## 2. SYNOPSIS

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| **NAME OF ACTIVE INGREDIENT**<br><br>ACP-196 | | |

**Title of Study:** A 2-Part, Open-Label, Single-Dose Study to Investigate the Influence of Hepatic Insufficiency on the Pharmacokinetics of ACP-196

**Investigators:**

PPD

PPD

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**Study Centers:**

University of Miami

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Miami, Florida 33136, US

Orlando Clinical Research Center

PPD

Orlando, Florida 32809, US

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Knoxville, Tennessee 37920, US

**Publication (Reference):** Not applicable.

**Studied Period:**
**(date of first enrollment)**
21 October 2014 (First subject dosed)
(**date of last completed**)
02 February 2015

**PHASE OF DEVELOPMENT:** I

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**Objectives:**

Part 1

Primary: To compare the pharmacokinetics (PK) after single-dose administration of ACP-196 50 mg to subjects with mild and moderate hepatic insufficiency with that of healthy (mean) matched control subjects (ie, by mean age and mean weight).

Secondary: To evaluate the safety and tolerability of ACP-196 in subjects with mild and moderate hepatic insufficiency and in healthy control subjects after single dose administration of ACP-196 50 mg.

Part 2 (Optional)

Primary: To compare the PK after single dose administration of ACP-196 50 mg to subjects with severe hepatic insufficiency with that of healthy control subjects from Part 1.

Secondary: To evaluate the safety and tolerability of ACP-196 in subjects with severe hepatic insufficiency after single dose administration of ACP-196 50 mg.

Following a review of the safety and PK data from Part 1, a decision was made to not conduct Part 2 of the study.

**Methodology:** This was a 2-part, non-randomized, open label, single-dose study. Part 1 of the study compared the PK of ACP-196 in subjects with mild and moderate hepatic insufficiency (based on the Child-Pugh classification) to healthy (mean) matched control subjects for age and weight. Part 2 of the study, if conducted, was to compare the PK of ACP-196 in subjects with severe hepatic insufficiency to the healthy control subjects from Part 1. As per Sponsor's decision, Part 2 of the study was not conducted.

**Number of Subjects (Planned and Analyzed):** A total of 18 subjects entered the study. All 18 subjects completed the study and were included in the PK, statistical, and safety analyses.

**Diagnosis and Main Criteria for Inclusion:** All subjects enrolled in this study were approved by the principal investigators.

**Product, Dose, Duration, Mode of Administration, and Batch Number:** Each subject received a single dose of ACP-196 50 mg (2 x 25-mg hard gelatin capsule) administered orally with approximately 240 mL of water on the morning of Day 1, at Hour 0, following an overnight fast.

**Duration of Treatment:** The total duration of participation, including the screening period for each subject, was 17 to 37 days.

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**Criteria for Evaluation:**

**Pharmacokinetics:** Blood samples for the determination of ACP-196 and for assessment of protein binding were collected through 48 hours postdose. Plasma concentrations of ACP-196 were determined using validated bioanalytical methods at BASi, Sample Management (West Lafayette, Indiana). The following noncompartmental PK parameters were calculated from the total plasma ACP-196 concentration-time data: $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $C_{max}$, $T_{max}$, $T_{last}$, $\lambda_z$, $t_{½}$, CL/F, and $V_z$/F.

Unbound PK parameters for ACP-196 were to be computed from unbound ACP-196 concentration-time data. However, unbound ACP-196 concentrations could not be determined due to problems related to validation of an assay of ACP-196 in dialysate.

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

**Statistical Methods:**

**Pharmacokinetics:** Summary statistics, including sample size (N), arithmetic mean, standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum were calculated for all nominal concentration time points and PK parameters. In addition, geometric mean and geometric CV% were calculated for $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-inf}}$, and $C_{max}$. The plasma concentrations and PK parameters of ACP-196 were tabulated by severity of liver disease (mild or moderate hepatic insufficiency, or healthy control) and listed by subject and nominal sample time, or parameter as appropriate, for all subjects in the PK Population. Mean and individual plasma ACP-196 concentration-time profiles were presented on linear and semi-log scales.

