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Title of Invention

Methods of Use of ACP-196

Attorney Docket Number (if applicable)

055112-5000

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Product: ACP-196
Date: 01 October 2013
Protocol: ACE-CL-001

**A Phase 1, Multicenter, Open-label, and Dose-escalation Study
of ACP-196 in
Subjects with Chronic Lymphocytic Leukemia**

Protocol Number:	ACE-CL-001
IND Number:	118717
Drug Product:	ACP-196
Medical Monitor:	Ahmed Hamdy, MD a.hamdy@acerta-pharma.com 831.421.1757 (cell)
sponsor:	Acerta Pharma, LLC 1509 Industrial Rd San Carlos, CA 94070
Protocol Date:	01 October 2013

Confidentiality Statement

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Product: ACP-196
Date: 01 October 2013
Protocol: ACE-CL-001

Investigator's Agreement

I have read the attached protocol entitled "A Phase 1, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia" and agree to abide by all provisions set forth therein.

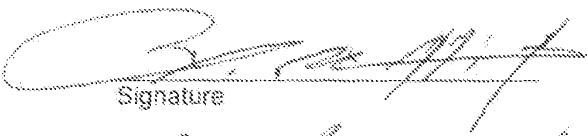
I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice and applicable FDA regulations/guidelines set forth in 21 CFR Parts 11, 50, 54, 56, and 312.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Acerta Pharma, LLC.

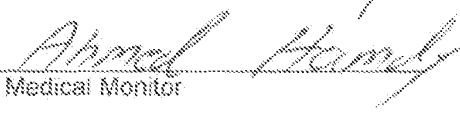
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Print Name of Principal Investigator

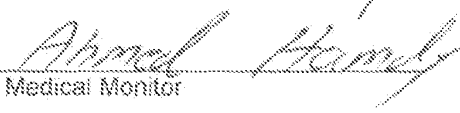
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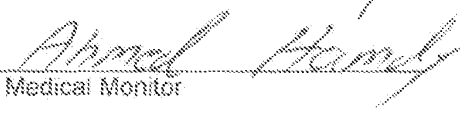
Signature



Medical Monitor



Date (DD Month YYYY)



Date (DD Month YYYY)

Product: ACP-196
Date: 01 October 2013
Protocol: ACE-CL-001

Protocol Synopsis

Protocol Number:	ACE-CL-001
Study Drug:	ACP-196
Protocol Title:	A Phase 1, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia
Phase:	Phase 1
Comparator:	None
Background and Rationale for Study	Clinical studies have shown that targeting the B-cell receptor (BCR) signaling pathway by inhibiting Bruton's tyrosine kinase (BTK) produces significant clinical benefit in patients with non-Hodgkin lymphoma (NHL). Acerta Pharma LLC (Acerta Pharma) has developed a novel second generation BTK inhibitor, ACP-196, that achieves significant oral bioavailability and potency. The purpose of this study is to evaluate the safety and efficacy of ACP-196 in treating subjects with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).
Study Design:	This study is a multicenter, open-label, nonrandomized, sequential group, dose-escalation study. The following dose cohorts will be evaluated: Cohort 1: 100 mg/day for 28 days (= 1 cycle) Cohort 2: 175 mg/day for 28 days (= 1 cycle) Cohort 3: 250 mg/day for 28 days (= 1 cycle) Cohort 4: 350 mg/day for 28 days (= 1 cycle) Cohort 5: 450 mg/day for 28 days (= 1 cycle) Cohort 6: TBD mg/day for 28 days (= 1 cycle) Each cohort will be enrolled sequentially with 6 subjects per cohort. If ≤ 1 dose-limiting toxicity (DLT; see Section 3.8 for definition) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Subjects may be enrolled in the next cohort if 4 of the 6 subjects enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining 2 subjects are completing evaluation. If ≥ 2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the maximum tolerated dose (MTD) will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Dose escalation will end when either the MTD is achieved or at 3 dose levels above full BTK occupancy, whichever occurs first. Full BTK occupancy is

	defined as ACP-196 active-site occupancy of > 80% (average of all subjects in cohort) at 24 hours postdose. Should escalation to Cohort 6 be necessary, the dose will be determined based on the aggregate data from Cohorts 1 to 5, which includes safety, efficacy, and pharmacokinetic (PK)/pharmacodynamic (PD) results. The dose for Cohort 6 will not exceed 900 mg/day. Treatment with ACP-196 may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. Subjects with disease progression will be removed from the study. All subjects who discontinue study drug will have a safety follow-up visit 30 ($\pm$7) days after the last dose of study drug unless they have started another cancer therapy within that timeframe. Radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 12 and at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment. All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) due to the pancreatic findings in the 28-day Good Laboratory Practice (GLP) rat toxicity study. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected during the first week of treatment for PK/PD assessments. Electrocardiograms (ECGs) will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6. ECGs are done in triplicate for screening only. Thereafter, single ECGs are done unless a repeat ECG is required (see Section 4.1 for a more detailed description of ECG assessments). Refer to Table 4-1 for a comprehensive list of study assessments and their timing. A study schema is provided at the end of this synopsis.
Definition of Dose-limiting Toxicity	A DLT will be defined as any of the following events (if not related to disease progression): - Any Grade $\geq$ 3 nonhematologic toxicity (except alopecia) persisting despite receipt of a single course of standard outpatient symptomatic therapy (eg, Grade 3 diarrhea that responds to a single, therapeutic dose of Imodium® would not be considered a DLT) - Grade $\geq$ 3 prolongation of the corrected QT interval (QTc), as determined by a central ECG laboratory overread - Grade 4 neutropenia (absolute neutrophil count

	[ANC] < 500/μL) lasting > 7 days after discontinuation of therapy without growth factors or lasting > 5 days after discontinuation of therapy while on growth factors (ie, Grade 4 neutropenia not lasting as long as specified will not be considered a DLT) • Grade 4 thrombocytopenia (platelet count < 20,000/μL) lasting > 7 days after discontinuation of therapy or requiring transfusion (ie, Grade 4 thrombocytopenia not lasting as long as specified will not be considered a DLT) • Dosing delay due to toxicity for > 7 consecutive days
Study Objectives:	Primary Objective: • Establish the safety and the MTD of orally administered ACP-196 in subjects with CLL/SLL • Determine the PK of orally administered ACP-196 and identification of its major metabolite • Measure PD parameters including drug occupancy of BTK, the target enzyme, and effect on biologic markers of B-cell function Secondary Objective: Evaluate tumor response
Efficacy Parameters:	• Overall response rate • Duration of response • Progression-free survival
Safety Parameters:	• DLTs and MTD • Frequency, severity, and attribution of adverse events (AEs) based on the Common Terminology Criteria for Adverse Events (CTCAE v4.03) for nonhematologic AEs (See Table 5-1 for the grading scale used for hematologic toxicities)

Pharmacokinetic Parameters:	The plasma PK of ACP-196 and a metabolite 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) • $t_{1/2}$: 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) 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:	Twenty-four to 36 subjects depending on dose escalation into subsequent cohorts.
Inclusion Criteria:	• Men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL; however, subjects with 17p deletion are eligible if they have relapsed after, or been refractory to, 1 prior treatment for CLL/SLL. • Body weight ≥ 60 kg. • ECOG performance status of ≤ 2. • Agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children. • 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 or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction. - Any immunotherapy within 4 weeks of first dose of study drug. - For subjects with recent chemotherapy or experimental therapy the first dose of study drug must occur after 5 times the half-life of the agent(s). - Relapsed after, or refractory to, prior BTK inhibitor therapy. - Concomitant use of medicines known to cause QT prolongation or Torsades de pointes (see Appendix 1). - Central nervous system (CNS) involvement by lymphoma - 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.

