)	• Serum and urine M-component detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-component plus urine M-component < 100 mg per 24 h.
Partial response (PR)	• ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 h • If the serum and urine M-protein are unmeasurable at baseline, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are unmeasurable at baseline, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minor response (MR)	• MR includes subjects in whom some, but not all, criteria for PR are fulfilled providing the remaining criteria satisfy the requirements for MR. • Requires all of the following: ○ ≥ 25% to ≤ 49% reduction in the level of serum monoclonal protein for ≥ 2 determinations 6 weeks apart. ○ If present, a 50% to 89% reduction in 24-hour light chain excretion, which still exceeds 200 mg/24 h, for ≥ 2 determinations 6 weeks apart. ○ 25-49% reduction in the size of plasmacytomas (by clinical or radiographic examination) for ≥ 6 weeks. ○ No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Stable disease - SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	• Not meeting criteria for CR, VGPR, MR, PR or progressive disease
Progression Subcategory	**Progression Criteria[d]**
Progressive disease[a] —To be used for calculation of duration of response and progression-free survival end points for all subjects including those in CR (includes primary progressive disease and disease progression on or off therapy)[g]	Laboratory or biochemical relapse or progressive disease: requires the occurrence of ≥ 1 of any of the following: • Increase of ≥ 25% from lowest response value in serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)[e]. • Urine M-component and/or (the absolute increase must be ≥200 mg/24 h). • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL. • Bone marrow plasma cell percentage: the absolute % must be ≥ 10%[c]. • Definite development of new bone lesions or soft tissue

	plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.

Abbreviations: EBMT = European Group for Blood and Marrow Transplant; IMWG = International Myeloma Working Group; FLC = (serum) free light chains
Note: * Note clarification to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such subjects is defined as a > 90% decrease in the difference between involved and uninvolved free light chain FLC levels

a. All response categories require 2 consecutive assessments made at ≥4 weeks after the start of study therapy and anytime before the institution of any new therapy after study therapy; CR and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
b. Confirmation with repeat bone marrow biopsy not needed
c. Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.
d. All relapse categories require 2 consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
e. For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.
f. Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
g. For purposes of calculating time to progression and progression-free survival, CR subjects should also be evaluated using criteria listed above for progressive disease.

4.3 SAFETY FOLLOW-UP VISIT

Each subject should be followed for 30 (±7) days after his or her last dose of study drug (ie, the “safety follow-up visit”) to monitor for resolution or progression of AEs (see Section 6.2.5) and to document the occurrence of any new events; unless, the subject receives a new anticancer therapy within this timeframe. Subjects who withdraw consent should still be encouraged to complete the safety follow-up assessments, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Appendix 4) describes the procedures required for the safety follow-up.

4.4 MISSED EVALUATIONS

Missed evaluations should be rescheduled and performed as close to the original scheduled date as possible. An exception is made when rescheduling becomes, in the investigator’s opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

5.0 STATISTICAL METHODS OF ANALYSIS

5.1 GENERAL CONSIDERATIONS

Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate. Analyses will be done by dosing regimen and overall.

5.2 SAMPLE SIZE CONSIDERATIONS

This study will assess safety, PK, PD, and antitumor activity of ACP-196 alone or in combination with dexamethasone. Subjects will be equally randomized into 1 of the 2 dosing regimens (ACP-196 monotherapy or ACP-196 + dexamethasone) as an efficient method for allocating patients into these regimens. The study is not formally designed to compare these regimens but rather to obtain descriptive information that can be used in support of further ACP-196 development.

While the primary objective of this study is to determine the safety in each of the 2 dosing cohorts, the sample size has been determine to independently evaluate the activity of each dosing regimen. The trial seeks to exclude an uninteresting ORR of $\leq$ 15% (ie, the response rate that might be associated with single-agent dexamethasone therapy [Anderson 2013]) in favor a target response rate of $\geq$ 40%. Considering a sample size of 19 subjects per cohort, the power to detect the difference between a null-hypothesis response rate of 15% and an alternative-hypothesis response rate of 40% with a 0.025 one-sided significance level is 84% using a one-group, chi-square test and 69% using a one-group, exact binomial test. A sample size of 19 subjects per cohort will also provide a 97.5% 1-sided confidence interval centered around an expected ORR of 40% that excludes an ORR of 18.6% as a lower bound.

