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: A Phase 1, Single-Center, Open-Label, Fixed-Sequence, 2-Period, 3-Part Study to Evaluate the One-Way Interaction of Calcium Carbonate, Omeprazole, or Rifampin on ACP-196 in Healthy Adult Subjects

Investigator(s): PPD

Study Center(s):
Celerion
PPD
Tempe, Arizona 85283
USA

Publication (Reference): Not applicable

Studied Period: **PHASE OF DEVELOPMENT:** I
(date of first enrollment)
21 September 2014
(**date of last completed**)
16 October 2014

Objectives:
Part 1 (Calcium Carbonate)
Primary: To evaluate and compare the pharmacokinetic (PK) profile of ACP-196 after single dose administration with and without a single dose of calcium carbonate.
Secondary: To evaluate the safety and tolerability of a single dose of ACP-196 when administered alone and coadministered with a single dose of calcium carbonate.

Part 2 (Omeprazole)
Primary: To evaluate and compare the PK profile of ACP-196 after single dose administration with and without multiple doses of omeprazole.
Secondary: To evaluate the safety and tolerability of a single dose of ACP-196 when administered alone and coadministered with multiple doses of omeprazole.

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Part 3 (Rifampin)
Primary 1: To evaluate and compare the PK profile of ACP-196 after single dose administration with and without a single dose of rifampin.
Primary 2: To evaluate and compare the PK profile of ACP-196 after single dose administration with and without multiple doses of rifampin.
Secondary: To evaluate the safety and tolerability of a single dose of ACP-196 when administered alone and coadministered with multiple doses of rifampin.

Methodology: This was a 3-part, Phase 1 study. Each part was conducted as an open-label, single-center, 2-period, fixed-sequence study to evaluate the one-way interaction of calcium carbonate, omeprazole, or rifampin on ACP-196 in healthy non-tobacco using adult subjects under fasting conditions. Subjects received each treatment on 1 occasion and subjects only participated in 1 part of the study. Study parts may have been conducted concurrently. Screening of subjects occurred within 28 days before the first dose of study drug.

Part 1 (Calcium Carbonate)
On Day 1 of Period 1, a single oral dose of 100 mg ACP-196 (1 x 100 mg capsule) was administered (Treatment A) followed by PK sampling for 24 hours. In Period 2, a single oral dose of 1 g calcium carbonate (2 x 500 mg chewable tablets) was coadministered with a single oral dose of 100 mg ACP-196 (1 x 100 mg capsule) on Day 1 (Treatment B) followed by PK sampling for ACP-196 for 24 hours. There was no washout between the dose in Period 1 and the dose in Period 2.

Part 2 (Omeprazole)
On Day 1 of Period 1, a single oral dose of 100 mg ACP-196 (1 x 100 mg capsule) was administered (Treatment C) followed by PK sampling for 24 hours. In Period 2, multiple oral doses of 40 mg omeprazole (1 x 40 mg capsule) were administered QD for 5 consecutive days with a single oral dose of 100 mg ACP-196 (1 x 100 mg capsule) coadministered on Day 5 (Treatment D). PK samples for ACP-196 and omeprazole were taken for 24 hours after dosing on Day 5. There was no washout between the dose in Period 1 and the first dose in Period 2.

Part 3 (Rifampin)
On Day 1 of Period 1, a single oral dose of 100 mg ACP-196 (1 x 100 mg capsule) was administered (Treatment E) followed by PK sampling for 24 hours. In Period 2, multiple oral doses of 600 mg rifampin (2 x 300 mg capsules) were administered QD for 9 consecutive days with a single oral dose of 100 mg ACP-196 (1 x 100 mg capsule) coadministered on Day 1 and Day 9 (Treatment F). PK samples for ACP-196 and rifampin were taken for 24 hours after dosing on Day 1 and Day 9. Morning urine collection was used to measure 6β-hydroxycortisol and free cortisol concentrations on Days 1, 4, 7, and 9 to evaluate the level of CYP enzyme induction. There was no washout between the dose in Period 1 and the first dose in Period 2.

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All Parts
In each part of the study, subjects were housed from the day before dosing in Period 1, at the time indicated by the Clinical Research Unit (CRU), until after the last PK sample collection and/or study procedure in Period 2. At all times, a subject may have been required to remain at the CRU for longer at the discretion of the PI.

Safety was monitored throughout the study by repeated clinical and laboratory evaluations.

The clinic attempted to contact subjects using their standard procedures approximately 14 days after the last study drug administration to determine if any adverse event (AE) had occurred since the last dose of study drug(s). Subjects who terminated the study early were contacted if the PI deemed it necessary. Subjects may have been replaced at the discretion of the Sponsor.

Number of Subjects (Planned and Analyzed):
A total of 72 subjects entered the study and 24 subjects received treatment in one of 3 study parts. A total of 70 subjects completed the study, with 23 subjects each completing Parts 1 and 2, and 24 subjects completing Part 3. In Part 1, Subject PPD was dropped before Period 2 (Treatment B) dosing due to an AE. In Part 2, Subject PPD withdrew before Period 2 (Treatment D) due to personal reasons. All available data from the 72 subjects enrolled were included in the summary statistics and statistical comparisons of PK parameters. All 72 subjects were included in the safety analysis.

