2.0 STUDY SYNOPSIS

Name of Sponsor/Company: Acerta Pharma BV	Individual Study Table Referring to Part of the Dossier Volume: Page:	(For National Authority Use Only)
Name of Study Treatment: ACP-196		
Name of Active Ingredient: ACP-196		

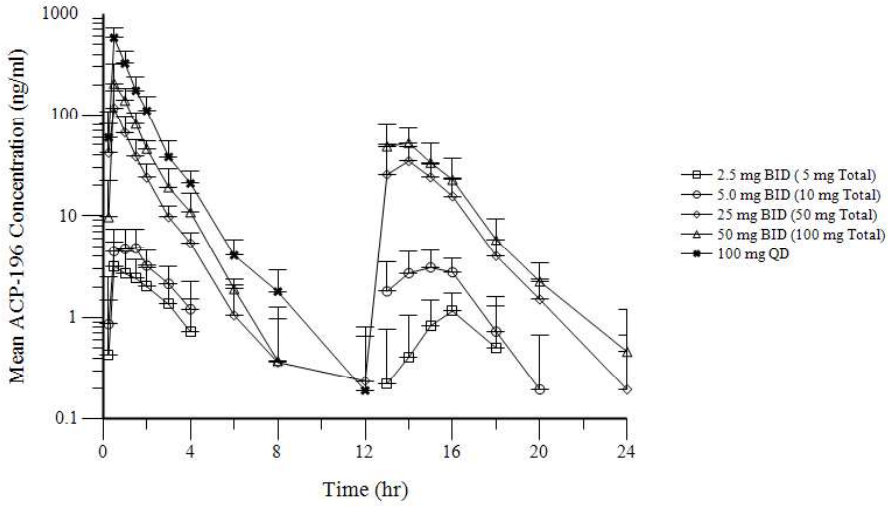
Title of Study:	A Phase 1, Single-center, Open-label, Sequential Dose-Escalation Study of ACP-196 in Healthy Subjects to Evaluate Safety, Pharmacokinetics, Pharmacodynamics, Food Effects, and Drug-Drug Interactions
Study Number:	ACE-HV-001
Investigator:	PPD
Study Site:	Celerion PPD Tempe, AZ 85283
Publications:	None
Study Period:	15 MAR 2014 (First subject dosed) 22 MAY 2014 (Last subject completed)
Phase of Development:	Phase 1

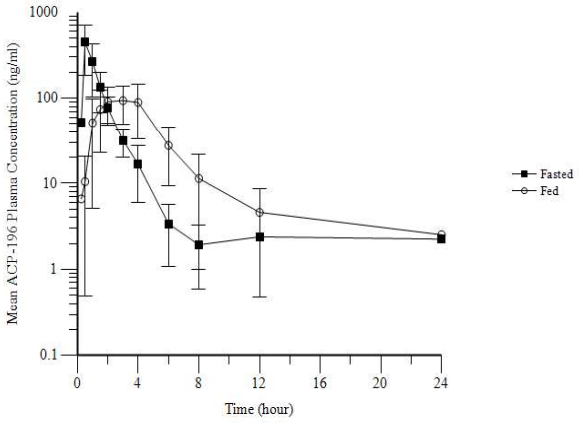
Objectives	**Primary:** • Determine pharmacokinetic (PK) profile of ACP-196 administered twice per day (BID) • Determine the effect of a high-calorie, high-fat meal on the PK profile of ACP-196 • To evaluate the effects of cytochrome P450 3A4 (CYP3A4) inhibition with itraconazole on the PK profile of ACP-196 • Evaluate the safety and tolerability of ACP-196 **Secondary:** • Evaluate the pharmacodynamic (PD) effects of ACP-196 administration on B-cell receptor (BCR)-induced B-cell activation in peripheral blood • Determine the dose at which full occupancy of Bruton tyrosine kinase (Btk) occurs
Methodology:	Open-label, escalating dose, safety, PK/PD, and food-effect, drug-drug interaction study of ACP-196 in healthy subjects. Enrollment was not randomized for Part 1 (Cohorts 1 to 5) and Part 3 (Cohort 7) of the study. Subjects in Part 2 of the study (Cohort 6) were randomized in a 1:1 ratio (6 subjects [3 men and 3 women] assigned to fasting/fed sequence and 6 subjects [3 men and 3 women] assigned to fed/fasting sequence).
Number of Subjects (Planned and Analyzed):	60 subjects planned 59 subjects analyzed