Product: ACP-196
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	• ANC < 0.75 x 10⁹/L or platelet count < 50 x 10⁹/L unless there is bone marrow involvement. • Creatinine > 1.5 x institutional upper limit of normal (ULN); total bilirubin > 1.5 x ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 x ULN unless disease related. • Serum amylase > 1.5 x ULN or serum lipase > 1.5 x ULN. • Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and QTc ≥ 480 ms • Lactating or pregnant.
Dosage Form and Strength:	ACP-196 is provided as 25-mg hard gelatin capsules prepared using standard pharmaceutical grade excipients. The color of the capsules is Swedish orange.
Dose Regimen/Route of Administration:	ACP-196 is an orally administered product. ACP-196 will be administered once daily on an empty stomach defined as no food 2 hours before and 30 minutes after dosing.
Statistics:	No formal statistical tests of hypotheses will be performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate. Twenty-four to 36 evaluable subjects will be enrolled in this study. The trial design is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1.

LIST OF ABBREVIATIONS

λ_z	terminal elimination rate constant
AE(s)	adverse event(s)
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the curve
BCR	B-cell receptor
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
cGMP	current Good Manufacturing Practices
Cl/F	oral clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed drug concentration
CNS	central nervous system
CR	complete remission (response)
CRi	CR with incomplete blood count recovery
CSSF	Clinical Supplies Shipping Form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
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
FDG	[¹⁸ F]fluorodeoxyglucose
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
G-CSF	granulocyte colony-stimulating factor
Hb	hemoglobin
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
ICH	International Conference on Harmonisation
Ig	immunoglobulin
IgHV	immunoglobulin heavy-chain variable
IRB	Institutional Review Board
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mos	months
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma
PBMCs	peripheral blood mononuclear cells
PE	physical exam
PET	positron emission tomography
PD	pharmacodynamics
PK	pharmacokinetics
PO	per os (oral)
PP	per-protocol (analysis set)
PR	partial remission (response)
QTc	corrected QT interval
SAE(s)	serious adverse event(s)
SD	stable disease
SLL	small lymphocytic lymphoma
SPD	sum of the product of the diameters
$t_{1/2}$	half life
TBD	to be determined
T_{max}	time to maximum drug concentration
ULN	upper limit of normal
WHO	World Health Organization
XLA	X-linked agammaglobulinemia

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1. INTRODUCTION

1.1. Role of BTK in Lymphoid Cancers

Bruton's 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.

1.2. BTK Inhibition as a Therapy for Lymphoid Cancers

Ibrutinib (PCI-32765), a first-generation oral, small-molecule BTK inhibitor has been developed clinically for the treatment for B-cell malignancies and is currently under review in the United States for marketing approval. The nonclinical and early clinical findings with ibrutinib have created the foundation on which second-generation agents, such as ACP-196, will be developed.

In Phase 1/2 clinical testing as a monotherapy in subjects with hematologic malignancies [Advani 2013, Byrd 2013, Wang 2013], ibrutinib was generally well tolerated at dose levels through 840 mg (the highest dose tested). No maximum tolerated dose (MTD) was apparent within the tested dose range. Furthermore, subjects typically found the drug tolerable over periods extending to > 2 years. No subject had tumor lysis syndrome. No overt pattern of myelosuppression was associated with ibrutinib treatment. No drug-related reductions in circulating CD4⁺ cells or serum immunoglobulins were noted. Adverse events with an apparent relationship to study drug included diarrhea and rash.

In subjects with heavily pretreated non-Hodgkin lymphoma (NHL), ibrutinib showed substantial antitumor activity, inducing durable regressions of lymphadenopathy and splenomegaly in most subjects. Improvements in disease-associated anemia and thrombocytopenia were observed. The pattern of changes in subjects with CLL was notable. Single-agent ibrutinib caused rapid and substantial reductions in lymph node size concomitant with a redistribution of malignant sites into the peripheral blood. An asymptomatic absolute lymphocyte

count increase was observed that was maximal during the first few months of treatment and generally decreased thereafter but could be persistent in some subjects or could be seen repeatedly in subjects who had interruption and resumption of drug therapy.

Collectively, these data with ibrutinib support the potential benefits of selective BTK inhibition in the treatment of subjects with relapsed lymphoid cancers. However, 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 [Acerta Pharma data on file]. For example, ibrutinib inhibits epidermal growth factor receptor (EGFR), which may be the cause of ibrutinib-related diarrhea and rash. In addition, it is a substrate for both cytochrome P450 (CYP) enzymes 3A4/5 and 2D6, which increases the possibility of drug-drug interactions. These liabilities support the development of alternative BTK inhibitors for use in the therapy of lymphoid cancers.

1.3. 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.

1.3.1. Chemistry

ACP-196 is an imidazopyrazine analogue with a molecular weight of 465.5 g/mol. The compound has 1 stereogenic center and ACP-196 is the S-enantiomer. 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).

1.3.2. Efficacy Pharmacology

ACP-196 is currently being evaluated in an ongoing study of canine spontaneous B-cell lymphoma. Six dogs have been treated with ACP-196 2.5 mg/kg once daily oral administration for an average of 22 days (range 14 to 42 days). To date, partial remission (PR), per Veterinary Cooperative Oncology Group criteria for assessment of response in peripheral nodal lymphoma [Vali 2010], has been observed in 2 of 6 dogs. No ACP-196-related adverse events have been reported to date in this study. These findings are preliminary and similar to the clinical responses (ie, 3 dogs with PR out of 8 dogs treated) observed with ibrutinib in dogs with spontaneous B-cell lymphoma [Honigberg 2010].

1.3.3. Safety Pharmacology

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

When screened at 10 μ M 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 μ M, suggesting a low clinical risk of off-target effects. ACP-196 at 10 μ M showed no inhibition of in vitro 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 μ M, 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.

1.3.4. Drug-drug Interaction Potential

In vitro experiments evaluating loss of parent drug as catalyzed by CYPs indicated that ACP-196 is metabolized by CYP3A4.

In vitro metabolism studies using mouse, rat, dog, rabbit, monkey, and human hepatocytes incubated with ¹⁴C-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.

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 CYP enzymes.