Diagnosis and Main Criteria for Inclusion: All subjects enrolled in this study were judged by the Investigator to be normal, healthy volunteers who met all inclusion and none of the exclusion criteria.

Test Product, Dose, Duration, Mode of Administration, and Batch Number:
The test products were ACP-196 hard gelatin capsules (Batch No. CCI), calcium carbonate supplied as TUMS® chewable tablets (Lot No. CCI), omeprazole supplied as Prilosec® omeprazole delayed-release capsules (Lot No. CCI), and rifampin supplied as Rifadin® rifampin capsules (Lot No. CCI).

All study drugs were administered orally, after an overnight fast, with approximately 240 mL of water.

Duration of Treatment: The total study duration for each part was up to 44, 48, and 52 days for Parts 1, 2, and 3, respectively, from screening to end of study procedures.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number:
Not applicable.

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Criteria for Evaluation:

Pharmacokinetics: Serial blood samples were obtained for the determination of ACP-196 in plasma and PK parameters were calculated including, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, $AUC_{0\text{-inf}}$, C_{max}, $AUC_{\%extrap}$, T_{max}, λ_z, CL/F and $t_{½}$, using Phoenix® WinNonlin® Version 6.3. The primary PK endpoints were $AUC_{0\text{-inf}}$ and C_{max}.

Serial blood samples were obtained for the determination of omeprazole in plasma and PK parameters were calculated including $AUC_{0\text{-last}}$, AUC_{τ}, $C_{max,ss}$, and $T_{max,ss}$ using Phoenix® WinNonlin® Version 6.3.

Serial blood samples were obtained for the determination of rifampin in plasma and PK parameters were calculated including, $AUC_{0\text{-last}}$, $AUC_{0\text{-}24}$, C_{max}, T_{max}, AUC_{τ}, $C_{max,ss}$, and $T_{max,ss}$ using Phoenix® WinNonlin® Version 6.3.

Pharmacodynamics: Urine samples were obtained for the determination of 6β-hydroxycortisol and free cortisol concentrations in urine. Ratios of 6β-hydroxycortisol to free cortisol were calculated using SAS® Version 9.3.

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

Statistical Methods:

Pharmacokinetics: All ACP-196, omeprazole, and rifampin PK concentrations and/or PK parameter descriptive statistics were generated using SAS® Version 9.3.

Summary statistics, including sample size (N), arithmetic mean (AM), standard deviation (SD), coefficient of variation (CV%), median, minimum, and maximum were calculated for all nominal concentration time points. Excluded subjects were included in the concentration table listings, but were excluded from the summary statistics and noted as such in the tables. Mean and individual concentration-time profiles were presented on linear and semi-log scales. Linear mean plots were presented with and without SD.

A comparison of natural-log (ln)-transformed ACP-196 PK parameters C_{max}, $AUC_{0\text{-}24}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ was performed to assess the effect of calcium carbonate (Part 1), omeprazole (Part 2), or rifampin (Part 3) on the single dose PK of ACP-196, by performing an analysis of variance (ANOVA) using PROC MIXED of SAS® Version 9.3. The ANOVA model included treatment as a fixed effect and subject as a random effect.

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In each study part, the test treatment was compared with the reference treatment. The test and reference treatments were as follows for each study part:

Part 1
Treatment A (Period 1): ACP-196 (reference)
Treatment B (Period 2): ACP-196 + calcium carbonate (test)
Part 2
Treatment C (Period 1): ACP-196 (reference)
Treatment D (Period 2): ACP-196 + omeprazole (test)
Part 3
Treatment E (Period 1): ACP-196 (reference)
Treatment F (Period 2, Day 1): ACP-196 + rifampin (single dose of rifampin) (test)
Treatment F (Period 2, Day 9): ACP-196 + rifampin (multiple dose of rifampin) (test)

Note that for Part 3, two separate ANOVAs were performed: Treatment F (Day 1) versus Treatment E and Treatment F (Day 9) versus Treatment E.

The least-square means (LSMs), differences between the LSMs, and the standard error (SE) and 90% confidence intervals (CIs) associated with these differences was determined for each parameter. These inferential results (LSMs, difference between LSMs, and 90% CIs of the difference) were exponentiated to the original scale. Geometric LSMs, geometric mean ratios (GMRs), 90% CIs, and intra-subject CV% were presented. Intra-subject CV% was calculated from the residual variance from PROC MIXED.

Evaluation and interpretation of drug-drug interaction was assessed based on the magnitude of any observed effect on the single-dose ACP-196 C_{max} and AUCs (eg, GMRs and 90% CIs for the GMRs) for each part individually.

