# Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia. N Engl J Med 2016;374:323-32. DOI: 10.1056/NEJMoa1509981

# PROTOCOL

This redacted protocol is from an ongoing study. The version of the protocol under which the reported study population was evaluated is provided by the authors to give readers additional information about their work.

Protocol for: Byrd JC, Harrington B, O'Brien S, et al. Acalabrutinib in Relapsed Chronic Lymphocytic Leukemia. New England Journal of Medicine.

# A Phase 1/2, Multicenter, Open-label, and Dose-escalation Study of ACP-196 in Subjects with Chronic Lymphocytic Leukemia

| | |
|---|---|
| Protocol Number: | ACE-CL-001 |
| Drug Product: | ACP-196 |
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## LIST OF ABBREVIATIONS

| | |
|---|---|
| $\lambda_z$ | terminal elimination rate constant |
| AE(s) | adverse event(s) |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| BID | twice daily |
| Btk | Bruton tyrosine kinase |
| BUN | blood urea nitrogen |
| CBC | complete blood count |
| 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 |
| 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 |
| FDA | Food and Drug Administration |
| FISH | fluorescence in situ hybridization |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| G-CSF | granulocyte colony-stimulating factor |
| Hb | hemoglobin |
| HBV | hepatitis B virus |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| ICF | informed consent form |

| | |
|---|---|
| ICH | International Conference on Harmonisation |
| Ig | immunoglobulin |
| IgVH | immunoglobulin variable region heavy chain |
| IRB | Institutional Review Board |
| IRC | Independent Review Committee |
| LDH | lactate dehydrogenase |
| LVEF | left ventricular ejection fraction |
| MedDRA | Medical Dictionary for Regulatory Activities |
| mos | months |
| MRD | minimal residual disease |
| MTD | maximum tolerated dose |
| NCI | National Cancer Institute |
| NHL | Non-Hodgkin lymphoma |
| PBMCs | peripheral blood mononuclear cells |
| PE | physical exam |
| PD | pharmacodynamics |
| PK | pharmacokinetics |
| PP | per-protocol (population) |
| PR | partial remission (response) |
| QTc | corrected QT interval |
| R/R | relapsed/refractory |
| 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 |
| $T_{max}$ | time to maximum drug concentration |
| ULN | upper limit of normal |
| WHO | World Health Organization |

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# 1. STUDY OBJECTIVES

## 1.1. 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

## 1.2. Secondary Objective

Evaluate tumor responses

# 2. INVESTIGATIONAL PLAN

## 2.1. Overall Study Design

### 2.1.1. Escalation Portion – Phase 1

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

**Once Daily (QD) Dosing Cohorts:**

- Cohort 1: 100 mg/day for 28 days (= 1 cycle)
- Cohort 2a: 175 mg/day for 28 days (= 1 cycle)
- Cohort 3: 250 mg/day for 28 days (= 1 cycle)
- Cohort 4a: 400 mg/day for 28 days (= 1 cycle)

**Twice Daily (BID) Dosing Cohorts:**

- Cohort 2b: 100 mg/day BID for 28 days (= 1 cycle)
- Cohort 4b: 200 mg/day BID for 28 days (= 1 cycle)

No DLTs (refer to Section 2.6 for definition) have occurred on the escalation cohorts; therefore the MTD has not been reached. Likewise, PD results show full coverage of the target is observed 4 hours after dosing starting with the 100-mg Cohort. Therefore escalation to dose levels above 400 mg will not occur and the DLT safety observation portion of the study is complete.

### 2.1.2. Expansion Cohorts – Phase 2

Due to the promising safety and efficacy data observed to date on the study, an expansion cohort of 200 mg QD (Cohort 2c) has been added under Amendment 4 of the protocol. Also Cohort 2b (100 mg BID) is being expanded from 6 to 30 subjects to further assess the safety and efficacy of these regimens in subjects with relapsed/refractory CLL/SLL as follows:

- Cohort 2b is 100 mg BID (N=30)
- Cohort 2c is 200 mg QD (N=30)

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, Cycle 6, Cycle 9, 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.

Refer to Table 3-1 for a comprehensive list of study assessments and their timing.
Study Parameters

#### 2.1.3. Efficacy Parameters

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

#### 2.1.4. Safety Parameters

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

#### 2.1.5. Pharmacokinetic and Pharmacodynamic Parameters

A description of the pharmacokinetic parameters for ACP-196 and its major metabolites in plasma are provided in Section 5.4.4.

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.