1.3.5. In Vivo General Toxicology

To date, the toxicology program has included 28-day GLP evaluations in both rats and dogs. In the 28-day study in male and female Sprague-Dawley rats, animals received oral gavage ACP-196 doses of 30, 100, and 300 mg/kg/day. In the 28-day study in male and female beagle dogs, animals received oral ACP-196 doses 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, the 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.

1.3.6. Summary and Conclusions

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 a first-generation BTK inhibitor, ibrutinib, in

subjects with hematologic cancers; and the available nonclinical information regarding ACP-196.

The collective data support the following conclusions:

- BTK expression plays an important role in the biology of lymphoid neoplasms, which represent serious and life-threatening disorders with continuing unmet medical need.
- Clinical evaluation of ACP-196 as a potential treatment for these disorders has sound scientific rationale based on observations that the compound selectively abrogates BTK activity and shows activity in nonclinical models of lymphoid cancers. These data are supported by clinical documentation that ibrutinib, a first-generation BTK inhibitor, is clinically active in these diseases.
- Ibrutinib clinical data and ACP-196 nonclinical safety pharmacology and toxicology studies support the safety of testing ACP-196 in subjects with B-cell malignancies.

2. STUDY OBJECTIVES

2.1. Primary Objectives

- Establish the safety and the MTD of orally administered ACP-196 in subjects with CLL/SLL.
- Determine pharmacokinetics (PK) of orally administered ACP-196 and identification of its major metabolite
- Measure pharmacodynamic (PD) parameters including drug occupancy of BTK, the target enzyme, and effect on biologic markers of B-cell function

2.2. Secondary Objective

Evaluate tumor responses

3. INVESTIGATIONAL PLAN

3.1. Overall Study Design

This study is a multicenter, open-label, nonrandomized, sequential group, dose-escalation study. The following dose cohorts will be evaluated:

- Cohort 1: 100 mg/day for 28 days (= 1 cycle)
- Cohort 2: 175 mg/day for 28 days (= 1 cycle)
- Cohort 3: 250 mg/day for 28 days (= 1 cycle)
- Cohort 4: 350 mg/day for 28 days (= 1 cycle)
- Cohort 5: 450 mg/day for 28 days (= 1 cycle)
- Cohort 6: TBD mg/day for 28 days (= 1 cycle)

Each cohort will be enrolled sequentially with 6 subjects per cohort. If ≤ 1 dose-limiting toxicity (DLT; see Section 3.8 for definition) is observed in the cohort during Cycle 1, escalation to the next cohort will proceed. Subjects may be enrolled in the next cohort if 4 of the 6 subjects enrolled in the cohort completed Cycle 1 without experiencing a DLT, while the remaining 2 subjects are completing evaluation. If ≥ 2 DLTs are observed during Cycle 1, dosing at that dose and higher will be suspended and the MTD will be established as the previous cohort. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1. Dose escalation will end when either the MTD is achieved or at 3 dose levels above full BTK occupancy, whichever occurs first. Full BTK occupancy is defined as ACP-196 active-site occupancy of $> 80\%$ (average of all subjects in cohort) at 24 hours postdose. Should escalation to Cohort 6 be necessary, the dose will be determined based on the aggregate data from Cohorts 1 to 5, which includes safety, efficacy, and PK/PD results. The dose for Cohort 6 will not exceed 900 mg/day.

Treatment with ACP-196 may be continued for > 28 days until disease progression or an unacceptable drug-related toxicity occurs. Subjects with disease progression will be removed from the study. 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.

Radiologic tumor assessment will be done at screening and at the end of Cycle 2, Cycle 4, and Cycle 12 and at investigator discretion. Confirmation of complete response (CR) will require bone marrow analysis and radiologic tumor assessment. For subjects who remain on study for > 11 months, a mandatory bone marrow aspirate and biopsy is required in Cycle 12 concurrent with the radiologic tumor assessment.

All subjects will have standard hematology, chemistry, and urinalysis safety panels done at screening. This study also includes pancreatic function assessment (serum amylase and serum lipase) due to the pancreatic findings in the 28-day GLP rat toxicity study. Once dosing commences, all subjects will be evaluated for safety once weekly for the first 4 weeks, every other week for Cycle 2, and monthly thereafter. Blood samples will be collected during the first week of treatment for PK/PD assessments. ECGs will be done at screening, and on Day 1-2, 8, 15, 22, 28 of Cycle 1, Day 15 and 28 of Cycle 2, and monthly thereafter through Cycle 6. ECGs are done in triplicate for screening only. Thereafter, single ECGs are done unless a repeat ECG is required (see Section 4.1 for a more detailed description of ECG assessments).

Refer to Table 4-1 for a comprehensive list of study assessments and their timing. A study schema is provided at the end of the protocol synopsis.

The occupancy of BTK by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) 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.

3.2. Study Parameters

3.2.1. Efficacy Parameters

- Overall response rate
- Duration of response
- Progression-free survival

3.2.2. Safety Parameters

- DLTs and MTD
- Frequency, severity, and attribution of adverse events (AEs)

3.2.3. Pharmacokinetic and Pharmacodynamic Parameters

A description of the pharmacokinetic parameters for ACP-196 and its major metabolites in plasma are provided in Section 6.4.4.

The occupancy of BTK by ACP-196 will be measured in peripheral blood mononuclear cells (PBMCs) 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

The starting ACP-196 dose of 100 mg was selected based on Food and Drug Administration (FDA) Guidances: Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (MSSD), and Nonclinical Evaluation for Anticancer Pharmaceuticals (ICH S9) [FDA 2005 and 2010]. Standard GLP 28-day nonclinical systemic toxicity studies in rats and dogs were conducted in support of this trial. 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, the 100 mg/kg/day was selected to conservatively represent the HNSTD. Following the S9 guidance and using conversion factors from Table 1 in the MSSD guidance, the conversion factor for mg/kg to mg/m² for rodents is 6, which converts to 600 mg/m² in rats. The starting human dose for oncology would be one-tenth the HNSTD, 60 mg/m², or approximately 100 mg for a 60-kg subject with a body surface area of 1.6 m².

3.4. Selection of Study Population

3.4.1. Inclusion Criteria

To be eligible to participate in this study, a subject must meet the following criteria:

1. Men and women ≥ 18 years of age with a confirmed diagnosis of CLL/SLL, which has relapsed after, or been refractory to, ≥ 2 previous treatments for CLL/SLL; however, subjects with 17p deletion are eligible if they have relapsed after, or been refractory to, 1 prior treatment for CLL/SLL.
2. Body weight ≥ 60 kg.
3. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2 .

4. Agreement to use contraception during the study and for 30 days after the last dose of study drug if sexually active and able to bear children.
5. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty.
6. 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

A subject meeting any of the following criteria will be excluded from this study:

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 or ulcerative colitis, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction.
5. Any immunotherapy within 4 weeks of first dose of study drug.
6. For subjects with recent chemotherapy or experimental therapy the first dose of study drug must occur after 5 times the half-life of the agent(s).
7. Relapsed after, or refractory to, prior BTK inhibitor therapy.
8. Concomitant use of medicines known to cause QT prolongation or Torsades de pointes (see Appendix 1).