5.3 DEFINITION OF ANALYSIS SETS

The following definitions will be used for the efficacy and safety analysis sets.

- **Safety analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug.
- **Per-protocol (PP) analysis set:** All enrolled subjects who receive ≥ 1 dose of study drug, have sufficient baseline measurements, and undergo ≥ 1 assessment for the endpoint of interest (eg, response and PK/PD parameters) after treatment.

The safety analysis set will be used for evaluating the safety and efficacy parameters in this study (with the exception of assessment of duration of response). The PP analysis sets will be analyzed for efficacy and PK/PD parameters in this study.

5.4 MISSING DATA HANDLING

No imputation of values for missing data will be performed except that missing or partial start and end dates for AEs and concomitant medication will be imputed according to prespecified, conservative imputation rules. Subjects lost to follow-up (or drop out) will be included in statistical analyses to the point of their last evaluation.

5.5 ENDPOINT DATA ANALYSIS

5.5.1 Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent AEs will be reported in each treatment group by MedDRA System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event (per CTCAE, v4.03) and by relationship to study drug.

Laboratory shift tables containing counts and percentages will be prepared by treatment assignment, laboratory parameter, and time. Summary tables will be prepared for each laboratory parameter. Figures of changes in laboratory parameters over time will be generated.

Results of vital sign assessments and physical exams will be tabulated and summarized.

5.5.2 Demographics and Baseline Characteristics

Additional analyses will include summaries of subject demographics, baseline characteristics, compliance, and concurrent treatments. Concomitant medications will be coded according to the World Health Organization (WHO) Drug Dictionary and tabulated.

5.5.3 Analysis of Efficacy Parameters

5.5.3.1 Response Rate

The individual and composite endpoints of response and progression will be determined. Tumor control will be documented at each assessment by response category (eg, CR, sCR, nCR, VGPR, PR, MR, SD, and disease progression) as defined for each response parameter, date that response is first documented, and date of MM disease progression.

ORR will be defined as the proportion of subjects who achieve a CR, sCR, nCR, VGPR, PR, or MR. ORR will be calculated and the corresponding 97.5% one-sided confidence interval will be derived.

5.5.3.2 Duration of Response

The duration of overall response defined as the interval from the first documentation of CR, sCR, nCR, VGPR, PR, or MR to the earlier of the first documentation of definitive disease progression or death from any cause. Kaplan-Meier methods will be used to estimate event-free curves and corresponding quantiles (including the median). Data from surviving, nonprogressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of definitive MM progression was objectively documented. Data from subjects who have MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time before the missing assessments that lack of MM progression was objectively documented.

5.5.3.3 Progression-free Survival

Progression-free survival is defined as the interval from the start of ACP-196 therapy to the earlier of the first documentation of objective MM disease progression or death from any cause. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of MM progression was objectively documented. Data from subjects who have MM progression or die after ≥ 2 consecutive missing tumor assessments will be censored at the last time prior to the missing assessments that lack of MM progression was objectively documented.

5.5.3.4 Time-to-Next Treatment

Time-to-next treatment defined as the time from start of ACP-196 therapy for MM on this protocol to the start of the next treatment for MM. Kaplan-Meier methods will be used to estimate the event-free curves and corresponding quantiles (including the median). Data from subjects who have not received subsequent therapy for MM will be censored at the earliest of death or the last time that lack of administration of a new therapy for MM was objectively documented.

5.5.4 Analysis of Pharmacokinetic/Pharmacodynamic Parameters

The plasma PK of ACP-196 and dexamethasone will be characterized using noncompartmental analysis. The following PK parameters will be calculated, whenever possible, from plasma concentrations of ACP-196:

- $AUC_{(0-t)}$ Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t).
- $AUC_{(0-24)}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation.
- $AUC_{(0-\infty)}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t / \lambda_z$, where λ_z is the apparent terminal elimination rate constant.
- C_{max} Maximum observed plasma concentration
- T_{max} Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- λ_z Terminal elimination rate constant (whenever possible)
- Cl/F Oral clearance

Missing dates or times may be imputed for PK and PD samples if the missing values can be established with an acceptable level of accuracy based on other information obtained during the visit in question. If PK and PD sampling for a given subject is not performed according to protocol instructions that subject may be excluded from the PK and PD analyses.