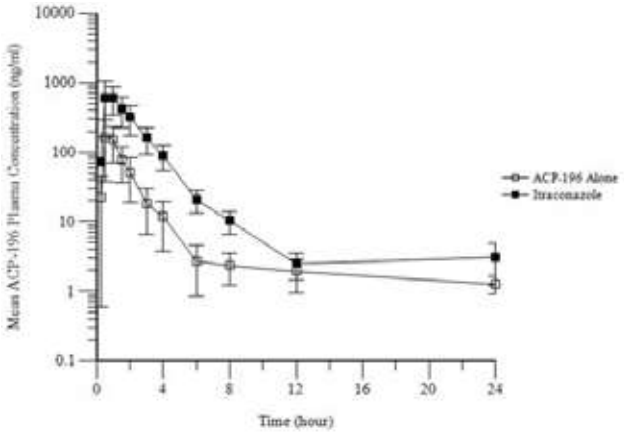
Diagnosis and Main Criteria for Inclusion:	**Diagnosis:** Not applicable for healthy volunteer study **Main Criteria for Inclusion:** • Age ≥ 18 years and ≤ 65 years at Visit 1 (screening). • Body mass index (BMI, weight/height^2) ≥ 18.0 and ≤ 30.0 kg/m^2. • Healthy as determined by medical history and physical examination and normal clinical laboratory and electrocardiogram (ECG) results. • Nonsmoker • Men of childbearing potential must be willing to abstain from heterosexual intercourse or use a barrier method of contraception during the study drug administration and follow-up periods and to refrain from sperm donation from the start of study administration throughout the study follow-up period and for 90 days after the last dose of study drug. • Women must be of non-childbearing status (ie, subject is surgically sterile due to a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range; or is menopausal [≥ 50 years of age with amenorrhea for ≥ 6 months]). • Willingness and ability to comply with scheduled visits, study drug administration, laboratory tests, other study procedures, and study restrictions. • Willingness and ability to swallow study drug capsules. • Personally signed informed consent for study participation.
Duration of Treatment:	**Part 1 Single Ascending Dose (Cohorts 1-5):** ACP-196 was administered orally either twice daily (BID) or once daily (QD) on Day 1 only, followed by a 2-day in-clinic observation period. Total duration of treatment was 1 day. **Part 2 Food Effect (Cohort 6):** ACP-196 was administered orally as a single dose of 75.0 mg QD in a fasting and a fed state, with a 7-day washout period between the 2 doses followed by a 2-day in-clinic observation period. Total duration of treatment was 2 days. **Part 3 Drug-Drug Interaction (Cohort 7):** ACP-196 was administered orally as a single dose of 50.0 mg QD alone on Day 1 and in combination with itraconazole on Day 9, followed by a 1-day in-clinic observation period. Total duration of treatment with ACP-196 was 2 days. Total duration of treatment with itraconazole was 6 days.

<table>
<tr><td>Test Product, Dose, Mode of Administration, and Batch No.:</td><td>ACP-196 was provided as 2.5- and 25.0-mg hard gelatin capsules prepared using standard pharmaceutical grade excipients.
<table>
<tr><th>Cohort</th><th>Dose (mg)</th><th>Total Dose (mg)</th><th>Capsule Strength (mg)</th><th>Number of Capsules per Dose</th><th>Total Number of Capsules</th></tr>
<tr><td>1</td><td>2.5 BID</td><td>5.0</td><td>2.5</td><td>1</td><td>2</td></tr>
<tr><td>2</td><td>5.0 BID</td><td>10.0</td><td>2.5</td><td>2</td><td>4</td></tr>
<tr><td>3</td><td>25.0 BID</td><td>50.0</td><td>25.0</td><td>1</td><td>2</td></tr>
<tr><td>4</td><td>50.0 BID</td><td>100.0</td><td>25.0</td><td>2</td><td>4</td></tr>
<tr><td>5</td><td>100.0 QD</td><td>100.0</td><td>25.0</td><td>4</td><td>4</td></tr>
<tr><td>6</td><td>75.0 QD</td><td>75.0</td><td>25.0</td><td>3</td><td>6 (Days 1 & 8)</td></tr>
<tr><td>7</td><td>50.0 QD</td><td>50.0</td><td>25.0</td><td>2</td><td>4 (Days 1 & 9)</td></tr>
</table>
ACP-196 2.5 mg Lot Number: CCI
ACP-196 25.0 mg Lot Number: CCI</td></tr>
<tr><td>Reference Therapy, Dose, Mode of Administration, and Lot No.:</td><td>Part 3 Drug-Drug Interaction Only:
Itraconazole (commercially available) was administered orally as 6 daily sequential dose administrations. The dose level was 200 mg BID for each dose administration (Day 4 to 8) except on Day 9 wherein a single dose was given in the morning and on a fasted state. On Day 4 to 8 each administration of itraconazole was given with a standard meal.
Itraconazole (Sporanox ®) Lot Number: CCI</td></tr>
<tr><td>Pharmacokinetics:</td><td>The following pharmacokinetic parameters were derived from the plasma concentrations of ACP-196: area under the concentration-time curve (AUC) from time 0 to last quantifiable concentration ($AUC_{0\text{-last}}$); AUC from time 0 to infinity ($AUC_{0\text{-inf}}$); maximum observed plasma concentration (C_{max}); time to reach C_{max} (T_{max}); terminal elimination half-life ($t_{1/2}$); terminal elimination rate constant (λz); and time delay between the time of dosing and the first measurable concentration (t_{lag}).</td></tr>
</table>

