2. 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 FINISHED PRODUCT TBD		
NAME OF ACTIVE INGREDIENT ACP-196		

Title of Study: Randomized, Double-Blind, Double-Dummy, Placebo- and Positive Controlled, 4-Way Crossover Study to Assess the Effect of Single-Dose ACP-196 on the QTc Interval in Healthy Adult Subjects

Investigator: PPD

Study Center: Celerion
PPD
Tempe, Arizona 85283, US

Publication (Reference): Not applicable.

Studied Period: **PHASE OF DEVELOPMENT:** I
(date of first enrollment)
01 April 2016
(**date of last completed**)
09 May 2016

Objectives:

Primary

To evaluate effects of single therapeutic and supratherapeutic oral doses of ACP-196 on QT corrected for heart rate using Fridericia's correction (QTcF).

Secondary

1. To demonstrate sensitivity of this QTc assay using moxifloxacin as a positive control.
2. To evaluate the safety and tolerability of single therapeutic and supratherapeutic oral doses of ACP-196.
3. To describe changes in other electrocardiogram (ECG) parameters including PR and RR intervals, QRS duration, T wave morphology, presence of U waves, and outlier assessment.
4. To explore the relationship between the pharmacokinetics (PK) of ACP-196 and corresponding QTc intervals.

Exploratory

The relationship between QTcF and RR was evaluated, and if it was determined that there was a meaningful relationship between the two, then other adjustments of QT for RR were assessed, including individual subject adjustments based on predose and placebo treatment data.

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Study Endpoints
Thorough QTc ECGs
The primary ECG endpoint was the QTcF change from baseline at postdose timepoints (dQTcF). QTcF was calculated by dividing the QT interval by the cube root of the RR interval, QTcF = ($QT/RR^{1/3}$).

The secondary endpoints were as follows:

1. To assess assay sensitivity by evaluating dQTcF after moxifloxacin administration compared with matching placebo.
2. Other ECG parameters such as HR, QT, PR, RR, and QRS.
3. Morphological changes (eg, T wave morphology and U wave morphology of ECG waveform).
4. The relationship between the PK of ACP-196 and corresponding QTcF intervals.
5. If deemed necessary, individual-subject heart-rate corrections to QT were determined as exploratory endpoints.

Pharmacokinetics
The PK endpoints included the following PK parameters: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, C_{max}, T_{max}, λ_z, $t_{1/2}$, and CL/F, as appropriate, for ACP-196 in plasma.

Safety
Safety endpoints were incidence of treatment-emergent adverse events (TEAEs), physical examinations, vital signs, safety 12-lead ECGs, and clinical laboratory tests (hematology, serum chemistry, and urinalysis). Summary statistics for the laboratory safety tests, safety 12-lead ECGs, and vital signs may have also been computed and provided, as deemed clinically appropriate.

Methodology: This was a single-dose, randomized, double-blind, double-dummy, placebo- and positive-controlled, 4-period, balanced crossover study under fasting conditions. Subjects were randomized to 1 of 4 treatment sequences selected from a Latin Square: ABCD, BDAC, CADB, or DCBA. The treatments were as follows:

Treatment A: 100 mg ACP-196 (1 x 100 mg capsule), ACP-196 matching placebo (3 × 100 mg matching placebo capsules), and moxifloxacin matching placebo (1 × 400 mg matching placebo tablet) at Hour 0 on Day 1 after an overnight fast.

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Treatment B: 400 mg ACP-196 (4 × 100 mg capsules) and moxifloxacin matching placebo (1 × 400 mg matching placebo tablet) at Hour 0 on Day 1 after an overnight fast.

Treatment C: 400 mg moxifloxacin (1 × 400 mg tablet) and ACP-196 matching placebo (4 × 100 mg matching placebo capsules) at Hour 0 on Day 1 after an overnight fast.

Treatment D: ACP-196 matching placebo (4 × 100 mg matching placebo capsules) and moxifloxacin matching placebo (1 × 400 mg matching placebo tablet) at Hour 0 on Day 1 after an overnight fast.