The PK parameters will be tabulated and summarized using descriptive statistics.

For each PD variable, the concentration at each assessment will be described. The change from baseline to each assessment will be summarized. The best change from baseline during the study will also be summarized. As appropriate, the on-treatment values will be compared with the pretreatment baseline values using paired t-tests. P-values of ≤ 0.05 will be considered significant.

5.5.5 Explorative or Correlative Analyses

Additional PK or PD analyses may be performed, as deemed appropriate.

Correlations between subject characteristics and outcome measures and correlations among outcomes measures will be explored using regression models or other appropriate techniques. Such evaluations may assist in determining if baseline parameters or early changes in PD biomarkers are predictive of response to Btk inhibition.

6.0 ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and recording AEs and SAEs; measurements of protocol-specified hematology, clinical chemistry, urinalysis, and other

laboratory variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drug(s).

6.1 DEFINITIONS

6.1.1 Adverse Events

An AE is any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational (medicinal) product or other protocol-imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with MM that were not present before the AE reporting period (see Section 6.2.1)
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies)
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period.

Abnormal laboratory values should not be reported as AEs; however, any clinical consequences of the abnormality (eg, withdrawal from study) should be reported as AEs.

6.1.2 Serious Adverse Event

The terms “severe” and “serious” are not synonymous. Severity (or intensity) refers to the grade of an AE (see below). “Serious” is a regulatory definition and is based on subject or event outcome or action criteria usually associated with events that pose a threat to a subject’s life or functioning. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities.

An AE should be classified as an SAE if it meets any 1 of the following criteria:

- It results in death (ie, the AE actually causes or leads to death).

- It is life-threatening (ie, the AE, in the view of the investigator, places the subject at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death).
- It requires or prolongs in-patient hospitalization.
- It results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the investigational product.
- It is considered a significant medical event by the investigator based on medical judgment (eg, may jeopardize the subject or may require medical/surgical intervention to prevent 1 of the outcomes listed above).

6.1.3 Severity

Definitions found in the CTCAE version 4.03 or higher will be used for grading the severity (intensity) of AEs. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

6.2 DOCUMENTING AND REPORTING OF ADVERSE AND SERIOUS ADVERSE EVENTS

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the eCRF. All SAEs also must be reported on the SAE/Product Complaint form (see Section 6.2.4).

6.2.1 Adverse Event Reporting Period

The AE reporting period for this study begins when the subject receives the first dose of study medication and ends with the safety follow-up visit. An exception to this reporting period is any AE occurring due to a protocol-defined screening procedure. Fatal AEs occurring 30 days after the last dose of ACP-196 ***AND*** assessed by the investigator as related to ACP-196 must be reported as an SAE.

6.2.2 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation time points during the study. All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE/Product Complaint form.

Disease progression itself is not considered an adverse event; however, signs and symptoms of disease progression may be recorded as AEs or SAEs.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (ie, ACP-196, dexamethasone, or both; see following guidance), and any actions taken. The relationship of AEs to the study drug will be assessed by means of the question: 'Is there a reasonable possibility that the event may have been caused by the study drug?' Answer Yes or No.

See Appendix 2 for more detail on assessing relationship.

6.2.3 Pregnancy

The investigator should report all pregnancies and pregnancies in the partners of subjects within 24 hours using the Pregnancy Report Form Part I. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported using the SAE report form, according to the usual timelines and directions for SAE reporting (Section 6.2.4).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 30 days after the last dose of study medication will be reported, followed to conclusion, and the outcome reported.

Monitoring of the pregnancy should continue until conclusion of the pregnancy at which point the Pregnancy Report Form Part II must be completed and submitted to Acerta Drug Safety. If a viable baby is born, then 2 months postpartum the Pregnancy Report Form Part III must be completed and submitted.

Pregnancy itself is not regarded as an AE unless there is suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Likewise, elective abortions without complications are not considered AEs. Any SAEs associated with pregnancy (eg, congenital abnormalities/birth defects/spontaneous miscarriages or any other serious events) must additionally be reported as such using the SAE report form.