Pharmacodynamics:	• Occupancy of Btk by ACP-196 in peripheral blood mononuclear cells (PBMCs) • Effect of ACP-196 on biologic markers of B-cell function (eg, CD69 and CD86 expression)
Safety:	Overall safety profile characterized by type, frequency, severity, timing, and relationship to study drug administration of any adverse events (AEs), laboratory abnormalities, or ECG abnormalities.
Sample Size Calculation:	**Part 1:** The sample size was not based on a formal statistical hypothesis but on experience from similar types of healthy volunteer Phase 1 trials conducted in the past that successfully met study objectives. Six subjects in each cohort were dosed and analyzed. **Part 2:** The 12-subject sample size in the food-effect evaluation represented the minimum acceptable sample size according to regulatory guidance. Twelve subjects were dosed and analyzed. **Part 3:** The 18-subject sample size in the drug-drug interaction evaluation represented an acceptable sample size according to regulatory guidance. Seventeen subjects enrolled and 16 subjects completed Part 3, which still provided an acceptable sample size for this analysis.
PK Statistical Methods:	PK parameters for ACP-196 were calculated using non-compartmental methods. In Part 2, the ratio of fed and fasted population geometric means and 90% confidence intervals (90% CIs) for C_{max} and AUC were computed based on natural-log-transformed data. Similarly, in Part 3, the ratio of population geometric means and 90% CIs for Cmax and AUC associated with combined administration of itraconazole and ACP-196 relative to administration of ACP-196 alone were computed based on natural-log-transformed data.
PD Statistical Methods:	For PD parameters, testing for statistically significant changes from baseline and for dose-response was performed using log-transformation and parametric or non-parametric analyses as appropriate for the data.

Safety Statistical Methods:	The safety population included data from all subjects who receive ≥ 1 dose of ACP-196 (N=59). By-subject listings were created for important variables from each electronic CRF (eCRF) module. Appropriate summary tables for continuous variables and categorical variables were created. Data were characterized by part (Part 1, Part 2, and Part 3), dose level (in Part 1), fed or fasted condition, and sex as appropriate for the outcome measure. In addition, subject disposition and characteristics, study drug dosing, protocol deviations, concomitant medication usage were listed and summarized.
PK Results:	In Part 1, PK properties of ACP-196 were evaluated after oral administration of 2 daily divided doses of 2.5 to 50 mg and a single dose of 100 mg. Of the 30 subjects evaluated, all observed systemic concentrations of ACP-196. ACP 196 plasma T_{max} values were between 0.5 and 1.0 hour for all dose cohorts and were independent of dose level. The increase in mean C_{max} values was greater than dose proportional based on the increases of C_{max} from the first dose administered. When evaluating AUC_{0-12}, AUC_{0-24} or AUC_{0-inf}, the mean values increased in a dose proportional manner based on the increases of the total dose administered. Mean half-life values ranged from 0.97 to 2.1 hours, and appeared to decrease as the dose increased. The mean calculated oral clearance (CL/F: 165 to 219 L/h) and volume of distribution values (Vz/F: 233 to 612 L) appeared to be independent of the dose administered. **Mean ACP-196 Plasma Concentrations vs Time – Log scale** 