Forty-eight (48) healthy adult non-tobacco using men and women were enrolled to have ≥ 40 evaluable subjects for QTc interval assessment.

Number of Subjects (Planned and Analyzed): A total of 48 subjects entered the study. A total of 41 subjects completed the study. Forty-eight (48) subjects were included in safety and ECG analyses. Data from 46 subjects who completed either Treatment A or Treatment B or both were included in the PK analysis.

Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were approved by the Principal Investigator (PI).

Product, Dose, Mode of Administration, and Lot Number: The study products were:

- Placebo to match acalabrutinib (ACP-196) 100 mg capsules for oral administration, Lot No. CCI .
- Moxifloxacin 400 mg Placebo film-coated tablets for oral administration, Lot No. CCI .
- ACP-196 100 mg capsules for oral administration, Lot No. CCI .
- AVELOX® (moxifloxacin hydrochloride) equivalent to 400 mg moxifloxacin tablets for oral administration, Lot No. CCI .

All study drugs were administered orally with approximately 240 mL of water.

Duration of Treatment: Total duration of the study was 14 days after the last study drug (or placebo) administration and last check for AE. The washout period was 7 days.

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Criteria for Evaluation:

Electrocardiograms:

The following ECG parameters were obtained for ECG analysis: Heart rate (HR), RR, PR, QRS, QT, and QTcF.

Pharmacokinetics:

The following PK parameters were calculated from the plasma ACP-196 individual concentration-time data: C_{max} (maximum plasma concentration), T_{max} (time of C_{max}), $AUC_{0\text{-}last}$ (area under the curve from time zero to last measurable concentration), $AUC_{0\text{-}inf}$ (area under the concentration-time curve from time zero to infinity), $AUC_{\%extrap}$ (percent of $AUC_{0\text{-}inf}$ extrapolated), $t_{1/2}$ (observed terminal elimination half-life), CL/F (apparent total body clearance), and K_{el} (apparent terminal elimination rate constant).

Safety:

Safety was evaluated by clinical laboratory tests, physical examination, vital signs, 12-lead ECGs, and adverse events (AEs).

Statistical Methods:

Electrocardiograms:

The QT was corrected for HR using Fridericia's correction. Each ECG parameter (HR, RR, PR, QRS, QT, and QTcF) was recorded in triplicate at each timepoint. The average of the triplicate ECG measurements was summarized and presented including average change from baseline values. The Holter monitoring times and the ECG data were listed by subject and timepoint. Any ECGs with comments were also listed separately. An analysis of covariance (ANCOVA) appropriate for a 4-period crossover design was used to analyze dQTcF at each timepoint post baseline. A categorical analysis for each ECG parameter and hysteresis assessment (U_{max}) was performed. The ECG – pharmacokinetic relationship was also analyzed and graphically presented.

Pharmacokinetics:

Summary statistics, including sample size (n), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV%), median, minimum, maximum were calculated for all nominal concentration timepoints and PK parameters. In addition, geometric means (Geom Mean) and geometric CV% (Geom CV%) were calculated for PK parameters.

Safety:

All AEs that occurred during this clinical trial were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) Version 19.0. Concomitant medications administered during the study were coded with the World Health Organization (WHO) Dictionary Version 01 Mar 2016.

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TEAEs were summarized for subject incidence and number of events reported. Actual values and change from baseline values were summarized by treatment and timepoint for safety laboratory and vital sign parameters. Shifts from baseline were presented for safety laboratory and safety ECG results. All safety data were presented in by-subject listings.

SUMMARY – CONCLUSIONS

Electrocardiogram Results:

Mean electrocardiogram parameter values from Holter ECG analysis were within normal limits throughout the study. Overall, mean HR values did not exceed 68.5 bpm and mean QTcF values did not exceed 421.4 msec. Mean values for all ECG parameters analyzed (HR, PR, QRS, QT, QTcF, and RR) after ACP-196 were comparable to placebo. There were no remarkable findings in the categorical analysis with similar trends observed with regard to subject incidence for ACP-196 and placebo. Individual (triplicate –average) QTcF values remained < 450 msec after treatment with ACP-196 throughout the electrocardiogram assessments for this study). Electrocardiogram abnormalities were minimally observed with no reports of U waves and minimal reports of T-wave abnormalities.