Subjects should be instructed to immediately notify the investigator of any pregnancies. Any female subjects receiving ACP-196 who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

6.2.4 Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on an SAE/Product Complaint form. Paper SAE/Product Complaint forms must be emailed or faxed to Acerta Pharma Drug Safety, or designee, within 24 hours of the discovery of the event or information. Alternatively, electronic SAE reporting may be available through the protocol-specific electronic data capture system. These must also be completed within 24 hours of the discovery of the SAE. Acerta Pharma may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results).

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. The primary cause of death on

the autopsy report should be the term reported. Autopsy and postmortem reports must be forwarded to Acerta Pharma Drug Safety, or designee, as outlined above.

If study drug is discontinued because of an SAE, this information must be included in the SAE report.

An SAE may qualify for mandatory expedited reporting to regulatory authorities if the SAE is attributable to the investigational product and is not listed in the current Investigator's Brochure (ie, an unexpected event). In this case, Acerta Pharma Drug Safety/Designee will forward a formal notification describing the SAE to all investigators. Each investigator must then notify his or her IRB/IEC of the SAE.

Drug Safety Contact Information	
Fax:	[redacted]
Email:	[redacted]

6.2.5 Type and Duration of Follow-up of Subjects After Adverse Events

All AEs and SAEs that are encountered during the protocol-specified AE reporting period should be followed to resolution, or until the investigator assesses the subject as stable, a new anticancer therapy is initiated, or the subject is lost to follow-up or withdraws consent.

7.0 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

Acerta Pharma retains the right to terminate the study and remove all study materials from a study site at any time. Specific circumstances that may precipitate such termination are:

- Unsatisfactory subject enrollment with regard to quality or quantity
- Significant or numerous deviations from study protocol requirements, such as failures to perform required evaluations on subjects and maintain adequate study records
- Inaccurate, incomplete and/or late data recording on a recurrent basis
- The incidence and/or severity of AEs in this or other studies indicating a potential health hazard caused by the study treatment

7.1 INSTITUTIONAL REVIEW BOARD AND INDEPENDENT ETHICS COMMITTEE

The investigator will submit this protocol, the informed consent, Investigator's Brochure, and any other relevant supporting information (eg, all advertising materials) to the appropriate IRB/IEC for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB/IEC approval of the protocol and informed consent; and a statement that the IRB/IEC is organized and operates according to GCP and the applicable laws and regulations; **must** be forwarded to Acerta Pharma **before** screening subjects for the study. Additionally, sites must forward a signed FDA 1572 form (Investigator Obligation Form) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB/IEC and local regulatory agency, as appropriate, before the implementation of changes in this study.

7.2 INFORMED CONSENT AND PROTECTED SUBJECT HEALTH INFORMATION AUTHORIZATION

A copy of the IRB/IEC-approved informed consent must be forwarded to Acerta Pharma for regulatory purposes. The investigator, or designee (designee must be listed on the Study Personnel Responsibility/Signature Log, see Section 7.11), **must** explain to each subject the purpose and nature of the study, the study procedures, the possible adverse effects, and all other elements of consent as defined in § 21CFR Part 50, and other applicable national and local regulations governing informed consent. Each subject must provide a signed and dated informed consent before enrollment into this study. In the case of a subject who is incapable of providing informed consent, the investigator (or designee) must obtain a signed and dated informed consent form from the subject's legal guardian. Signed consent forms must remain in each subject's study file and be available for verification by study monitors at any time.

In accordance to individual local and national subject privacy regulations, the investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Acerta Pharma and its designees, regulatory agencies, and IRBs/IECs. As the study Sponsor, Acerta Pharma will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject, or if appropriate, the subject's legal guardian. If a

subject or subject's legal guardian withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject or subject's legal guardian **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

7.3 SUBJECT SCREENING LOG

The investigator **must** keep a record that lists **all** subjects considered for enrollment (including those who did not undergo screening) in the study. For those subjects subsequently excluded from enrollment, record the reason(s) for exclusion.

7.4 CASE REPORT FORMS

Authorized study site personnel (see Section 7.11) will complete eCRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the eCRFs are accurate, complete, legible, and completed within 5 days of each subject's visit (unless required earlier for SAE reporting). The investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed.

7.5 STUDY MONITORING REQUIREMENTS

Representatives of Acerta Pharma or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data. This study is also subject to reviews or audits.