**Statistical Analysis**

Individual $AUC_{0\text{-inf,}}$ $AUC_{0\text{-last}}$, and $C_{max}$ values of ACP-196 after a single-dose administration of ACP-196 50 mg to subjects with mild or moderate hepatic insufficiency and healthy control subjects (matched by mean age and weight to subjects with hepatic impairment) were ln-transformed and evaluated with a linear mixed-effects analysis of covariance (ANCOVA). The ANCOVA model contained a categorical factor for group (mild or moderate hepatic impaired subjects, healthy [mean] matched control subjects), categorical covariate for sex and continuous covariates for age and weight. The 90% confidence interval (CI) of the difference was calculated for each comparison.

**Safety:** AEs were summarized by group for subject incidence and number of events reported. Laboratory values, vital sign results and 12-lead ECG results were summarized and change from baseline values were presented. All clinical safety data were listed chronologically by group (hepatic insufficiency [A and B] and normal hepatic function [N]) and subject, and assessment timepoints, including rechecks and unscheduled assessments.

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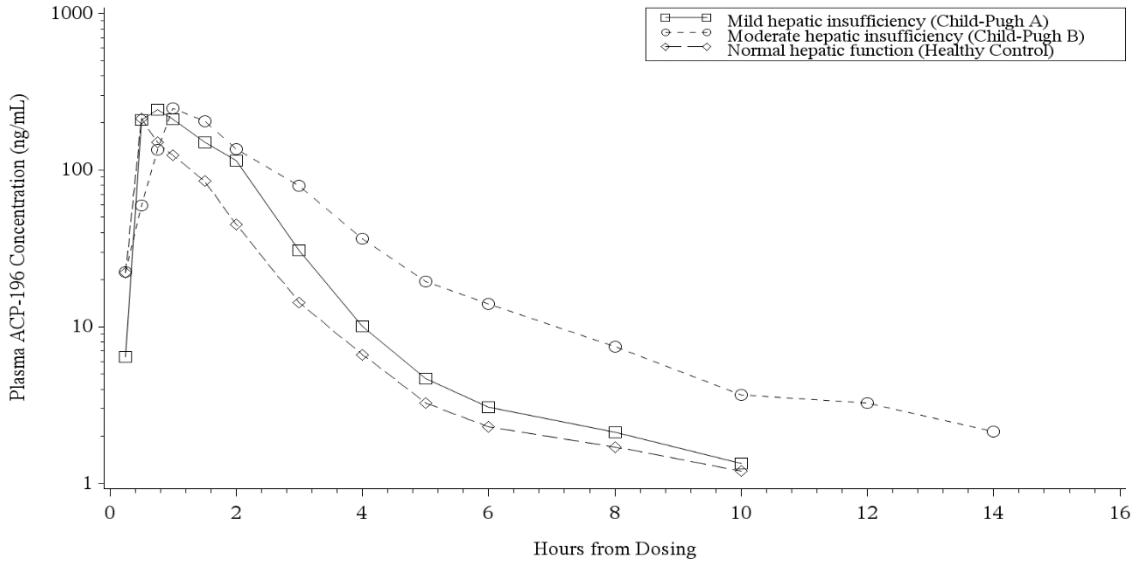
**SUMMARY – CONCLUSIONS**

**Pharmacokinetic Results:** Mean total plasma ACP-196 concentration-time profiles after a single oral dose of ACP-196 50 mg in subjects with mild and moderate hepatic insufficiency (Child-Pugh Groups A and B, respectively) and subjects with normal hepatic function (healthy control Group N) are presented below on a semi-log scale:

**Mean Plasma ACP-196 Concentrations Versus Time Comparing ACP-196 in Subjects with Mild and Moderate Hepatic Insufficiency and in Healthy Controls (Semi-Log Scale)**



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A summary of total plasma ACP-196 PK parameters is presented in the table below:

**Summary of Plasma ACP-196 Pharmacokinetic Parameters**

| Pharmacokinetic Parameters | ACP-196 in Group A (N=6) | ACP-196 in Group B (N=6) | ACP-196 in Group N (N=6)[f] |
|---|---|---|---|
| **Geometric Mean** | | | |
| $AUC_{0\text{-last}}$ (ng*hr/mL)[a] | 362 (61.6%) | 310 (191%) | 206 (102%) |
| $AUC_{0\text{-inf}}$ (ng*hr/mL)[a] | 366 (61.2%) | 326 (178%) | 293 (16.7%) |
| $AUC_{0\text{-}24}$ (ng*hr/mL)[a] | NA | 518 (NA)[e] | NA |
| $C_{max}$ (ng/mL)[a] | 292 (51.2%) | 156 (247%) | 159 (180%) |
| **Arithmetic Mean** | | | |
| $AUC_{0\text{-last}}$ (ng*hr/mL)[b] | 409 ± 206 (50.3%) | 535 ± 606 (113%) | 250 ± 114 (45.5%) |
| $AUC_{0\text{-inf}}$ (ng*hr/mL)[b] | 413 ± 206 (50.0%) | 548 ± 608 (111%) | 297 ± 53.1 (17.9%) |
| $AUC_{0\text{-}24}$ (ng*hr/mL)[b] | NA | 518 (NA)[e] | NA |
| $AUC_{\%extrap}$ (%)[c] | 1.16 ± 0.372 | 4.75 ± 5.94 | 1.41 ± 0.401 |
| $C_{max}$ (ng/mL)[b] | 323 ± 169 (52.5%) | 288 ± 338 (118%) | 224 ± 124 (55.1%) |
| $T_{max}$ (hr)[d] | 0.750 (0.50, 1.50) | 1.00 (0.50, 3.00) | 0.50 (0.25, 1.00) |
| $T_{last}$ (hr)[d] | 9.00 (6.00, 10.0) | 12.00 (5.00, 48.0) | 8.00 (8.00, 10.0) |
| $t_{½}$ (hr)[c] | 2.25 ± 0.873 | 7.92 ± 12.7 | 2.24 ± 0.470 |
| $\lambda_z$ (1/hr)[c] | 0.343 ± 0.118 | 0.312 ± 0.300 | 0.321 ± 0.0699 |
| CL/F (L/hr)[c] | 157 ± 91.1 | 281 ± 373 | 172 ± 26.5 |
| $V_z$/F (L)[c] | 471 ± 222 | 2135 ± 2715 | 545 ± 65.1 |

a: Presented as Geometric Mean (Geom. CV%)
b: Presented as Arithmetic Mean ± SD (CV%)
c: Presented as Arithmetic Mean ± SD
d: Presented as Median (Minimum, Maximum)
e: N = 1 for $AUC_{0\text{-}24}$ in Group B.
f: N = 5 for $AUC_{0\text{-inf}}$, $t_{½}$, $\lambda_z$, CL/F, and $V_z$/F in Group N.
Group A: A single oral dose of ACP-196 50 mg in subjects with mild hepatic insufficiency (Child-Pugh A)
Group B: A single oral dose of ACP-196 50 mg in subjects with moderate hepatic insufficiency (Child-Pugh B)
Group N: A single oral dose of ACP-196 50 mg in subjects with normal liver function (Healthy Control)
SD = Standard Deviation; Geom. CV% = Geometric Coefficient of Variation

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The statistical comparisons of plasma ACP-196 PK parameters are summarized in the following table:

**Statistical Comparison of ACP-196 Pharmacokinetic Parameters**
**Group A Versus Group N**

| | Geometric LSM | | | | |
|---|---|---|---|---|---|
| **Pharmacokinetic Parameter** | **ACP-196 in Group A (N=6)** | **ACP-196 in Group N (N=6)** | **GMR (%)** | **90% Confidence Intervals** | **Group Effect p-value** |
| $AUC_{0\text{-}inf}$ (ng*hr/mL) | 360.37 | 312.81[a] | 115.20 | 44.48 – 298.39 | 0.9273 |
| $AUC_{0\text{-}last}$ (ng*hr/mL) | 377.05 | 198.66 | 189.80 | 59.39 - 606.54 | 0.6135 |
| $C_{max}$ (ng/mL) | 291.34 | 153.03 | 190.38 | 46.30 - 782.73 | 0.6721 |

Parameters were ln-transformed before analysis.
Geometric least-squares means (LSMs) were calculated by exponentiating the LSM from ANOVA.
% Geometric Mean Ratio (GMR) = 100 × (test/reference)
Group A: A single oral dose of ACP-196 50 mg in subjects with mild hepatic insufficiency (Child-Pugh A, Test)
Group N: A single oral dose of ACP-196 50 mg in subjects with normal liver function (Healthy Control, Reference)
[a] N=5