### 2.2. Rationale for Study Design and Dosing Regimen

The starting ACP-196 dose of 100 mg was selected based on Food and Drug Administration (FDA) Guidance: 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, the

highest non-severely toxic dose (HNSTD) was 100 mg/kg/day. Following the S9 guidance and using conversion factors from the MSSD guidance, the conversion factor for mg/kg to mg/$m^2$ for rodents is 6, which converts to 600 mg/$m^2$ in rats. The starting human dose for oncology would be one-tenth the HNSTD, 60 mg/$m^2$, or approximately 100 mg for a 60-kg subject with a body surface area of 1.6 $m^2$.

## 2.3. Selection of Study Population

### 2.3.1. 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, ≥ 1 previous treatments for CLL/SLL.
2. Body weight ≥ 45 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 or beget children. (eg, condoms, implants, injectables, combined oral contraceptives, IUDs, true sexual abstinence [Please note that periodic abstinence, eg, calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable methods of contraception], or sterilized partner).
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).
7. Male subjects must agree to refrain from sperm donation during the study and for 30 days after the last dose of study drug.

### 2.3.2. 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, or left ventricular ejection fraction (LVEF) ≤ 40%.

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. Any history of Richter's transformation.

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. Uncontrolled autoimmune hemolytic anemia.

13. History of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug.

14. Requires anticoagulation with warfarin.

15. Major surgery within 4 weeks before first dose of study drug.

16. Absolute neutrophil count (ANC) < 0.75 x $10^9$/L or platelet count < 50 x $10^9$/L unless there is bone marrow involvement.

17. 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.

18. Serum amylase > 1.5 x ULN or serum lipase > 1.5 x ULN.

19. Significant screening ECG abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, Grade 2 or higher bradycardia, and QTc ≥ 480 ms.

20. Breast feeding or pregnant.

## 2.4. Study Drug: ACP-196 Hard Gelatin Capsule

### 2.4.1. Premedications

No premedications are required for administration of ACP-196.

### 2.4.2. Administration of ACP-196

ACP-196 is intended to be administered orally once or twice daily with 8 ounces (approximately 240 mL) of water (avoid grapefruit juice due to CYP450 3A4 inhibition). The capsules should be swallowed intact and subjects should not attempt to open capsules or dissolve them in water.

### 2.4.3. Assuring Subject Compliance

Refer to Table 3-1 and Section 3.1 for doses that must be administered in the clinic to comply with predose and postdose PK/PD measurements and /or ECG assessments. 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.

### 2.4.4. Study Treatment Schedule

Subjects will receive study treatment as detailed in Section 2.4.2 and assessments will be performed as outlined in the Schedule of Assessments (Table 3-1). 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.

## 2.5. Concomitant Therapy

### 2.5.1. 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.

### 2.5.2. 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.

## 2.6. Assessment of Dose Limiting Toxicity (DLT)

The DLT review period of the protocol is over. However, during the dose-escalation portion of the study a DLT was defined as any of the following events unless the adverse event is clearly related to disease progression or the subject's current medical history and associated comorbidities:

1. Any Grade 3 or greater nonhematologic toxicity with the exception of alopecia and Grade 3 nausea, vomiting and diarrhea that respond to supportive therapy.
2. The following hematologic toxicities should be considered as DLTs:
    a. Grade 4 neutropenia lasting more than 5 days.
    b. Grade 4 thrombocytopenia, or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion.
    c. Grade 3 or greater febrile neutropenia (temperature ≥ 38.5 °C).
    d. Grade 4 anemia, unexplained by underlying disease.
3. Dosing delay due to toxicity for > 7 consecutive days.

## 2.7. Assessment of QTc Interval Prolongation by Central ECG Testing

Central ECG testing will be used for the dose-escalation portion of the study only.

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 2-1.

**Table 2-1. QTc Toxicity Grading Defined by CTCAE**

| Grade | Definition |
|---|---|
| 1 | QTc 450 to 480 ms |
| 2 | QTc 481 to 500 ms |
| 3 | QTc ≥ 501 ms on at least 2 separate ECGs |
| 4 | QTc ≥ 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.

### 2.8. 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:

- Dosing delayed due to study drug-related toxicity for > 14 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.

### 2.9. 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 days, may restart treatment at the original dose if the abnormality returns to baseline or Grade 1.

### 2.10. 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. Mandatory safety calls will occur before enrollment of subjects into the next cohort level.