9. Central nervous system (CNS) involvement by lymphoma.
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 study drug.
13. Absolute neutrophil count (ANC) $< 0.75 \times 10^9/L$ or platelet count $< 50 \times 10^9/L$ unless there is bone marrow involvement.
14. Creatinine $> 1.5 \times$ institutional upper limit of normal (ULN); total bilirubin $> 1.5 \times$ ULN (unless due to Gilbert's disease); and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 2.5 \times$ ULN unless disease related.
15. Serum amylase $> 1.5 \times$ ULN or serum lipase $> 1.5 \times$ ULN.
16. Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, and corrected QT interval (QTc) ≥ 480 ms.
17. Lactating or pregnant.

3.4.3. Replacement of Subjects

Subjects who meet any of the following criteria will be replaced:

- Did not receive at least 21 of 28 doses in Cycle 1, unless due to DLT or another safety-related issue
- Did not undergo a DLT assessment at the start of Cycle 2
- Discontinued treatment during Cycle 1 for reasons other than DLT

It is not necessary to replace subjects if ≥ 4 subjects in a cohort have completed Cycle 1 without a DLT.

3.4.4. Enrollment 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 to receive current dose level information and ensure availability on study.

- After the subject has signed and dated the Informed Consent Form (ICF), eligibility has been confirmed, and all screening procedures have been completed, the subject can be officially enrolled in the study.
- To enroll a subject, the study center will fax/email a completed Enrollment 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.

Treatment must begin within 10 days after the enrollment form is faxed or emailed to the sponsor.

3.5. Study Drug: ACP-196 Hard Gelatin Capsule

3.5.1. Premedications

No premedications are required for administration of ACP-196.

3.5.2. Formulation, Packaging, and Storage

ACP-196 drug substance and drug product are manufactured according to cGMP and will be provided to the investigational site by Acerta Pharma or a designee.

ACP-196 will be provided in capsules intended for oral administration. Each capsule contains 25 mg of ACP-196 drug substance. Capsules also include the following inactive excipients: microcrystalline cellulose, gelatin, and globally acceptable colorant. Capsules are Swedish orange in color.

ACP-196 will be provided in white, high-density polyethylene bottles. Each bottle contains 30 capsules (25 mg per capsule of ACP-196).

Labels for study drug bottles will meet all applicable requirements of the United States FDA, Annex 13 of cGMP (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations, as applicable. Each bottle is closed with a white, continuous-thread, child-resistant, polypropylene screw cap.

Bottles containing ACP-196 will be shipped and stored at controlled room temperature (~15°C to 30°C). While stability of the drug when stored at controlled room temperature has been confirmed, brief excursions to temperatures as high as 40°C or as low as 5°C will not adversely affect the drug substance. Stability data at the start of study will support the use of the drug product capsules for at

least 3 months. Ongoing stabilities studies will support the use of the drug product for longer than 3 months.

If a drug shipment arrives damaged, or if there are any other drug complaints, a SAE/Product Complaint Form should be completed and 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.

3.5.3. Administration of 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 once daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice due to CYP450 3A4 inhibition). **Subjects should be instructed to take each dose of ACP-196 on an empty stomach defined as no food 2 hours before and 30 minutes after dosing.** 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 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.

3.5.4. Assuring Subject Compliance

Subjects will receive their first, second, eighth, and fifteenth dose in the clinic, as predose PK/PD measurements and /or ECG assessment 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 capsules to the clinic at their next visit. The administrator will review the diary and ask the subject if all of the capsules were

administered. Any remaining or returned capsules will be counted and recorded as described in Section 7.6. Returned capsules must not be redispensed to the same subject or to another subject. The study staff will resupply the subject with the correct number of capsules needed for use until the next visit.

3.5.5. Study Treatment Schedule

Subjects will receive study treatment as detailed in Section 3.5.3 and assessments will be performed as outlined in the Schedule of Assessments (Table 4-1). If no DLT is experienced during Cycle 1, subjects with stable disease or tumor response may continue on therapy until disease progression (radiologic or clinical) or until the investigator considers the study treatment to be no longer tolerable or in the subject's best interest.

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. Use of hematopoietic growth factors is permitted per the American Society of Clinical Oncology (ASCO) guidelines [Smith 2006].

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

3.6.2. Prohibited Concomitant Therapy

Any chemotherapy (eg, bendamustine, cyclophosphamide, pentostatin, or fludarabine), immunotherapy (eg, rituximab, GA101, alemtuzumab, or ofatumumab), corticosteroids (at dosages equivalent to prednisone > 20 mg/day), kinase inhibitors (eg, ibrutinib and idelalisib), bone marrow transplant, experimental therapy, and radiotherapy are prohibited.

Use of medications known to prolong QTc interval or that may be associated with Torsades de pointes (see Appendix 1) are prohibited within 7 days of starting study drug and during treatment.

3.7. Precautions

3.7.1. Drug-drug Interactions

At the systemic exposure levels expected in this study, ACP-196 inhibition of CYP metabolism is not anticipated.

However, ACP-196 may be metabolized by CYP3A4. Therefore, any medications that are strong inhibitors CYP3A4 (eg, see Appendix 2) should be avoided.

3.7.2. Reproductive Toxicity

Reproductive toxicity studies have not been done with ACP-196. Therefore, subjects with reproductive potential who are sexually active must use reliable, approved methods of contraception during the study and for 30 days after the last dose of ACP-196. 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 in the same manner as any serious adverse event (SAE; see Section 5.2).

3.7.3. Overdose Instructions

For any subject experiencing an ACP-196 overdose (administration of a dose ≥ 1.5 time the intended dose level in the clinical study protocol), observation for any symptomatic side effects should be instituted, and vital signs, biochemical and hematologic parameters, and ECGs 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. Assessment of Dose Limiting Toxicity (DLT)

A DLT will be defined as any of the following events (if not related to disease progression):

- Any Grade ≥ 3 nonhematologic toxicity (except alopecia) persisting despite receipt of a single course of standard outpatient symptomatic therapy (eg, Grade 3 diarrhea that responds to a single, therapeutic dose of Imodium® would not be considered a DLT)
- Grade ≥ 3 prolongation of the QTc interval, as determined by a central ECG laboratory overread

- Grade 4 neutropenia (ANC < 500/ μ L) lasting > 7 days after discontinuation of therapy without growth factors or lasting > 5 days after discontinuation of therapy while on growth factors (ie, Grade 4 neutropenia not lasting as long as specified will not be considered a DLT)
- Grade 4 thrombocytopenia (platelet count < 20,000/ μ L) lasting >7 days after discontinuation of therapy or requiring transfusion (ie, Grade 4 thrombocytopenia not lasting as long as specified will not be considered a DLT)
- Dosing delay due to toxicity for > 7 consecutive days

3.9. Assessment of QTc Interval Prolongation

The potential of ACP-196 to delay cardiac repolarization will be evaluated using ECGs for the measurement of the QTc interval. The study will be carried out in collaboration with a centralized cardiac safety monitoring laboratory that specializes in cardiac monitoring who will provide centralized ECG functions.