The upper bounds of the 90%, 2-sided CI of the LSM difference in QTcF change from baseline (dQTcF) for both 100 mg ACP-196 and 400 mg ACP-196 were < 10 msec at all 12 postdose timepoints over 24 hours, with results ranging from 0.699 msec to 3.527 msec for 100 mg ACP-196, and from 1.757 msec to 4.181 msec for 400 mg.

Since none of the mean ddQTcF exceeded 5 msec for the supratherapeutic dose of ACP-196 (400 mg) across all sampling timepoints, no further assessment of hysteresis was needed, and a direct relationship between ddQTcF and ACP-196 concentrations was assessed. The predicted value (90% 2-sided confidence limits) of ddQTcF at the geometric mean value of C_{max} for 100 mg ACP-196 was 0.025 msec (-0.369, 0.419) and for 400 mg ACP-196 was 0.240 msec (-0.579, 1.059), based on the modeling of the ACP-196 concentrations and ddQTcF relationship.

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A moxifloxacin treatment arm was included in the study to serve as a positive control and to demonstrate that the study could detect a QTcF prolongation of > 5 msec. The assay was adequately sensitive to test for prolongation as the lower bounds of the 97.5% 2-sided CI were > 5 msec at Hours 1 through 4 for dQTcF least-squares means (LSM) differences between moxifloxacin and placebo, with results ranging from 6.6564 to 10.788 msec.

This study demonstrated that there is no significant effect of ACP-196 on QTc prolongations at either the therapeutic or supratherapeutic dose. These results are consistent with previous findings of ECG results obtained from healthy volunteers (ACE-HV-001) as well as in subjects with hematologic malignancies (ACE-CL-001).

Pharmacokinetic Results:
A summary of plasma ACP-196 PK parameters is presented in the following table.

Summary of Plasma ACP-196 Pharmacokinetic Parameters Following Treatments A and B

	Treatment A (100 mg ACP-196)		Treatment B (400 mg ACP-196)	
Pharmacokinetic Parameters	**Geometric Mean (Geom. CV%)**	**n**	**Geometric Mean (Geom. CV%)**	**n**
AUC0-last (ng*hr/mL)	677.48 (50.5)	44	3965.5 (60.4)	43
AUC0-inf (ng*hr/mL)	662.53 (47.7)	38	4652.9 (51.9)	31
AUC%extrap (%)	1.7016 ± 3.2520	38	0.44140 ± 0.58351	31
Cmax (ng/mL)	465.87 (83.2)	44	1672.3 (64.5)	43
Tmax (hr)	0.7507 (0.50, 3.05)	44	1.5006 (0.50, 4.00)	43
t1/2 (hr)	2.6442 ± 2.7156	38	3.5127 ± 2.6253	31

Treatment A: 100 mg ACP-196 (therapeutic dose)
Treatment B: 400 mg ACP-196 (supratherapeutic dose)
Tmax is presented as Median (Minimum, Maximum)
AUC%extrap and t1/2 are presented as Mean ± SD
Acerta Project No.: ACE-HV-005

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Mean plasma ACP-196 peak concentration and total exposures (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) were respectively 3.6-, 5.9-, and 7-fold higher after administration of 400 mg ACP-196 (supratherapeutic dose, Treatments B) compared to the administration of 100 mg ACP-196 (therapeutic dose, Treatment A).

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Median time to reach C_{max} (ie, T_{max}) was 1.5 hours after Treatment B compared with 0.75 hours for Treatment A. Mean half-life for Treatment B was slightly longer than for Treatment A (3.5 versus 2.6 hours).

Comparison of ACP-196 AUC and C_{max} by H. pylori status did not reveal an effect of H. pylori infection on ACP-196 exposure at either dose level.

Safety Results:

There were no deaths, SAEs, or subject discontinuations due to AEs in this study.