Every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/IEC, representatives of Acerta Pharma, its designated agents, and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. This includes providing by fax, email, or regular mail de-identified copies of radiology, pathology, and/or laboratory results when requested by the sponsor. A statement to this effect will be included in the informed consent and permission form authorizing the use of protected health information.

7.6 INVESTIGATIONAL STUDY DRUG ACCOUNTABILITY

ACP-196 capsules must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply ACP-196 capsules to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Acerta Pharma.

Study drug accountability records must be maintained and readily available for inspection by representatives of Acerta Pharma and are open to inspections by regulatory authorities at any time.

Each shipment of study drug will contain a Clinical Supplies Shipping Receipt Form (CSSF) that must be appended to the site's drug accountability records. Additionally a Drug Re-order Form for requesting more study drug is provided in the pharmacy binder. If it is used, then the Drug Re-order Form must also be included in the site's drug accountability records.

Contents of each shipment must be visually inspected to verify the quantity and document the condition of study drug capsules. Then the designated recipient completes and signs the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/emailing address listed on the form.

An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. study identification number (ACE-MY-001)
2. subject identification number
3. lot number(s) of ACP-196 dispensed for that subject
4. date and quantity of drug dispensed
5. any unused drug returned by the subject

At study initiation, the monitor will evaluate and approve the site's procedure for investigational product disposal/destruction to ensure that it complies with Acerta Pharma's requirements. If the site cannot meet Acerta Pharma's requirements for disposal/destruction, arrangements will be made between the site and Acerta Pharma or its representative, for return of unused investigational product. Before disposal/destruction, final drug accountability and reconciliation must be performed by the monitor.

All study supplies and associated documentation will be regularly reviewed and verified by the monitor.

7.7 RECORD RETENTION

The investigator and other appropriate study staff are responsible for maintaining all documentation relevant to the study. Mandatory documentation includes copies of study protocols and amendments, each FDA Form 1572, IRB/IEC approval letters, signed ICFs, drug accountability records, SAE forms transmitted to Acerta Pharma, subject files (source documentation) that substantiate entries in eCRFs, all relevant correspondence and other documents pertaining to the conduct of the study.

An investigator shall retain records for a period of at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified. The investigator must notify Acerta Pharma and obtain written approval from Acerta Pharma before destroying any clinical study records at any time. Acerta Pharma will inform the investigator of the date that study records may be destroyed or return to Acerta Pharma.

Acerta Pharma must be notified in advance of, and Acerta Pharma must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Acerta Pharma to store such documents in sealed containers away from the study site so that they can be returned sealed to the investigator for audit purposes.

7.8 PROTOCOL AMENDMENTS

Acerta Pharma will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/IEC together with, if applicable, a revised model ICF. If the change in any way increases the risk to the subject or changes the scope of the study, then written documentation of IRB/IEC approval must be received by Acerta Pharma before the amendment may take effect. Additionally under this circumstance, information on the increased risk and/or change in scope must

be provided to subjects already actively participating in the study, and they must read, understand, and sign any revised ICF confirming willingness to remain in the trial.

7.9 PUBLICATION OF STUDY RESULTS

Acerta Pharma may use the results of this clinical study in registration documents for regulatory authorities in the United States or abroad. The results may also be used for papers, abstracts, posters or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. The study is being conducted as part of a multicenter clinical trial. Data from all study centers shall be pooled and analyzed for publication in a final report (Primary Publication). The investigator agrees that the Primary Publication, which will be coordinated by Acerta Pharma, will be the first publication to present the pooled study results. After the Primary Publication, or if the Primary Publication is not published within 1 year of termination of the study, the investigator may freely publish or present the results of his or her work conducted under the clinical trial agreement subject to providing Acerta Pharma with the opportunity to review the contents of any proposed presentation, abstract or publication about such work, including any results of this study, 90 days in advance of any presentation or submission for publication. Within that 90-day period, Acerta Pharma may review the proposed publication to identify patentable subject matter and/or any inadvertent disclosure of its confidential information, which must be redacted from any final publication or presentation. If necessary, to permit the preparation and filing of patent applications, Acerta Pharma may elect an additional review period not to exceed 60 days.