## 3. 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 2.4.

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 3-1. Schedule of Assessments**

| | Screening[a] | | Cycle 1 | | | | | Cycle 2 | | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Cycles 9,15,21 | Cycles 12, 18, 24[b] | Follow Up[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Days (± 2) | | | | | Day(s) (±2) | | Day(s) (±2) | Day(s) (±2) | Day(s) (±2) | Day(s) (±2) | Day(s) (±2) | Day(s) (±2) | 30 days after last dose |
| | | 1 | 2 | 8 | 15 | 22 | 28 | 15 | 28 | 28 | 28 | 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 | x | x | x |
| ECOG status | x | x | | x | x | x | x | x | x | x | x | x | x | x | x | x |
| ECG[f] (dose escalation only) | x | x | x | x | x | x | x | x | x | x | x | x | x | | | x |
| ECG[f] (expansion cohorts) | x | | | | | | | | | | | | | | | x |
| Echocardiogram[t] | x | | | | | | | | | | | | x | | | x |
| Lab assessments: | | | | | | | | | | | | | | | | |
| Urine pregnancy test[g] | x | | | | | | | | | | | | | | | x |
| Hematology[h] | x | | | x | x | 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 | x | x | x |
| Amylase & Lipase | x | x | | | | | x | | x | x | x | x | x | | | x |
| Urinalysis[j] | x | | | | | | | | | | | | | | | |
| T/B/NK/monocyte cell count[k] | | x | | | | | | | x | | | | | x | | |
| Serum Ig[l] | | x | | | | | | | x | | | | | x | | |
| Bone marrow (aspirate/biopsy) | | | | | | | | | | | | | | | Cycle 12 only | |
| Pharmacodynamics | | x[m] | x[n] | x[m] | | | x[n] | | | | | | x[n] | | | 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 | x | x | x | x | |
| Study drug compliance | | x | x | x | x | x | x | x | x | x | x | x | | x | x | |
| Tumor assessment | x[r] | | | | | | | | x[s] | | x[s] | | x[s] | x[s] | x[s] | |
| Concomitant medications | x | x | | x | 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 | 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 10 days before the first administration of study drug, unless otherwise indicated.
b. Any subjects who have not progressed while receiving study drug treatment may 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 for all subjects. The intensive ECG schedule, which follows, is only for the subjects in the dose escalation portion of the study. The calculated QTc average of the 3 ECGs must be <480 ms for eligibility. ECGs will be done 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 1 h postdose. Starting with Cycle 2 and ending with Cycle 6, 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, CD16/56). Testing will be performed on Cycle 1 Day 1; end of Cycles 2, 9, 15 and 21.
l. Serum immunoglobulin: IgG, IgM, IgA, and total immunoglobulin (if available).
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 0.25, 0.5, 0.75, 1, 2, 4, 6 and 24 h (before dose on Day 2) postdose. Samples for Cycle 1 Day 8 are drawn predose and at 0.25, 0.5, 0.75, 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 (if applicable), which is 1 h postdose. PK sampling will be done at select centers and on up to 10 subjects per cohort.
p. Includes, but is not limited to, interphase cytogenetics, stimulated karyotype, CLL FISH panel, IgVH 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.
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.
s. Radiologic tumor assessments are mandatory at the end of Cycle 2 (-7 days), Cycle 4 (- 7days), Cycle 6 (- 7days), Cycle 9 (- 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 (and any other relevant diseased area such as the neck) is required. Bone marrow and radiologic assessments are both required for confirmation of a complete response (CR). Testing for minimal residual disease will be done on subjects with confirmed CRs.

### 3.1. 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 4.1. 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 4.6.

**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 10 days before the subject's first dose of ACP-196.

**Physical Examination & Vital Signs & Weight**
*Per Table 3-1*

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

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

Symptom-directed physical exams 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 – Dose Escalation Portion Only**
*Per Table 3-2*

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.

**Table 3-2. 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 1st 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 8th dose; window for ECGs at 1, 2, 4, 6 h is ±10 min |
| Cycle 1 | 15, 22, 28 | Single ECG 1 h (±10 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 |

**Electrocardiogram – Expansion Cohorts**
*Screening and safety follow-up visit*

Central ECG testing is not required for subjects in the expansion cohorts. Sites can use their own 12-lead ECG machines for the screening ECGs and the ECG done at the safety follow-up 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. Hematology samples done at response assessment timepoints must be done within 7 days of the CT scan. 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, 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, Cycle 1 Day 1 then Day 28 visits on all cycles starting with Cycle 2 through end of Cycle 6 and safety follow-up visit*

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**
*Cycle 1 Day 1; end of Cycles 2/9/15 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**
*Cycle 1 Day 1; end of Cycle 2 then every 6 months thereafter*

Testing for IgG, IgM, IgA and total immunoglobulin (if available) 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 3-1*

Blood samples will be used for PD testing (eg, Btk occupancy and B-cell activation, measurement of chemokines) 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.