Pharmacodynamics: Summary statistics (N, AM, SD, CV%, Geom. Mean, Geom. CV%, median, minimum, and maximum) were calculated for urine 6β-hydroxycortisol and free cortisol concentrations and ratios. The change from Day 1 in 6β-hydroxycortisol/free cortisol was calculated for each subject on Days 4, 7, and 9 of Period 2 (Part 3). The mean changes and corresponding p-values, based on a paired t-test, were provided for each time point.

Safety: AEs were summarized by treatment for each study part. Safety laboratory parameters for serum chemistry, hematology, and urinalysis were summarized and change from baseline results were presented. Shift tables were also presented for laboratory results. Vital sign results were summarized and changes from baseline were presented. All safety data were listed individually.

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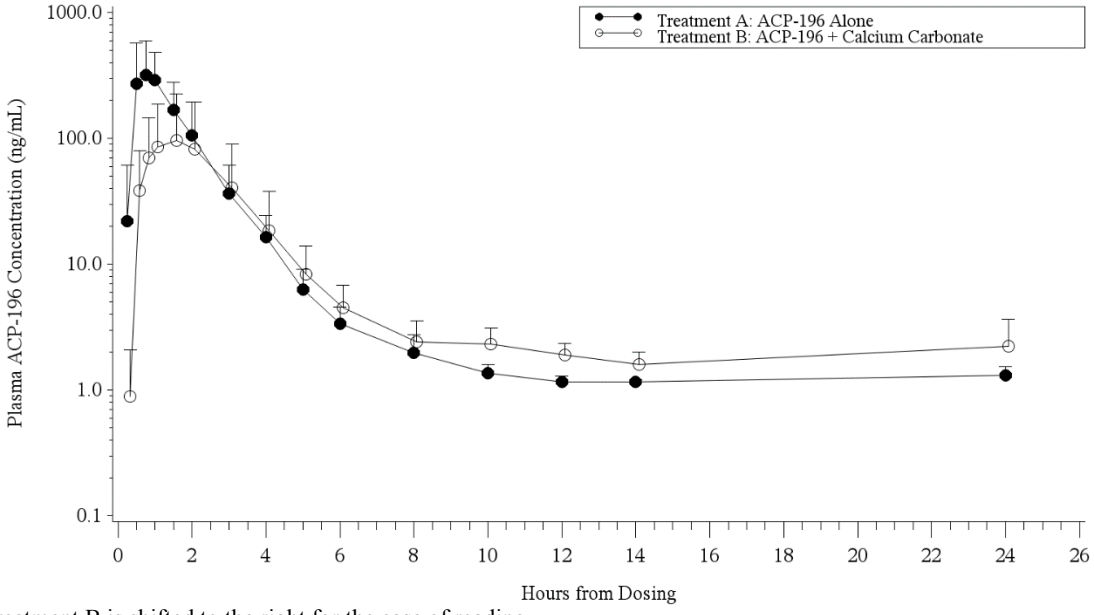
SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Part 1 (Calcium Carbonate Coadministration)

Mean plasma ACP-196 concentration-time profiles after a single oral dose of 100 mg ACP-196 on Day 1 (Treatment A, Period 1) and a single oral dose of 1 g calcium carbonate with a single oral dose of 100 mg ACP-196 coadministered on Day 1 (Treatment B, Period 2) on semi-log scale are presented in the figure below.

Mean (SD) Plasma ACP-196 Concentration Versus Time Comparing ACP-196 (Treatment A) and ACP-196 + Calcium Carbonate (Treatment B) (Semi-Log Scale)



Treatment B is shifted to the right for the ease of reading.

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The summary of plasma ACP-196 PK parameters is presented in the following table.

Summary of Plasma ACP-196 Pharmacokinetic Parameters (Part 1)

Pharmacokinetic Parameters	Treatment A (Period 1) ACP-196 Alone (N=24)[e]	Treatment B (Period 2) ACP-196 + Calcium Carbonate (N=23)[f]
	Geometric Mean	
C_{max} (ng/mL)[a]	237 (200)	57.8 (254)
$AUC_{0\text{-last}}$ (ng*hr/mL)[a]	386 (98.6)	178 (112)
$AUC_{0\text{-inf}}$ (ng*hr/mL)[a]	484 (61.4)	221 (124)
	Arithmetic Mean	
C_{max} (ng/mL)[b]	373 ± 281 (75.2%)	121 ± 130 (107%)
T_{max} (hr)[c]	0.751 (0.50, 2.00)	1.50 (0.50, 4.00)
$AUC_{0\text{-last}}$ (ng*hr/mL)[b]	497 ± 307 (61.8%)	264 ± 258 (97.8%)
$AUC_{0\text{-inf}}$ (ng*hr/mL)[b]	556 ± 288 (51.8%)	330 ± 310 (94.0%)
$AUC_{\%extrap}$ (%)[d]	0.762 ± 0.642	5.66 ± 12.02
$t_{1/2}$ (hr)[d]	1.64 ± 0.687	4.07 ± 7.54
λ_z (1/hr)[d]	0.497 ± 0.216	0.385 ± 0.195
CL/F (L/hr)[d]	243 ± 162	689 ± 737

[a]: Presented as Geometric Mean (GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (%CV)
[c]: Presented as Median (Minimum, Maximum)
[d]: Presented as Arithmetic Mean ± SD

[e]: N = 20 for λ_z and associated parameters ($AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, and CL/F) because λ_z values could not be estimated for 2 subjects.
[f]: N = 12 for λ_z and associated parameters ($AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, and CL/F) because λ_z values could not be estimated for 11 subjects.