In most cases, the principal investigators at the sites with the highest accruals of eligible subjects, who have provided significant intellectual input into the study design, shall be listed as lead authors on manuscripts and reports of study results. The Medical Monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be adjusted upon mutual agreement of the authors and Acerta Pharma.

7.10 CLINICAL TRIAL INSURANCE

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

7.11 GENERAL INVESTIGATOR RESPONSIBILITIES

The principal investigator must ensure that:

1. He or she will personally conduct or supervise the study.
2. His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
3. The study is conducted according to the protocol and all applicable regulations.
4. The protection of each subject's rights and welfare is maintained.
5. Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each subject before conducting nonstandard of care study procedures. If a subject or subject's legal guardian withdraws permission to use protected health information, the investigator will obtain a written request from the subject or subject's legal guardian and will ensure that no further data be collected from the subject.
6. The consent process is conducted in compliance with all applicable regulations and privacy acts.
7. The IRB/IEC complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
8. Any amendment to the protocol is submitted promptly to the IRB/IEC.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB/IEC according to the guidelines at each study site.
10. Electronic CRF pages are completed within 5 days of each subject's visit (unless required earlier for SAE reporting).
11. All IND Safety Reports/ Suspected Unexpected Serious Adverse Reaction (SUSAR) Reports are submitted promptly to the IRB/IEC.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge and to the IRB/IEC per their requirements.

8.0 REFERENCES

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9.0 APPENDICES

Appendix 1. Performance Status Scores

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, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am J Clin Oncol:

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

Credit: Eastern Cooperative Oncology Group Chair: Robert Comis, MD

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 23 August 2013.

Appendix 2. Adverse Event Assessment of Causality

Is there a reasonable possibility that the event may have been caused by study drug?

No___ Yes___

The descriptions provided below will help guide the principal investigator in making the decision to choose either “yes” or “no”:

No = There is no reasonable possibility that the event may have been caused by study drug.

The adverse event:

- may be judged to be due to extraneous causes such as disease or environment or toxic factors
- may be judged to be due to the subject’s clinical state or other therapy being administered
- is not biologically plausible
- does not reappear or worsen when study drug is re-administered
- does not follow a temporal sequence from administration of study drug

Yes = There is a reasonable possibility that the event may have been caused by study drug.

The adverse event:

- follows a temporal sequence from administration of study drug
- is a known response to the study drug based on clinical or preclinical data
- could not be explained by the known characteristics of the subject’s clinical state, environmental or toxic factors, or other therapy administered to the subject
- disappears or decreases upon cessation or reduction of dose of study drug
- reappears or worsens when study drug is re-administered

Appendix 3. Inhibitors of CYP3A4

Inhibitors		
Strong (≥5-fold Increase in AUC)	**Moderate (2- to 5-fold Increase in AUC)**	**Weak (1.25- to <2-fold Increase in AUC)**
Boceprevir Chloramphenicol Clarithromycin Cobicistat Conivaptan Indinavir Itraconazole Ketoconazole Lopinavir Mibefradil Nefazodone Nelfinavir Posaconazole Ritonavir Saquinavir Suboxone Telaprevir Telithromycin Voriconazole	Amprenavir Aprepitant Atazanavir Ciprofloxacin Darunavir Diltiazem Erythromycin Fluconazole Fosamprenavir Grapefruit juice[1] Imatinib Verapamil	Alprazolam Amiodarone Amlodipine Atorvastatin Bicalutamide Buprenorphine Cilostazol Cimetidine Cyclosporine Fluoxetine Fluvoxamine Ginkgo[1] Goldenseal[1] Isoniazid Nilotinib Oral contraceptives Ranitidine Ranolazine Tipranavir Zileuton
Inducers		
Strong (≥80% Decrease in AUC)	**Moderate (50 to 80% Decrease in AUC)**	**Weak (20 to 50% Decrease in AUC)**
Avasimibe Carbamazepine Phenytoin Rifampin St. John's wort[1]	Bosentan Efavirenz Etravirine Modafinil Nafcillin	Amprenavir Aprepitant Armodafinil Echinacea[1] Pioglitazone Prednisone Rufinamide