**Pharmacokinetics**
*Per Table 3-3*

Refer to the laboratory binder for instructions on collecting and processing these samples. Testing will be performed at a central clinical laboratory. PK testing will only be done at select centers and on a subset of subjects for each cohort (≤ 10 subjects/cohort).

**Table 3-3. Pharmacokinetic Sample Schedule**

| | | | Hours Postdose | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle** | **Day** | **Predose** | **0.25 (±1 min)** | **0.5 (±5 min)** | **0.75 (±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 | X | X*before Day 2 dose |
| | **8** | X | X | X | X | X | X | X | X | |
| | **15, 22, 28** | Predose and 1 h (±10 min) | | | | | | | | |

**Molecular Testing**
*Screening*

Blood will be drawn for molecular testing including, but not limited to, interphase cytogenetics, stimulated karyotype, CLL fluorescence in situ hybridization (FISH) panel, IgVH mutational status, ZAP-70, 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 and must be done within 4 weeks of the CT scan. 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 6/Cycle 9/Cycle 12*

Pretreatment 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 and any other diseased area (eg, the neck) for the pretreatment tumor assessment for subjects. Bone marrow and radiologic assessments are both required for confirmation of a CR. In addition, 4-color flow cytometry will be used to determine the presence or absence of residual minimal disease (MRD) in subjects who achieve a CR per the response criteria outlined in Section 3.2.

### 3.2. Investigator's Assessment of Response to Treatment

The investigator must rate the subject's response to treatment based on recent guidelines for CLL and SLL (Table 3-4) with incorporation of the clarification for treatment-related lymphocytosis (Cheson 2012). For all response assessments, hematology samples must be drawn within 7 days of the scan. Bone marrow biopsy done to confirm a complete response must be done within 4 days of the response assessment scan.

**Table 3-4. Response Assessment Criteria for CLL/SLL (Hallek 2008)**

| Response | Peripheral Blood | Bone Marrow if done | Nodes, Liver, and Spleen[a] |
|---|---|---|---|
| CR | Lymphocytes <4 x $10^9$/L<br>ANC >1.5 x $10^9$/L[b]<br>Platelets >100 x $10^9$/L[b]<br>Hemoglobin >11.0 g/dL (untransfused)[b] | Normocellular<br><30% lymphocytes<br>No B-lymphoid nodules | Normal (eg, no lymph nodes >1.5 cm) |
| CRi | Lymphocytes <4 x $10^9$/L<br>Persistent anemia, thrombocytopenia, or neutropenia related to drug toxicity | Hypocellular<br><30% lymphocytes | Normal (eg, no lymph nodes >1.5 cm) |
| PR | Lymphocytes ≥50% decrease from baseline<br>ANC >1.5 x $10^9$/L<br>Or<br>Platelets >100 x $10^9$/L or 50% improvement over baseline[b]<br>Or<br>Hemoglobin >11.0 g/dL or 50% improvement over baseline (untransfused)[b] | Not assessed | ≥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

Note: isolated elevation of treatment-related lymphocytosis by itself will not be considered progressive disease unless subject becomes symptomatic from this (Cheson 2012)

### 3.3. 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 3-1 for the assessments done at these visits. Subjects who withdraw consent should still be encouraged to complete the safety follow up assessments, but these assessments cannot be mandated once consent is withdrawn. The Schedule of Assessments (Table 3-1) describes the procedures required for the safety follow-up.

### 3.4. 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.

# 4. 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).

## 4.1. Definitions

### 4.1.1. 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 4.3)
- 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.

### 4.1.2. 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).

#### 4.1.3. 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
- 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 4-1.

**Table 4-1. Grading Scale for Hematologic Toxicity in CLL (Hallek 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 | ≥ 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 x $10^9$/L (20,000/µL), this will be considered Grade 4 toxicity, unless a severe or life-threatening decrease in the initial platelet count (eg, < 20 x $10^9$/L [20,000/µL]) 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 x $10^9$/L (1000/µL), 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 x $10^9$/L (1000/µL) 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.

## 4.2. Documenting and Reporting of Adverse and Serious Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, as outlined in the prior sections, are recorded on the electronic CRF (eCRF). All SAEs also must be reported on the SAE/Product Complaint form (see Section 4.6).