Treatment A (Period 1): A single oral dose of 100 mg ACP-196 on Day 1 (reference)
Treatment B (Period 2): Single oral doses of 1 g calcium carbonate and 100 mg ACP-196 coadministered on Day 1 (test)

SD = Standard Deviation; Geom. CV% = Geometric Coefficient of Variation

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

Statistical Comparisons of Plasma ACP-196 Pharmacokinetic Parameters: ACP-196 + Calcium Carbonate (Treatment B) Versus ACP-196 (Treatment A) (Part 1)

Pharmacokinetic Parameter	Geometric LSM		Geometric Mean Ratio (%)	90% Confidence Intervals	Intra-Subject CV%
	Treatment B (Period 2) ACP-196 + Calcium Carbonate (Test, N=23[a])	Treatment A (Period 1) ACP-196 Alone (Reference, N=24[b])			
C_{max} (ng/mL)	60.33	237.4	25.41	17.05 - 37.89	93.3
$AUC_{0\text{-last}}$ (ng*hr/mL)	182.5	386.1	47.28	36.05 - 62.01	57.9
$AUC_{0\text{-inf}}$ (ng*hr/mL)	229.0	483.6	47.35	32.21 - 69.61	60.1

[a] : N = 12 for $AUC_{0\text{-inf}}$
[b] : N = 20 for $AUC_{0\text{-inf}}$
Parameters were ln-transformed before analysis.
Geometric Least-squares means (LSMs) were calculated by exponentiating the LSM from ANOVA.
% Geometric Mean Ratio = 100*(test/reference)
Intra-subject CV% = 100 × sqrt[exp(residual)-1]
Treatment A (Period 1): A single oral dose of 100 mg ACP-196 on Day 1 (reference)
Treatment B (Period 2): Single oral doses of 1 g calcium carbonate and 100 mg ACP-196 coadministered on Day 1 (test)

The geometric mean C_{max} was approximately 0.25-fold lower (25.41% of ACP-196 alone) when ACP-196 was coadministered with calcium carbonate. The geometric mean $AUC_{0\text{-inf}}$ and $AUC_{0\text{-last}}$ were approximately 0.47-fold lower (47.35% and 47.28% of ACP-196 alone), respectively, when ACP-196 was coadministered with calcium carbonate.

Part 2 (Omeprazole Coadministration)

Mean plasma ACP-196 concentration-time profiles after a single oral dose of 100 mg ACP-196 on Day 1 (Treatment C, Period 1) and multiple oral doses of 40 mg omeprazole administered daily for 5 days with a single oral dose of 100 mg ACP-196 coadministered on Day 5 (Treatment D, Period 2) on semi-log scale are presented in the figure below.

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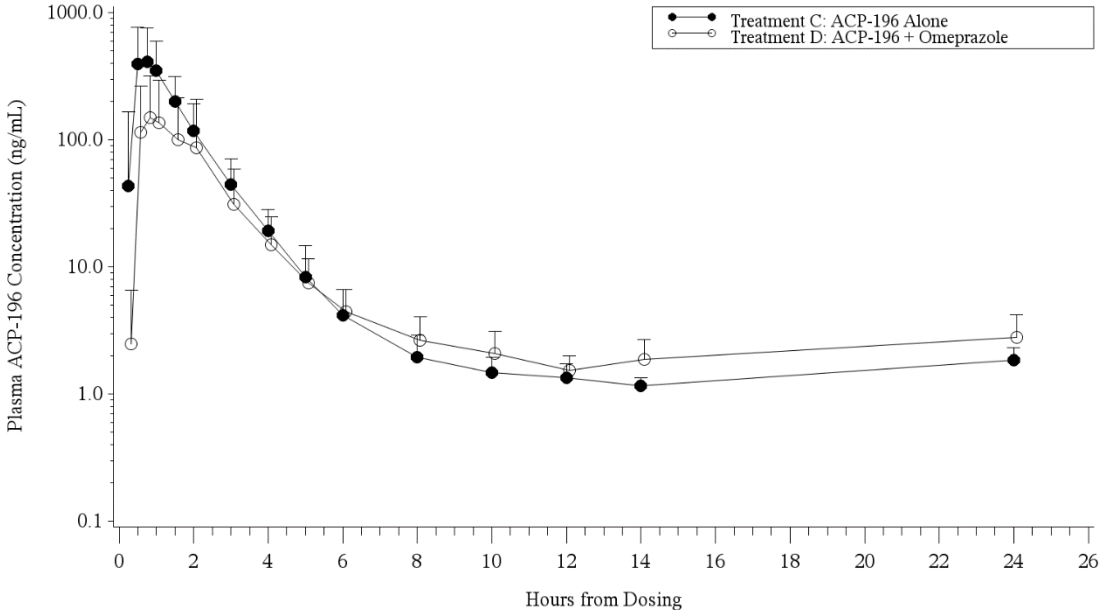
Mean (SD) Plasma ACP-196 Concentration Versus Time Comparing ACP-196 (Treatment C) and ACP-196 + Omeprazole (Treatment D) (Semi-Log Scale)



Treatment D is shifted to the right for the ease of reading.