There was 1 event of Grade 1 abnormal electrocardiogram ST-T segment after treatment with100 mg ACP-196 in Period 1 and considered by the PI to be related to the study treatment. This event was not further noted in the succeeding periods. Five (5) subjects were discontinued from treatment on the study due to out-of-range ECG parameters; these were noted at check-in assessments and were not considered by the PI to be clinically significant.

There were 3 abnormal laboratory values reported as AEs: increased AST (100 mg ACP-196) and increased neutrophil count and WBC count (400 mg ACP-196). All laboratory values reported as AEs were reported as Grade 1 in intensity and considered by the PI to be unrelated to the study treatments, although the reported event of increased AST (which occurred in a subject after drinking 12 beers, and occurred with an AST:ALT ratio of approximately 2:1 consistent with an alcohol effect) met CTCAE 4.03 criteria for Grade 3.

A total of 66 AEs were experienced by 26 (54%) subjects. Subject incidence and number of AEs reported was similar for 100 mg ACP-196, moxifloxacin, and placebo, but were higher for the supratherapeutic dose, 400 mg ACP-196 particularly for events of headache, nausea, and diarrhea. These were the most common events reported across the study, and occurred as non-serious Grade 1 events except for one event of diarrhea which was non-serious Grade 2. Sixty-three (63) AEs were Grade 1 (mild) in intensity and 3 were Grade 2 (moderate). The PI considered 46 events to be related to the study treatment and 20 events to be unrelated.

There were no further remarkable findings in the safety assessments for clinical laboratory, vital signs, or physical examinations.

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Conclusions:

Pharmacokinetics:

Pharmacokinetics

- ACP-196 AUC and C_{max} at the therapeutic dose of 100 mg were generally comparable to previous studies in healthy volunteers and subjects with hematologic malignancies.
- Comparison of acalabrutinib AUC and C_{max} by H. pylori status did not reveal an effect of H. pylori infection on ACP-196 exposure at either dose level.
- A slightly greater-than dose-proportional increase in AUC from 100 to 400 mg established a supratherapeutic ACP-196 exposure suitable to explore the relationship between the PK of ACP-196 and corresponding QTc intervals.

Electrocardiograms:

- Electrocardiogram parameter LSM and mean values for ECG parameters (HR, PR, QRS, QT, QTcF, and RR) were comparable between ACP-196 treatments and placebo with no remarkable observations in mean change from baseline values or within categorical analysis for each ECG parameter.
- Electrocardiogram wave form abnormalities were minimally reported. There were no U waves reported in this study. T-wave abnormalities occurred in ≤ 3 [7%] subjects after ACP-196 treatment.
- The upper bounds of the 90%, 2-sided CI of the LSM difference in QTcF change from baseline (dQTcF) for both 100 mg ACP-196 and 400 mg ACP-196 were < 10 msec at all 12 postdose timepoints over 24 hours; These results conclude that 100 mg ACP-196 and 400 mg ACP-196 do not prolong QT intervals.
- The predicted value (90% 2-sided confidence limits) of ddQTcF at the geometric mean value of C_{max} for 100 mg ACP-196 was 0.025 msec (-0.369, 0.419) and for 400 mg ACP-196 was 0.240 msec (-0.579, 1.059) based on the modeling concentrations – ddQTcF relationship. The upper limit of the 90% 2-sided CI of the predicted ddQTcF at C_{max} was < 10 msec for both treatments.

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- The lower bounds of the 97.5% 2-sided CI were > 5 msec at Hours 1 through 4 for dQTcF LSM differences between moxifloxacin and placebo; therefore, the assay was adequately sensitive to test for QT prolongation.

Safety:

- ACP-196 administered at 100 mg and at the supratherapeutic dose of 400 mg was generally well tolerated by the healthy volunteers in this study.

- Incidence rates of headache, nausea, and diarrhea were higher after the supratherapeutic dose of 400 mg ACP-196 than the 100 mg dose or moxifloxacin or placebo; however, these AEs were primarily Grade 1 and were self-limited.

Date of Report: 24 October 2016