## 4.3. Adverse Event Reporting Period

The AE reporting period for this study begins when the subject takes the first dose of study drug and ends with the safety follow-up visit. The exception to this reporting period would be any complications that occur as a result of protocol-mandated interventions in screening or before first dose of study drug. 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.

### 4.4. 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 Complaint form.

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

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria, if applicable, suspected relationship to the study drug (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.

### 4.5. Pregnancy

The investigator should report all pregnancies and pregnancies of the partners of subjects within 24 hours using the Pregnancy Report Form Part I. This form should be faxed or emailed to Acerta Pharma Drug Safety. Any pregnancy-associated SAE must be reported using the SAE report form, according to the usual timeline and direction for SAE reporting (Section 4.6).

Any uncomplicated pregnancy that occurs with the subject or with the partner of a treated subject during this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study will be reported. All pregnancies and partner pregnancies that are identified during or after this study, wherein the estimated date of conception is determined to have occurred from the time of consent to 30 days after the last dose of study medication with be reported, followed to conclusion, and the outcome reported.

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

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

### 4.6. Expedited Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on an SAE/Product Complaint 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: | xxx xxx xxxx |
| Email: | xxx@acerta-pharma.com |

### 4.7. 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.

# 5. STATISTICAL METHODS OF ANALYSIS

## 5.1. 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.

The design of the Phase 1 (ie, dose-escalation portion) of the study 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. The MTD was not reached in this study.

The Phase 2 (expansion portion) of the study will test the null hypothesis that the ORR is ≤ 10% against the alternative hypothesis that it is ≥ 35%. Using Simon's optimal 2-stage design (Simon 1989), a total sample size of 30 subjects per cohort has power = 0.90 to achieve a 1-sided significance level of ≤ 0.025. In Stage 1, 11 subjects will be enrolled per cohort; if ≥ 1 subject (9.1%) achieves an objective response of a PR/PR+L or better within the first 4 cycles of treatment, then that cohort will continue to full enrollment. Under the Simon design, an ORR of ≥ 23% (ie, ≥ 7 subjects responding of 30 subjects evaluated) will achieve a significance level of ≤ 0.025. Using an exact binomial confidence interval (CI), an ORR of 23% (ie, 7 subjects responding of 30 subjects evaluated) will achieve a 1-sided 90% lower bound of 11.5%.

Considering the planned expansion cohort size of 30 subjects, Table 5-1 shows the 2-sided exact 90% binomial CIs on the true response rate for the range of possible values for the observed response rate.

**Table 5-1. Two-Sided Exact 90% CIs for ORR in Expansion Cohorts (N=30)**

| Responses, n | Response Rate, % | 90%CI | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 0 | 0% | 0.0% | 9.5% |
| 1 | 3.3% | 0.2% | 14.8% |
| 2 | 6.7% | 1.2% | 19.6% |
| 3 | 10.0% | 2.8% | 23.9% |
| 4 | 13.3% | 4.7% | 27.9% |
| 5 | 16.7% | 6.8% | 31.9% |
| 6 | 20.0% | 9.1% | 35.7% |
| 7 | 23.3% | 11.5% | 39.4% |
| 8 | 26.7% | 14.0% | 43.0% |

**Abbreviation:** CI=confidence interval, ORR = overall response rate

## 5.2. 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.

## 5.3. 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.

## 5.4. Endpoint Data Analysis

### 5.4.1. 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.

### 5.4.2. 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.

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

### 5.4.4. 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:

- $AUC_{0\text{-last}}$ Area under the plasma concentration-time curve calculated using linear trapezoidal summation from time 0 to time last, where "last" is the time of the last measurable concentration.
- $AUC_{0\text{-}24}$ Area under the plasma concentration-time curve from 0 to 24 hours, calculated using linear trapezoidal summation.
- $AUC_{0\text{-ing}}$ Area under the plasma concentration-time curve from 0 to infinity, calculated using the formula: $AUC_{0\text{-ing}} = AUC_{0\text{-last}} + C_{last} / \lambda_z$, where $\lambda_z$ is the apparent terminal elimination rate constant.
- $C_{max}$ Maximum observed plasma concentration
- $T_{max}$ Time of the maximum plasma concentration (obtained without interpolation)
- $t_{½}$ Terminal elimination half-life (whenever possible)
- $\lambda_z$ 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 explored. Additional PK or PD analyses may be performed, as deemed appropriate.