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The summary of plasma ACP-196 PK parameters is presented in the following table.

Summary of Plasma ACP-196 Pharmacokinetic Parameters (Part 2)

Pharmacokinetic Parameters	Treatment C (Period 1) ACP-196 Alone (N=24)[e]	Treatment D (Period 2) ACP-196 + Omeprazole (N=23)[f]
	Geometric Mean	
C_{max} (ng/mL)[a]	383 (113)	81.1 (383)
$AUC_{0\text{-last}}$ (ng*hr/mL)[a]	512 (74.0)	222 (112)
$AUC_{0\text{-inf}}$ (ng*hr/mL)[a]	548 (66.3)	433 (59.3)
	Arithmetic Mean	
C_{max} (ng/mL)[b]	506 ± 346 (68.3%)	206 ± 196 (95.3 %)
T_{max} (hr)[c]	0.750 (0.50, 4.02)	1.00 (0.50, 3.01)
$AUC_{0\text{-last}}$ (ng*hr/mL)[b]	612 ± 358 (58.5 %)	312 ± 231 (73.9 %)
$AUC_{0\text{-inf}}$ (ng*hr/mL)[b]	638 ± 358 (56.1 %)	479 ± 174 (36.4 %)
$AUC_{\%extrap}$ (%)[d]	0.904 ± 1.45	1.60 ± 2.52
$t_{1/2}$ (hr)[d]	1.85 ± 1.29	2.26 ± 1.41
λ_z (1/hr)[d]	0.485 ± 0.228	0.446 ± 0.296
CL/F (L/hr)[d]	226 ± 214	281 ± 264

[a]: Presented as Geometric Mean (GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (%CV)
[c]: Presented as Median (Minimum, Maximum)
[d]: Presented as Arithmetic Mean ± SD

[e]: N = 22 for λ_z and associated parameters ($AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, and CL/F) because λ_z values could not be estimated for 2 subjects..
[f]: N = 13 for λ_z and associated parameters ($AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, and CL/F) because λ_z values could not be estimated for 10 subjects.

Treatment C (Period 1): A single oral dose of 100 mg ACP-196 on Day 1 (reference)
Treatment D (Period 2): Multiple oral doses of 40 mg omeprazole administered daily for 5 days with a single oral dose of 100 mg ACP-196 coadministered on Day 5 (test)

SD = Standard Deviation; GeomCV% = Geometric Coefficient of Variation

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

Statistical Comparisons of Plasma ACP-196 Pharmacokinetic Parameters: ACP-196 + Omeprazole (Treatment D) Versus ACP-196 (Treatment C) (Part 2)

Pharmacokinetic Parameter	Geometric LSM		Geometric Mean Ratio (%)	90% Confidence Intervals	Intra-Subject CV%
	Treatment D (Period 2) ACP-196 + Omeprazole (Test, N=23[a])	Treatment C (Period 1) ACP-196 Alone (Reference, N=23[b])			
C_{max} (ng/mL)	80.81	382.7	21.12	11.27 - 39.56	194.9
$AUC_{0\text{-last}}$ (ng*hr/mL)	221.6	512.0	43.29	29.61 - 63.27	88.0
$AUC_{0\text{-inf}}$ (ng*hr/mL)	451.6	548.5	82.33	61.72 - 109.82	45.1

[a]: N = 13 for $AUC_{0\text{-inf}}$: Geometric mean comparisons of $AUC_{0\text{-inf}}$ were biased when λ_z could not be calculated for as many subjects in Period 2 as in Period 1 –see text.
[b]: N = 22 for $AUC_{0\text{-inf}}$

Parameters were ln-transformed before analysis.
Geometric Least-squares means (LSMs) were calculated by exponentiating the LSM from ANOVA.
% Geometric Mean Ratio = 100*(test/reference)
Intra-subject CV% = 100 × sqrt[exp(residual)-1]

Treatment C (Period 1): A single oral dose of 100 mg ACP-196 on Day 1 (reference)
Treatment D (Period 2): Multiple oral doses of 40 mg omeprazole administered daily for 5 days with a single oral dose of 100 mg ACP-196 coadministered on Day 5 (test)

The geometric mean C_{max} was approximately 0.21-fold lower (21.12 % of ACP-196 alone) when ACP-196 was coadministered with omeprazole. The geometric mean $AUC_{0\text{-last}}$ was based on data from 23 of 24 subjects and was approximately 0.43-fold lower (43.29% of ACP-196 alone) when ACP-196 was coadministered with omeprazole.