**Statistical Comparison of ACP-196 Pharmacokinetic Parameters**
**Group B Versus Group N**

| | Geometric LSM | | | | |
|---|---|---|---|---|---|
| **Pharmacokinetic Parameter** | **ACP-196 in Group B (N=6)** | **ACP-196 in Group N (N=6)** | **GMR (%)** | **90% Confidence Intervals** | **Group Effect p-value** |
| $AUC_{0\text{-}inf}$ (ng*hr/mL) | 298.09 | 312.81[a] | 95.29 | 40.04 – 226.81 | 0.9273 |
| $AUC_{0\text{-}last}$ (ng*hr/mL) | 293.94 | 198.66 | 147.96 | 51.70 - 423.47 | 0.6135 |
| $C_{max}$ (ng/mL) | 156.03 | 153.03 | 101.96 | 28.36 – 366.54 | 0.6721 |

Parameters were ln-transformed before analysis.
Geometric least-squares means (LSMs) were calculated by exponentiating the LSM from ANOVA.
% Geometric Mean Ratio (GMR) = 100 × (test/reference)
Group B: A single oral dose of ACP-196 50 mg in subjects with moderate hepatic insufficiency (Child-Pugh B, Test)
Group N: A single oral dose of ACP-196 50 mg in subjects with normal liver function (Healthy Control, Reference)
[a] N=5

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ACP-196 absorption was slightly delayed and exposure was slightly higher in subjects with mild and moderate hepatic insufficiency, compared with healthy control subjects.

Large intersubject variability was observed in geometric mean $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and $C_{max}$ in all cohorts, with the moderate hepatic insufficiency cohort being the most variable, followed by the normal and mild hepatic insufficiency cohorts.

Geometric mean $C_{max}$ values were 1.90-fold greater in subjects with mild hepatic insufficiency (90% CI: 0.46 to 7.83) and were similar (1.02-fold) in subjects with moderate hepatic insufficiency (95% CI: 0.28 to 3.67), relative to subjects with normal hepatic function.

Geometric mean $AUC_{0\text{-last}}$ values were 1.90-fold greater in subjects with mild hepatic insufficiency (90% CI: 0.59 to 6.07) and 1.48-fold in subjects with moderate hepatic insufficiency (90% CI: 0.52 to 4.23), relative to subjects with normal hepatic function.

Geometric mean $AUC_{0\text{-inf}}$ values were 1.15-fold greater in subjects with mild hepatic insufficiency (90% CI: 0.44 to 2.98) and 0.95-fold in subjects with moderate hepatic insufficiency (90% CI: 0.40 to 2.27), relative to subjects with normal hepatic function.

Differences in geometric mean ratio for $AUC_{0\text{-inf}}$ in hepatic impairment groups relative to normal subjects were generally smaller than differences in $AUC_{0\text{-last}}$ primarily because $AUC_{0\text{-inf}}$ data could not be calculated for a low exposure subject in the normal cohort (N=5).

No sex, age, or weight effects were observed for ACP-196 $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and $C_{max}$.

No apparent trends were observed between Child-Pugh scores, albumin levels, or bilirubin levels and ACP-196 $AUC_{0\text{-inf}}$ and $C_{max}$ values.

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**Safety Results:** ACP-196 50 mg was well tolerated. No deaths, serious adverse events (SAEs), or subject discontinuations due to AEs occurred in this study. Overall, treatment-emergent adverse events (TEAEs) were experienced by 11% of subjects. TEAEs were Grade 1 in severity, and the PI considered 1 event (headache) possibly related and 1 event (dyspepsia) not related to the study treatments. No remarkable findings occurred in the clinical laboratory parameters, vital signs, ECGs, or physical examinations.

**Conclusions:**

ACP-196 absorption was slightly delayed and exposure appeared slightly higher in subjects with mild and moderate hepatic insufficiency, compared with healthy control subjects.

Large intersubject variability was observed in geometric mean AUC0-inf, AUC0-last and Cmax in all cohorts, with the moderate hepatic insufficiency cohort being the most variable, followed by the normal and mild hepatic insufficiency cohorts.

ACP-196 is metabolized in the liver. In this hepatic impairment study, data showed an increase in ACP-196 exposure. After a single dose administration the AUC of ACP-196 increased 1.90- and 1.48-fold in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment compared with subjects with normal liver function.

No apparent trends were observed between Child-Pugh scores, albumin levels, or bilirubin levels and ACP-196 AUC0-inf and Cmax values.

Single oral administration of ACP-196 50 mg was safe and well tolerated by the subjects with mild and moderate hepatic insufficiency (Child Pugh A and B) and by the healthy control subjects in this study.

**Date of Report:** 11 May 2016