Toxicity grading of QTc interval prolongation is defined by the Common Terminology Criteria for Adverse Events (CTCAE) and provided in Table 3-1.

Table 3-1. QTc Toxicity Grading Defined by CTCAE

Grade	Definition
1	QTc 450 to 480 ms
2	QTc 481 to 500 ms
3	QTc $\geq$ 501 ms on at least 2 separate ECGs
4	QTc $\geq$ 501 ms or > 60 ms change from baseline and Torsades de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
5	Death

Refer to Section 4.1 for instructions on ECG evaluation.

3.10. Stopping Rules

Subjects with stable disease or tumor response may continue on therapy until disease progression (radiologic or clinical) or until the investigator considers the study treatment to be no longer tolerable or in the subject's best interest.

Treatment of subjects with study drug is terminated if:

- A DLT(s) occurs in Cycle 1 (28 days of treatment).
- Dosing delayed due to study drug-related toxicity for > 7 consecutive days.
- Disease progression.
- Subject decides to withdraw from the study.
- Intercurrent illness develops which compromises further participation in the study.
- Investigator determines that continuation on study is no longer in the best interest of the subject or change in the subject's condition renders them ineligible for further treatment.

3.11. Dosing Delays and Modifications

Clinical judgment should be used to determine appropriate management of the subject during any adverse event. Temporary interruption or permanent discontinuation of the study drug should be considered if clinically indicated.

Subjects who experience a non-DLT adverse event resulting in interruption of treatment for ≤ 7 missed doses, may restart treatment at the original dose if the abnormality returns to baseline or Grade 1.

3.12. 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. Monthly 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). In addition, mandatory safety calls will occur before enrollment of subjects into the next cohort level.

4. STUDY ACTIVITIES AND ASSESSMENTS

The schedules of events are shown in Schedule of Assessments. 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.

Table 4-1. Schedule of Assessments

	Screening ^a	Cycle 1						Cycle 2				Cycle 3	Cycle 4	Cycles 5-24 ^b	Follow Up ^c
		Days (± 2)						Day(s) (±2)				Day(s) (±2)	Day(s) (±2)	Day(s) (±2)	30 days after last dose
		1	2	8	15	22	28	1-14	15	16-27	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	x	x	x	x		x		x	x	x	x	x
Lab assessments:															
Urine pregnancy test ^g	x														x
Hematology ^h	x			x	x	x	x		x		x	x	x	x	x
Serum chemistry ⁱ	x			x	x	x	x		x		x	x	x	x	x
Amylase & Lipase	x	x					x				x	x	x	x	x
Urinalysis ^j	x														
T/B/NK/monocyte cell count ^k		x									x			Every 6 mos	
Serum Ig ^l		x									x			Every 6 mos	
Bone marrow (aspirate/biopsy)														Cycle 12 only	
Pharmacodynamics		x ^m	x ⁿ	x ^m											x
Pharmacokinetics ^o		x	x	x	x	x	x								
Molecular markers ^p	x														
ACP-196 dispensed ^q		x	x	x	x	x	x				x	x	x	x	
Study drug compliance		x	x	x	x	x	x		x		x	x	x	x	
Tumor assessment	x ^r										x ^s		x ^s	x ^s	
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	x	x	x	x

Abbreviations: ECG = electrocardiogram, ECOG = Eastern Cooperative Oncology Group, Ig = immunoglobulin; mos = months; PE = physical exam

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

- a. Screening tests should be performed within 7 (± 3) 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. 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. On Cycle 1 Day 1 and Cycle 1 Day 8, single ECGs are done predose and at 1, 2, 4, and 6 h postdose. The single ECG on Cycle 1 Day 2 is done predose. On Cycle 1 Day 15, Day 22, and Day 28, a single ECG is done 2 h postdose. Starting with Cycle 2, a single ECG is done per visit. Subjects should be in supine position and resting for at least 10 minutes before study-related ECGs. Two consecutive machine-read QTc > 500 ms or > 60 ms above baseline require central ECG review.
- 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.
- i. Serum chemistry: albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid.
- j. Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.
- k. T/B/NK/monocyte cell count (ie, CD3, CD4, CD8, CD14, CD19, CD19, CD16/56)
- l. Serum immunoglobulin: IgG, IgM, IgA, and total immunoglobulin
- m. Pharmacodynamic samples are drawn predose and 4 hours (± 10 minutes) postdose on the days indicated.
- n. Pharmacodynamic samples are drawn predose on the day indicated.
- o. Pharmacokinetic samples for Cycle 1 Day 1 are drawn predose and at 0.5, 1, 2, 4, 6 and 24 h (before dose on Day 2) postdose. Samples for Cycle 1 Day 8 are drawn predose and at 0.5, 1, 2, 4, and 6 h postdose. On Cycle 1 Day 15, 22, and 28, a PK sample is drawn predose and the second PK sample must be drawn before (up to 10 minutes before) the ECG acquisition, which is 2 h postdose.
- p. Includes, but is not limited to, interphase cytogenetics, stimulated karyotype, IgHV mutational status, Zap-70 methylation, and beta-2 microglobulin levels
- q. **ACP-196: For Cycle 1 Day 1, 2, 8, 15, 22, and 28 study drug is administered at the site. Therefore, only dispense enough study drug for the days between visits.** Thereafter, starting with the end of Cycle 1, dispense enough capsules for 1 complete cycle.
- r. Pretreatment radiologic tumor assessment should be performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is required of the chest, abdomen, and pelvis. In addition a positron emission tomography (PET) or PET/CT must be done for subjects with SLL.
- s. Radiologic tumor assessments are mandatory at the end of Cycle 2 (~ 7 days), Cycle 4 (~ 7 days), and Cycle 12 (~ 7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a complete response (CR). Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter.

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4.1. Description of Procedures

Informed Consent

Screening

The subject must read, understand and sign the Institutional Review Board (IRB)-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.

Medical History

Screening

Collect and record the subject's complete history 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.

Adverse Events

At all visits

The accepted regulatory definition for an AE is provided in Section 5.1. All medical occurrences from the time of signing the ICF that meet this definition must be recorded. Important additional requirements for reporting SAEs are explained in Section 5.6.

Concomitant Medications and Therapy

At all visits

Document all concomitant medications and procedures from within 14 days before the start of ACP-196 administration through 30 days after the last dose of ACP-196.

Confirmation of Eligibility

Screening

Perform all necessary procedures and evaluations to document that the subject meets each eligibility criterion. Screening evaluations must be completed within 7 (+3) days before the subject's first dose of ACP-196.

Physical Examination & Vital Signs & Weight

Per Table 4-1

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

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of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

Symptom-directed physical exams 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. Vital signs and weight will be measured at every visit.

ECOG Performance Status

At all visits

The ECOG performance index is provided in Appendix 3.