Geometric mean comparisons of $AUC_{0\text{-inf}}$ were biased when λ_z could not be calculated for as many subjects in Period 2 as in Period 1. The λ_z-dependent parameters $AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, and CL/F could not be calculated for 10 generally lower exposure subjects in Period 2, as opposed to 2 subjects in Period 1. Accordingly, the geometric mean $AUC_{0\text{-inf}}$ was approximately 0.82-fold lower (82.33 % of ACP-196 alone), when ACP-196 was coadministered with

omeprazole. Since these $AUC_{0\text{-}inf}$ GMR data were biased high, AUC comparisons for omeprazole should be based on the 23 of 24 subjects with measured $AUC_{0\text{-}last}$ data.

The summary of plasma omeprazole PK parameters is presented in the following table.

Summary of Plasma Omeprazole Pharmacokinetic Parameters (Part 2)

Pharmacokinetic Parameters	Treatment D (Period 2) ACP-196 + Omeprazole (N=23)
	Geometric Mean
$C_{max,ss}$ (ng/mL)[a]	1260 (39.0)
$AUC_{0\text{-}last}$ (ng*hr/mL)[a]	4120 (53.5)
	Arithmetic Mean
$C_{max,ss}$ (ng/mL)[b]	1340 ± 435 (32.4%)
$T_{max,ss}$ (hr)[c]	2.01 (1.00, 4.04)
$AUC_{0\text{-}last}$ (ng*hr/mL)[b]	4570 ± 1920 (41.9%)

[a]: Presented as Geometric Mean (GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (%CV)
[c]: Presented as Median (Minimum, Maximum)
Treatment D (Period 2): Multiple oral doses of 40 mg omeprazole administered daily for 5 days with a single oral dose of 100 mg ACP-196 coadministered on Day 5 (test)
SD = Standard Deviation; GeomCV% = Geometric Coefficient of Variation

Plasma omeprazole mean peak exposure ($C_{max,ss}$) of 1260 ng/mL was reached at a median $T_{max,ss}$ value of 2 hours after multiple oral doses of omeprazole administered daily for 5 days with a single oral dose of ACP-196 coadministered on Day 5.

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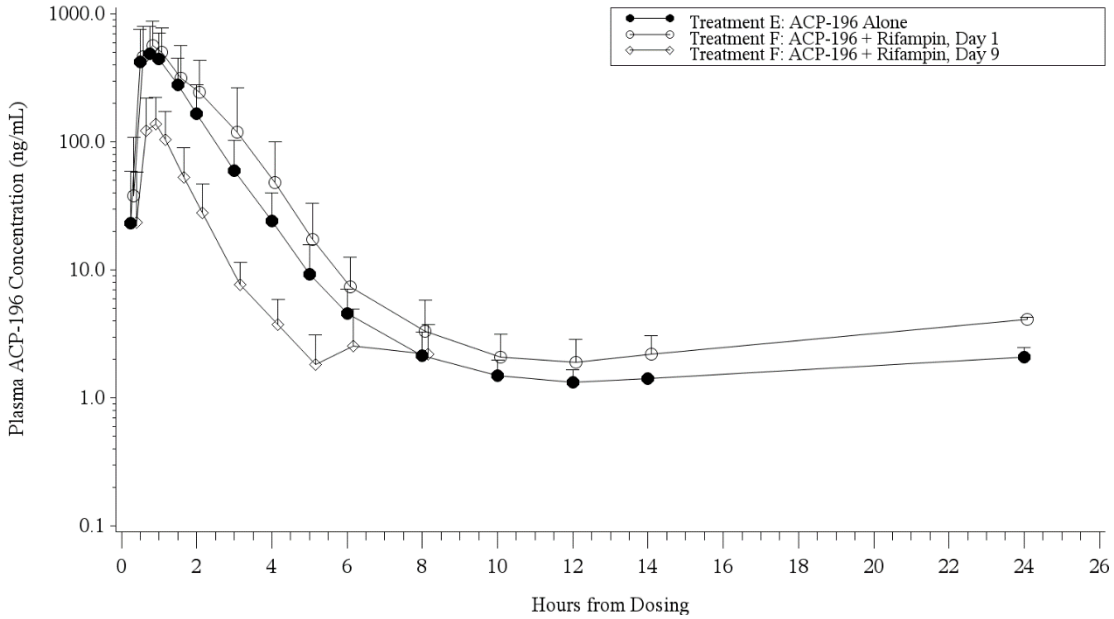
Part 3 (Rifampin Coadministration)

Mean plasma ACP-196 concentration-time profiles after a single oral dose of 100 mg ACP-196 on Day 1 (Treatment E, Period 1), a single oral dose of 600 mg rifampin with a single oral dose of 100 mg ACP-196 coadministered on Day 1 (Treatment F, Day 1, Period 2), and multiple oral doses of 600 mg rifampin administered daily for 9 days with a single oral dose of 100 mg ACP-196 coadministered on Day 9 (Treatment F, Day 9, Period 2) on semi-log scale are presented in the figure below.