1. Food or herbal product
2. Primary reference: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

Appendix 4. Schedule of Assessments

	Screening[a]	Cycle 1					Cycle 2		Cycle 3	Cycle 4	Cycles 5-12[b]	Follow Up[c]	LTFU[q]
		Days (± 2)					Days (± 2)		Days (± 2)	Days (± 2)	Days (± 2)	Days (± 2)	
		1	8	15	22	28	15	28	28	28	28		
Informed consent	x												
Confirm eligibility	x												
Medical history	x												
PE[d]/Vital signs[e]/Weight	x	x	x	x	x	x	x	x	x	x	x	x	
ECOG status	x	x	x	x	x	x	x	x	x	x	x	x	
ECG[f]	x	x											
Lab assessments:													
Urine pregnancy test[g]	x											x	
Hematology[h]	x	x[r]	x	x	x	x	x	x	x	x	x	x	
Serum chemistry[i]	x	x[r]	x	x	x	x	x	x	x	x	x	x	
Urinalysis[j]	x					x		x	x	x	Every 2 mos		
T/B/NK cell count[k]		x[r]	x	x		x		x			Every 6 mos		
Disease markers[l]	x			x		x		x	x	x	Every 2 mos	x	
Bone marrow (aspirate/biopsy) /Skeletal survey[p]	x							Bone Marrow only	As clinically indicated or to confirm a CR	As clinically indicated or to confirm a CR	As clinically indicated or to confirm a CR		
Pharmacodynamics		x[m]	x[m]			x[n]		x[n]				x	
Pharmacokinetics[o]		x	x	x	x	x							
ACP-196/ dexamethasone dispensed		x	x	x	x	x	x	x	x	x	x		
Study drug compliance		x	x	x	x	x	x	x	x	x	x		
Tumor assessment[p]	x					x		x	x	x	x		
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse events		x	x	x	x	x	x	x	x	x	x	x	
Time-to-next treatment													x

Abbreviations: CR = complete remission; ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, Ig = immunoglobulin; mos = months; PE = physical exam; LTFU = long-term follow up

Footnotes for ACE-MY-001 Schedule of Study Activities:

a. Screening tests should be performed within 21 days before the first administration of study drug, unless otherwise indicated.
b. Any subjects who have not progressed while receiving study drug treatment, may be eligible to enroll into a long-term follow up study and continue to receive ACP-196.
c. A 30-day (± 7 days) safety follow-up visit is required when subjects discontinue study drug unless they start another anticancer therapy within that timeframe.
d. The screening physical examination will include, at a minimum, the general appearance of the subject, height (screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Symptom-directed physical exams are done thereafter.
e. Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be assessed after the subject has rested in the sitting position.
f. Subjects should be in supine position and resting for ≥ 10 minutes before study-related ECGs. 12-lead electrocardiogram (ECG) will be done in triplicate (≥ 1 minute apart) at screening. The calculated QTc average of the 3 ECGs must be ≤ 480 ms for eligibility.
g. Women of childbearing potential only. If positive, pregnancy must be ruled out by ultrasound to be eligible.
h. Hematology includes complete blood count with differential and platelet and reticulocyte counts. Cycle 1 Day 1 hematology does not need to be repeated if screening hematology was within 5 days.
i. Serum chemistry: albumin, alkaline phosphatase, bone-specific alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, C-terminal telopeptide, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. Cycle 1 Day 1 serum chemistry does not need to be repeated if screening hematology was within 5 days.
j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, N-terminal telopeptide, and glucose.
k. T/B/NK cell count (ie, CD3, CD4, CD8, CD19, CD16/56). During Cycle 5-12, only done at end of Cycle 6 and 12.
l. Refer to Sectin 4.1 for a list of myeloma disease markers.
m. Pharmacodynamic samples are drawn predose and 4 hours (±10 minutes) postdose on the days indicated. Note: These timepoints are relative to the morning dose.
n. Pharmacodynamic samples are drawn predose on the days indicated.
o. Pharmacokinetic samples are drawn per Table 4-1.
p Refer to Section 4-2. Bone marrow aspirate/biopsy and skeletal survey are required at baseline (ie, before the first dose of study drug). Thereafter they are required as indicated in the table above.
q. Subjects who discontinue study therapy will continue on study for follow-up of safety and time-to-next therapy for myeloma unless they withdraw consent for further follow-up.
r. The indicated samples at this timepoint (Cycle 1 Day 1) must be drawn predose.