Electrocardiogram

Per Table 4-2

A centralized cardiac safety monitoring laboratory will be used in this study. The service provider will provide the ECG equipment (12-lead surface), instructions, and training (when requested). At screening, results from the central ECG reader (ie, 3 ECGs) will be averaged to determine eligibility and must meet the eligibility criteria of QTc < 480 ms. Thereafter single ECGs are done at each timepoint. However, if a machine read ECG registers a QTc (either Bazett's or Fredericia's) of ≥ 501 ms or > 60 ms above baseline then a second ECG must be done after 5 minutes. If at any point, a subject experiences a Grade 3 QTc prolongation (ie, 2 consecutive ECGs taken at least 5 minutes apart with QTc that are both ≥ 501 ms and/or > 60 ms change from baseline), per the machine on site, the dose must be held pending the QTc results from the centralized review. If centralized review confirms both ECG QTc readings are ≥ 501 ms or > 60 ms change from baseline then the subject must be withdrawn from the study. Conversely, if the centralized review shows that both ECG QTc readings are ≤ 500 ms and ≤ 60 ms change from baseline, dosing may be restarted at the same dose level, but missed doses will not be made up.

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Table 4-2. ECG Acquisition Times

Study Segment	Day	ECG Acquisition Times
Screening	--	Triplicate at least 1 min apart
Cycle 1	1-2	Single ECG predose, and 1, 2, 4, 6, and 24 h (before Day 2 dose) after 1 st dose; window for ECGs at 1, 2, 4, 6 h is ± 10 min. The 24-h ECG must be predose on Day 2.
Cycle 1	8	Single ECG predose, and 1, 2, 4, and 6 h after 8 th dose; window for ECGs at 1, 2, 4, 6 h is ± 10 min
Cycle 1	15, 22, 28	Single ECG 2 h (± 30 min) postdose
Cycle 2	15, 28	Single ECG anytime during the visit
Cycles 3 to 6	28	Single ECG anytime during the visit
30-day follow up	--	Single ECG anytime during the visit

Urine Pregnancy Test

Screening and safety follow-up visit

Pregnancy tests are required only for women with childbearing potential.

Hematology

Screening, then all visits starting with Cycle 1 Day 8

Hematology studies must include complete blood count (CBC) with differential and platelet and reticulocyte counts. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Chemistry

Screening, then all visits starting with Cycle 1 Day 8

Chemistry must include albumin, alkaline phosphatase, ALT, AST, bicarbonate, blood urea nitrogen (BUN), calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), magnesium, phosphate, potassium, sodium, total bilirubin, total protein, and uric acid. If an unscheduled ECG is done at any time,

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then an electrolyte panel (ie, calcium, magnesium, and potassium) must be done to coincide with the ECG testing. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Amylase and Lipase

Screening, then all visits starting with Cycle 1 Day 8

Serum amylase and serum lipase testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Urinalysis

Screening

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

T/B/NK/Monocyte Cell Count

Screening; end of Cycle 2 then every 6 months thereafter

Flow cytometry testing for CD3⁺, CD4⁺, CD8⁺, CD14⁺, CD19⁺, CD16/56⁺ cells. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Serum Immunoglobulin

Screening; end of Cycle 2 then every 6 months thereafter

Testing for IgG, IgM, IgA and total immunoglobulin levels. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Pharmacodynamics

Per Table 4-1

Blood samples will be used for PD testing (eg, BTK occupancy and B-cell activation) as well as for the investigation of marker(s) predictive of response to ACP-196. Refer to the laboratory binder for instructions on collecting and processing these samples.

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Pharmacokinetics

Per Table 4-3

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory.

Table 4-3. Pharmacokinetic Sample Schedule

		HOURS POSTDOSE						
Cycle	Day	Predose	0.5 (±5 min)	1 (±10 min)	2 (±10 min)	4 (±10 min)	6 (±10 min)	24 (±30 min)
1	1	X	X	X	X	X	X	X*before Day 2 dose
	8	X	X	X	X	X	X	
	15, 22, 28	Predose and 2 h (±30 min)						

Molecular Testing

Screening

Blood will be drawn for molecular testing including, but not limited to, interphase cytogenetics, stimulated karyotype, IgHV mutational status, ZAP-70 methylation, and beta-2 microglobulin levels. Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at central clinical laboratories.

Bone Marrow

Cycle 12 and to confirm CR

Bone marrow aspirate/biopsy is required to confirm a CR. A mandatory bone marrow aspirate/biopsy is required at the end of Cycle 12 concurrent with the radiologic tumor assessment as outlined below. Testing will be performed at the study center's local laboratory or other clinical laboratory listed on the investigator's form FDA 1572.

Tumor Assessment

Screening and end of Cycle 2/Cycle 4/Cycle 12

See Section 4.2 for response assessment criteria. Pretreatment tumor assessment should be performed within 30 days before the first dose. A computed tomography (CT) scan (with contrast unless contraindicated) is

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required of the chest, abdomen, and pelvis for the pretreatment tumor assessment for subjects with CLL. In addition, positron emission tomography (PET)/CT is required for subjects with SLL. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (- 7days) and Cycle 12 (-7 days). Otherwise, radiologic tumor assessments are done at investigator discretion. A CT (with contrast unless contraindicated) scan of the chest, abdomen, and pelvis is required for subjects with CLL. In addition, a PET/CT is required in subjects with SLL. Bone marrow and radiologic assessments are both required for confirmation of a CR. Clinical assessments of tumor response should be done at the end of Cycle 6 and every 3 months thereafter or as clinically indicated.

Study Drug Accountability

Cycle 1 Day 1, 2, 8, 15, 22, and 28, and end of every cycle

See Section 7.6.

4.2. Investigator's Assessment of Response to Treatment

The investigator must rate the subject's response to treatment based on recent guidelines for CLL (Table 4-4) and SLL (Table 4-5).

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Table 4-4. Response Assessment Criteria for CLL [Hallek 2008]

Response	Peripheral Blood	Bone Marrow if done	Nodes, Liver, and Spleen^a
CR	Lymphocytes $<4 \times 10^9/L$ ANC $>1.5 \times 10^9/L^b$ Platelets $>100 \times 10^9/L^b$ Hemoglobin $>11.0 \text{ g/dL}$ (untransfused) ^b	Normocellular $<30\%$ lymphocytes No B-lymphoid nodules	Normal (eg, no lymph nodes $>1.5 \text{ cm}$)
CRi	Lymphocytes $<4 \times 10^9/L$ Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity	Hypocellular $<30\%$ lymphocytes	Normal (eg, no lymph nodes $>1.5 \text{ cm}$)
PR	Lymphocytes $\geq 50\%$ decrease from baseline ANC $>1.5 \times 10^9/L$ Or Platelets $>100 \times 10^9/L$ or 50% improvement over baseline ^b Or Hemoglobin $>11.0 \text{ g/dL}$ or 50% improvement over baseline (untransfused) ^b	Not assessed	$\geq 50\%$ reduction in lymphadenopathy ^c and/or in spleen or liver enlargement