Mean (SD) Plasma ACP-196 Concentration Versus Time Comparing ACP-196 (Treatment E) and ACP-196 + Rifampin (Treatment F) on Day 1 in Period 2 and Day 9 in Period 2 (Semi-Log Scale)



Treatment F, Days 1 and 9 are shifted to the right for the ease of reading.

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The summary of plasma ACP-196 PK parameters is presented in the following table.

Summary of Plasma ACP-196 Pharmacokinetic Parameters (Part 3)

Pharmacokinetic Parameters	Treatment E (Period 1) ACP-196 Alone (N=24)[e]	Treatment F (Day 1, Period 2) ACP-196 + Rifampin (N=24)[e]	Treatment F (Day 9, Period 2) ACP-196 + Rifampin (N=24)
	Geometric Mean		
C_{max} (ng/mL)[a]	450 (149)	552 (106)	142 (90.4)
$AUC_{0\text{-last}}$ (ng*hr/mL)[a]	641 (86.0)	874 (62.5)	150 (56.2)
$AUC_{0\text{-inf}}$ (ng*hr/mL)[a]	773 (45.4)	993 (40.4)	154 (50.6)
	Arithmetic Mean		
C_{max} (ng/mL)[b]	606 ± 323 (53.3%)	678 ± 319 (47.0%)	173 ± 99.0 (57.2%)
T_{max} (hr)[c]	0.882 (0.50, 3.02)	0.751 (0.50, 4.00)	0.752 (0.49, 3.00)
$AUC_{0\text{-last}}$ (ng*hr/mL)[b]	771 ± 370 (47.9%)	996 ± 471 (47.3%)	169 ± 83.0 (49.0%)
$AUC_{0\text{-inf}}$ (ng*hr/mL)[b]	837 ± 318 (38.0%)	1070 ± 429 (40.2%)	172 ± 81.9 (47.7%)
$AUC_{\%extrap}$ (%)[d]	0.438 ± 0.181	0.373 ± 0.190	2.51 ± 6.53
$t_{1/2}$ (hr)[d]	1.56 ± 0.399	1.66 ± 0.610	0.834 ± 0.611
λ_z (1/hr)[d]	0.479 ± 0.146	0.461 ± 0.138	0.976 ± 0.246
CL/F (L/hr)[d]	143 ± 76.7	108 ± 40.6	724 ± 372

[a]: Presented as Geometric Mean (GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (%CV)
[c]: Presented as Median (Minimum, Maximum)
[d]: Presented as Arithmetic Mean ± SD
[e]: N = 22 for λ_z and associated parameters ($AUC_{0\text{-inf}}$, $AUC_{\%extrap}$, $t_{1/2}$, and CL/F) because λ_z values could not be estimated for 2 subjects.
Treatment E (Period 1): A single oral dose of 100 mg ACP-196 on Day 1
Treatment F (Day 1, Period 2): A single oral dose of 600 mg rifampin with a single oral dose of 100 mg ACP-196 coadministered on Day 1
Treatment F (Day 9, Period 2): Multiple oral doses of 600 mg rifampin administered daily for 9 days with a single oral dose of 100 mg ACP-196 coadministered on Day 1
SD = Standard Deviation; GeomCV% = Geometric Coefficient of Variation

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The statistical comparisons of plasma ACP-196 PK parameters are summarized in the following tables.

Statistical Comparisons of Plasma ACP-196 Pharmacokinetic Parameters: ACP-196 + Rifampin (Day 1, Treatment F) Versus ACP-196 (Treatment E) (Part 3)

Pharmacokinetic Parameter	Geometric LSM		Geometric Mean Ratio (%)	90% Confidence Intervals	Intra-Subject CV%
	Treatment F (Day 1, Period 2) ACP-196 + Rifampin (Test, N=24[a])	Treatment E (Period 1) ACP-196 Alone (Reference, N=24[a])			
C_{max} (ng/mL)	552.2	450.2	122.65	102.92 - 146.16	36.6
$AUC_{0\text{-last}}$ (ng*hr/mL)	874.2	641.1	136.36	121.71 - 152.78	23.3
$AUC_{0\text{-inf}}$ (ng*hr/mL)	993.0	772.8	128.50	117.88 - 140.07	16.7

[a]: N = 22 for $AUC_{0\text{-inf}}$

Parameters were ln-transformed before analysis.

Geometric Least-squares means (LSMs) were calculated by exponentiating the LSM from ANOVA.