PK Results (continued):	ACP-196 was not detected in the urine of subjects receiving the 2.5- or 5.0-mg BID doses of ACP-196. ACP-196 was detected in urine of other subjects (0.4% to 0.6% of dose) and amounts increased in a dose-dependent manner. In Part 2, the effect of food on the PK of ACP-196 (75 mg) after a single oral administration was evaluated in 6 men and 6 women. Median ACP-196 plasma T_{max} values were increased in the fed state (2.5 hours) relative to the fasted state (0.5 hour). The mean plasma ACP-196 C_{max} values decreased to 27.3% of the values observed in the fasted state. In contrast, the relative exposure of ACP-196 remained mostly unchanged in the fed state. **Mean ACP-196 Plasma Concentration (ng/mL) versus Time (hour) Data Following 75 mg ACP-196 Administration in Fed (○) and Fasted (■) State.** 

PK Results (continued):	In Part 3, the effect of itraconazole on the PK of ACP-196 (50 mg) after a single oral administration was evaluated in 17 subjects. No difference in ACP-196 T_{max} values was observed in the presence or absence of itraconazole. Mean ACP-196 exposures (as assessed by C_{max}, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-inf}}$) increased in the presence of itraconazole. The mean plasma ACP-196 C_{max} values increased 3.7-fold in the presence of itraconazole. The mean plasma $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, and $AUC_{0\text{-inf}}$ values also increased between 4.9- to 5.1-fold in the presence of itraconazole. Mean CL/F and Vz/F values decreased in the presence of itraconazole (CL/F: 217 vs 44 L/h; Vz/F: 1190 vs 184 L). No differences in half-life values were observed (3.3 vs 2.5 hours). **Mean ACP-196 Plasma Concentration (ng/mL) versus Time (hour) Data Following 50 mg ACP-196 Administration in the Absence (□) or Presence (■) of Itraconazole.** 
PD Results:	The PD of ACP-196 was evaluated using a Btk occupancy assay and correlated with a functional assay that determines the level of Btk inhibition by measuring expression of CD69 and CD86 on B cells. A dose-dependent increase in Btk occupancy and corresponding decrease in CD69/86 expression was observed in this study. Full Btk occupancy (≥ 90%) and complete CD86 and CD69 inhibition (≥ 90%) occurred at the 75- and 100-mg single dosed cohorts 1 to 3 hours after administration. However, only the 100-mg cohort maintained high Btk occupancy (91.5%) and high BCR functional inhibition (CD86: 86 ± 3% and CD69: 78 ± 8%) at 24 hours. For subjects receiving a second dose of ACP-196 12 hours after the first administration, full Btk target occupancy was observed 3 hours after the second dose for the 50-mg dosed cohort (Btk occupancy 97 ± 4%).

Safety Results:	Sixteen of 59 (27%) enrolled subjects reported ≥ 1 AE. No SAEs occurred on the study. Of the AEs reported, 3 were assessed as related to ACP-196. Subject PPD (2.5 mg BID) experienced Grade 1 constipation reported as related to study drug. The constipation resolved with prunes; no medication was given to treat the constipation. Subject PPD (75 mg QD) experienced Grade 1 somnolence reported as related to study drug. The somnolence occurred the day after dosing and resolved after 1 day without any medication for treatment. Subject PPD (75 mg QD) experienced feeling cold (Grade 1) after study drug administration. The AE was reported as related to study drug. The AE resolved the same day without any medication. No study-drug related AEs lead to discontinuation from the study. However, Subject PPD (50 mg QD) was discontinued early due to an unrelated AE. This AE was hyperthyroidism and precluded the subject from further participation on the study. This condition was believed to have been present at study entry; however, the hyperthyroidism was not detected by the protocol-specified screening procedures. No effect was observed of ACP-196 on any of the laboratory parameters (ie, hematology, serum chemistry, urinalysis, cardiac troponin I, and C-reactive protein). No effect was observed of ACP-196 on physical exams, vital signs, or ECG parameters.
Conclusions:	ACP-196 is an orally bioavailable Btk inhibitor with fast absorption and rapid clearance that maintains target coverage over 24 hours with either 100 mg QD or 50 mg BID. ACP-196 was well tolerated in this study.