ANC = absolute neutrophil count; CR = complete remission; CRi = CR with incomplete blood count recovery; PR = partial remission

a Computed tomography (CT) scan of abdomen, pelvis, and chest is required for this evaluation

b without need for exogenous growth factors

c in the sum products of ≤ 6 lymph nodes or in the largest diameter of the enlarged lymph node(s) detected before therapy and no increase in any lymph node or new enlarged lymph nodes

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Table 4-5. Response Assessment Criteria for SLL [Cheson 2007]

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	If infiltrate present at screening, infiltrate cleared on repeat biopsy; if indeterminate by morphology, immuno-histochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; ≥ 1 PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or progressive disease	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease, and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

Abbreviations: CR = complete remission, CT = computed tomography, FDG = [¹⁸F]fluorodeoxyglucose, PET = positron-emission tomography, PR = partial remission, SD = stable disease, SPD = sum of the product of the diameters

4.3. Safety Follow-up Visit

The safety follow-up visit is conducted 30 (± 7) days after the last ACP-196 dose unless a subject receives a new anticancer therapy within this timeframe. Refer to Table 4-1 for the assessments done at these visits.

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. 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).

5.1. Definitions

5.1.1. 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 CLL/SLL that were not present before the AE reporting period (see Section 5.3)
- 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 adverse events; however, any clinical consequences of the abnormality (eg, withdrawal from study) should be reported as adverse events

5.1.2. 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 study drug.
- 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).

5.1.3. Severity

Definitions found in the CTCAE version 4.03 (CTCAE v4.03) or later will be used for grading the severity (intensity) of **nonhematologic** AEs. The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any nonhematologic AE not listed in the CTCAE v4.03, 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

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- 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

The grading scale for hematologic toxicity in subjects with CLL is in Table 5-1.

Table 5-1. Grading Scale for Hematologic Toxicity in CLL [Halleck 2008]

Grade ¹	Decrease in platelets ² or Hb ³ (nadir) from pretreatment value	Absolute neutrophil count/ μL ⁴ (nadir)
0	No change to 10%	≥ 2000
1	11%-24%	≥ 1500 and < 2000
2	25%-49%	≥ 1000 and < 1500
3	50%-74%	≥ 500 and < 1000
4	$\geq 75\%$	< 500

1. Grades: 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death occurring as a result of toxicity at any level of decrease from pretreatment will be reported as Grade 5.
2. Platelet counts must be below normal levels for Grades 1 to 4. If, at any level of decrease, the platelet count is $< 20 \times 10^9/\text{L}$ ($20,000/\mu\text{L}$), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, $< 20 \times 10^9/\text{L}$ [$20,000/\mu\text{L}$]) was present pretreatment, in which case the patient is not evaluable for toxicity referable to platelet counts.
3. Hemoglobin (Hb) levels must be below normal levels for Grades 1 to 4. Baseline and subsequent Hb determinations must be performed before any given transfusions. The use of erythropoietin is irrelevant for the grading of toxicity, but should be documented.
4. If the ANC reaches $< 1 \times 10^9/\text{L}$ ($1000/\mu\text{L}$), it should be judged to be Grade 3 toxicity. Other decreases in the white blood cell count, or in circulating neutrophils, are not to be considered because a decrease in the white blood cell count is a desired therapeutic endpoint. A gradual decrease in granulocytes is not a reliable index in CLL for stepwise grading of toxicity. If the ANC was $< 1 \times 10^9/\text{L}$ ($1000/\mu\text{L}$) before therapy, the patient is not evaluable for toxicity referable to the ANC. The use of growth factors such as granulocyte colony-stimulating factor (G-CSF) is not relevant to the grading of toxicity, but should be documented.

5.2. 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

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recorded on the electronic CRF (eCRF). All SAEs also must be reported on the SAE/Product Compliant form (see Section 5.6).

5.3. Adverse Event Reporting Period

The AE reporting period for this study begins when the subject signs informed consent and ends with the safety follow-up visit. 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.

5.4. 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, clinically significant laboratory test (ie, requiring change in study drug dose or discontinuation of study drug or any other medical intervention), or other means will be recorded in the subject's medical record and on the AE eCRF and, when applicable, on an SAE/Product Compliant 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 (see following guidance), and any actions taken. The relationship of adverse events 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 4 for more detail on assessing relationship.

5.5. Pregnancy

Report any pregnancy that occurs in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug. Record any occurrence of pregnancy on the Pregnancy Report Form Part I and fax to Acerta Pharma Drug Safety, or designee, within 24 hours of learning of the event. After the birth of the baby, additional information on the mother, pregnancy and baby will be

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collected by completing the Pregnancy Report Form Part II. Abortion, whether therapeutic, elective or spontaneous, will be reported as an SAE.

A subject must immediately inform the investigator if the subject or subject's partner becomes pregnant from the time of consent to 30 days after the last dose of study drug. 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.

5.6. Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on an SAE/Product Compliant form and faxed or emailed to Acerta Pharma Drug Safety, or designee, within 24 hours of the discovery of the event or information. 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 study drug 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 of the SAE.

Drug Safety Contact Information	
Fax:	+1.650.591.2816
Email:	DrugSafety@acerta-pharma.com

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5.7. 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.

6. STATISTICAL METHODS OF ANALYSIS

6.1. General Considerations and Determination of Sample Size

No formal statistical tests of hypotheses will be performed. Descriptive statistics (including means, standard deviations, and medians for continuous variables and proportions for discrete variables) will be used to summarize data as appropriate.

Twenty-four to 36 evaluable subjects will be enrolled in this study. The trial design is specified because of its practical simplicity, use of a biomarker, and not because of power considerations. The MTD is defined as the largest daily dose for which fewer than 33% of the subjects experience a DLT during Cycle 1.

6.2. Definition of Analysis Sets

The following definitions will be used for the safety and efficacy 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 and with ≥ 1 tumor response assessment after treatment.

The safety analysis set will be used for evaluating the safety parameters in this study. The PP analysis sets will be analyzed for efficacy parameters in this study.

6.3. Missing Data Handling

No imputation of values for missing data will be performed except for missing or partial start and end dates for adverse events 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.

6.4. Endpoint Data Analysis

6.4.1. Safety Endpoint

Safety summaries will include summaries in the form of tables and listings. The frequency (number and percentage) of treatment emergent adverse events will

be reported in each treatment group by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term. Summaries will also be presented by the severity of the adverse event 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.

Vital signs, ECGs, and physical exams will be tabulated and summarized.

6.4.2. 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.

6.4.3. Analysis of Efficacy Parameters

Overall Response Rate

The point estimate of the overall response rate will be calculated for the PP analysis set. The corresponding 95% confidence interval also will be derived.

Duration of Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier methodology will be used to estimate event-free curves and corresponding quantiles (including the median).

Progression-free Survival

Progression-free survival is measured from the time of first study drug administration until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Kaplan-Meier

methodology will be used to estimate the event-free curves and corresponding quantiles (including the median).

6.4.4. Analysis of Pharmacokinetic/Pharmacodynamic Parameters

The plasma PK of ACP-196 and a metabolite 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)
- $t_{1/2}$ 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. Pharmacokinetic relationships to PD measures of efficacy or toxicity may also be

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

7. 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 for review and approval before study initiation. A signed protocol approval page; a letter confirming IRB approval of the protocol and informed consent; and a statement that the IRB is organized and operates according to Good Clinical Practice (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) to Acerta Pharma before screening subjects for study enrollment. Amendments to the protocol must also be approved by the IRB 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-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. 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. 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, 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. 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 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 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.

ACP-196 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 ACP-196 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 ACP-196 is provided in

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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 ACP-196. The person receiving the shipment and inspecting it must complete and sign the CSSF. A copy of the signed CSSF must be faxed or emailed to Acerta Pharma at the fax number/email address listed on the form.

A Study 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-CL-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 study drug 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 study drug. 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 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.

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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 coordinate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB 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 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. Given their contribution to the project, 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.

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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 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 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.
9. Any significant protocol deviations are reported to Acerta Pharma and the IRB according to the guidelines at each study site.
10. eCRF pages are completed within 5 days of each subject's visit.
11. All Safety Reports are submitted promptly to the IRB.
12. All SAEs are reported to Acerta Pharma Drug Safety/Designee within 24 hours of knowledge and to the IRB per their requirements.

8. REFERENCES

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Appendix 1. Risk Factors for Drug-induced Torsades de Pointes

- History of congenital long QT syndrome
- Baseline QTc prolongation (> 450 ms)
- Hypokalemia (potassium $\leq$ 3.0 mEq/L)
- Severe hypomagnesemia (magnesium $\leq$ 1.2 mEq/L)
- Bradycardia (resting heart rate < 55 beats per minute)
- Current or recent past use (within 7 days before study entry) of drugs known to prolong QTc interval and may be associated with Torsades de Pointes (listed below)

amiodarone, dofetilide, ibutilide, terfenadine, quinidine, procainamide, disopyramide, sotalol, probucol, bepridil, haloperidol, droperidol, quetiapine, thioridazine, ziprasidone, risperidone, indapamide, levofloxacin, ciprofloxacin, gatifloxacin, moxifloxacin, clarithromycin, erythromycin, ketoconazole, itraconazole, amitriptyline, desipramine, imipramine, doxepin, fluoxetine, sertraline, venlafaxine, cisapride, sumatriptan, zolmitriptan, arsenic, dolasetron, methadone, chloroquine, chlorpromazine, astemizole, halofantrine, levomethadyl, mesoridazine, pentamidine, pimozone, domperidone, procainamide, quinidine, sparfloxacin

This list is not exhaustive and new information regarding drugs with dysrhythmic potential emerges on a regular basis. Please refer to the following site (or similar sites) for additional information on drugs with dysrhythmic potential:

<http://www.azcert.org/medical-pros/drug-lists/drug-lists.cfm>.

Appendix 2. Inhibitors of CYP3A4

A strong inhibitor is one that causes a > 5-fold increase in plasma AUC values or > 80% decrease in clearance.

<http://www.medicine.lupui.edu/Flockhart/table.htm>

Strong inhibitors are highlighted in **BOLD** below.

HIV antivirals:

INDINAVIR

NELFINAVIR

RITONAVIR

Strong inhibitors:

CLARITHROMYCIN

ITRACONAZOLE

KETOCONAZOLE

NEFAZODONE

Moderate inhibitors:

erythromycin

grapefruit juice

verapamil

diltiazem

Weak inhibitors:

cimetidine

All other inhibitors:

amiodarone

fluvoxamine

mibefradil

troleandomycin

Appendix 3. ECOG Performance Status

<u>Grade</u>	<u>ECOG</u>
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 4. 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

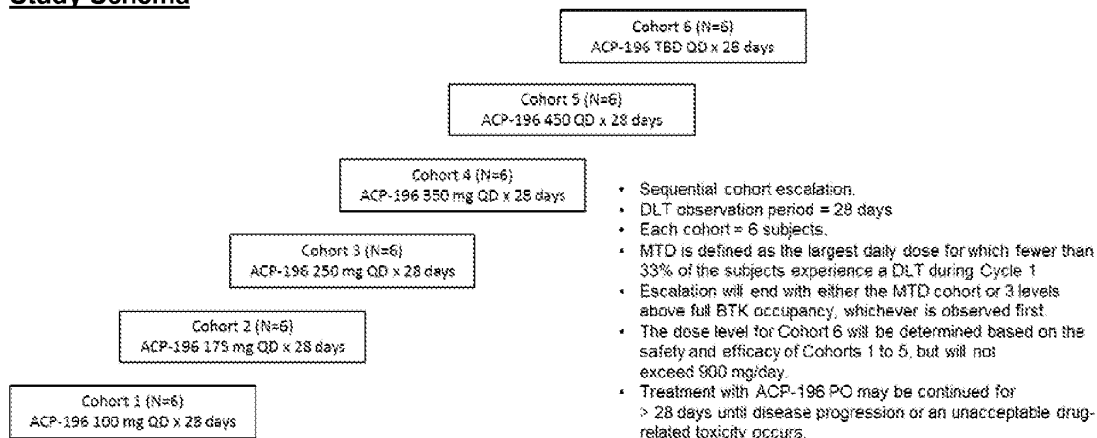
Yes = There is a reasonable possibility that the event may have been caused by study drug.

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

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Study Schema



BTK = Bruton's tyrosine kinase; DLT = dose-limiting toxicity; MTD = maximum tolerated dose;
PO = per os (oral); TBD = to be determined; QD= once daily

Electronic Acknowledgement Receipt	
EFS ID:	17975130
Application Number:	61929742
International Application Number:	
Confirmation Number:	7002
Title of Invention:	Methods of Use of ACP-196
First Named Inventor/Applicant Name:	Ahmed Hamdy
Customer Number:	28977
Filer:	Frederick Vogt
Filer Authorized By:	
Attorney Docket Number:	055112-5000
Receipt Date:	21-JAN-2014
Filing Date:	
Time Stamp:	16:18:16
Application Type:	Provisional

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	\$ 260
RAM confirmation Number	2596
Deposit Account	500310
Authorized User	
The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows: Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees) Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)	

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)					
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)					
File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Provisional Cover Sheet (SB16)	20140121_Coversheet.pdf	1477302 912a43066431b32ecd62a72b6b70972736 071665	no	3
Warnings:					
Information:					
2	Specification	20140121_Specification_asfiled.pdf	601159 fb48b4693309bd4fb72d7a134f97ae12f2f5 d2ed	no	65
Warnings:					
Information:					
3	Drawings-only black and white line drawings	20140121_Drawings_asfiled.pdf	92827 e20efec61ae695ea746c63ae0912172ebe03 367d9	no	1
Warnings:					
Information:					
4	Fee Worksheet (SB06)	fee-info.pdf	28918 6eae79eb1715d566589fc957c89089320c2 41c2f	no	2
Warnings:					
Information:					
Total Files Size (in bytes):			2200206		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					