% Geometric Mean Ratio = 100*(test/reference)

Intra-subject CV% = 100 × sqrt[exp(residual)-1]

Treatment E (Period 1): A single oral dose of 100 mg ACP-196 on Day 1

Treatment F (Day 1, Period 2): A single oral dose of 600 mg rifampin with a single oral dose of 100 mg ACP-196 coadministered on Day 1

The geometric mean C_{max} of ACP-196 coadministered with the first dose of rifampin on Day 1 of Period 2, was approximately 1.2-fold higher (122.65% of ACP-196 alone). The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were approximately 1.4- and 1.3-fold higher (136.36% and 128.50% of ACP-196 alone), respectively, when ACP-196 was coadministered with the first dose of rifampin. On this basis, rifampin dosed at 600 mg for 1 day, resulted in a weak increase in ACP-196 exposure.

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Statistical Comparisons of Plasma ACP-196 Pharmacokinetic Parameters: ACP-196 + Rifampin (Day 9, Treatment F) Versus ACP-196 (Treatment E) (Part 3)

Pharmacokinetic Parameter	Geometric LSM		Geometric Mean Ratio (%)	90% Confidence Intervals	Intra-Subject CV%
	Treatment F (Day 9, Period 2) ACP-196 + Rifampin (Test, N=24)	Treatment E (Period 1) ACP-196 Alone (Reference, N=24[a])			
C_{max} (ng/mL)	142.0	450.2	31.54	23.63 - 42.11	63.8
$AUC_{0\text{-last}}$ (ng*hr/mL)	150.1	641.1	23.41	19.09 - 28.72	43.1
$AUC_{0\text{-inf}}$ (ng*hr/mL)	154.4	748.6	20.62	17.51 - 24.29	32.5

[a]: N = 22 for $AUC_{0\text{-inf}}$
Parameters were ln-transformed before analysis.
Geometric Least-squares means (LSMs) were calculated by exponentiating the LSM from ANOVA.
% Geometric Mean Ratio = 100*(test/reference)
Intra-subject CV% = 100 × sqrt[exp(residual)-1]
Treatment E (Period 1): A single oral dose of 100 mg ACP-196 on Day 1
Treatment F (Day 9, Period 2): Multiple oral doses of 600 mg rifampin administered daily for 9 days with a single oral dose of 100 mg ACP-196 coadministered on Day 1

The geometric mean C_{max} of ACP-196 coadministered with the last dose of rifampin on Day 9 of Period 2, was approximately 0.32-fold lower (31.54% of ACP-196 alone). The geometric mean $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were approximately 0.23- and 0.21-fold lower (23.41% and 20.62% of ACP-196 alone), respectively, when ACP-196 was coadministered with the last dose of rifampin. Based on the definition in the 2012 draft CDER guidance, a moderate CYP enzyme inducer results in a 50% to 80% decrease in AUC of a substrate. On this basis, rifampin dosed at 600 mg for 9 days, resulted in moderate induction of ACP-196 metabolism.

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The summary of plasma rifampin PK parameters is presented in the following table.

Summary of Plasma Rifampin Pharmacokinetic Parameters (Part 3)

Pharmacokinetic Parameters	Treatment F (Day 1, Period 2) ACP-196 + Rifampin (N=24)	Treatment F (Day 9, Period 2) ACP-196 + Rifampin (N=24)[d]
	Geometric Mean	
C_{max} (µg/mL)[a]	13.8 (25.4)	.
$C_{max,ss}$ (µg/mL)[a]	.	13.8 (40.0)
$AUC_{0\text{-}last}$ (µg*hr/mL)[a]	97.3 (33.9)	59.1 (42.7)
AUC_{τ} (µg*hr/mL)[a]	.	67.3 (44.7)
	Arithmetic Mean	
C_{max} (µg/mL)[b]	14.2 ± 3.36 (23.7%)	.
$C_{max,ss}$ (µg/mL)[b]	.	14.7 ± 5.24 (35.5%)
T_{max} (hr)[c]	1.51 (1.00, 4.00)	.
$T_{max,ss}$ (hr)[c]	.	1.01 (1.00, 3.99)
$AUC_{0\text{-}last}$ (µg*hr/mL)[b]	103 ± 38.3 (37.2%)	63.6 ± 24.7 (38.8%)
AUC_{τ} (µg*hr/mL)[b]	.	73.1 ± 37.7 (51.5%)

.: Value not reportable
[a]: Presented as Geometric Mean (GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (%CV)
[c]: Presented as Median (Minimum, Maximum)
[d]: N = 5 for AUC_{τ} because the 24 hour plasma concentration was BLQ for 19 subjects.
Treatment F (Day 1, Period 2): A single oral dose of 600 mg rifampin with a single oral dose of 100 mg ACP-196 coadministered on Day 1
Treatment F (Day 9, Period 2): Multiple oral doses of 600 mg rifampin administered daily for 9 days with a single oral dose of 100 mg ACP-196 coadministered on Day 1
SD = Standard Deviation; GeomCV% = Geometric Coefficient of Variation

Plasma rifampin mean peak exposure after a single oral dose (Day 1, C_{max}) or multiple oral doses of rifampin (Day 9, $C_{max,ss}$) was the same at 13.8 µg/mL and was reached at a median T_{max} value of 1.5 hours after a single oral dose of rifampin with a single oral dose of ACP-196

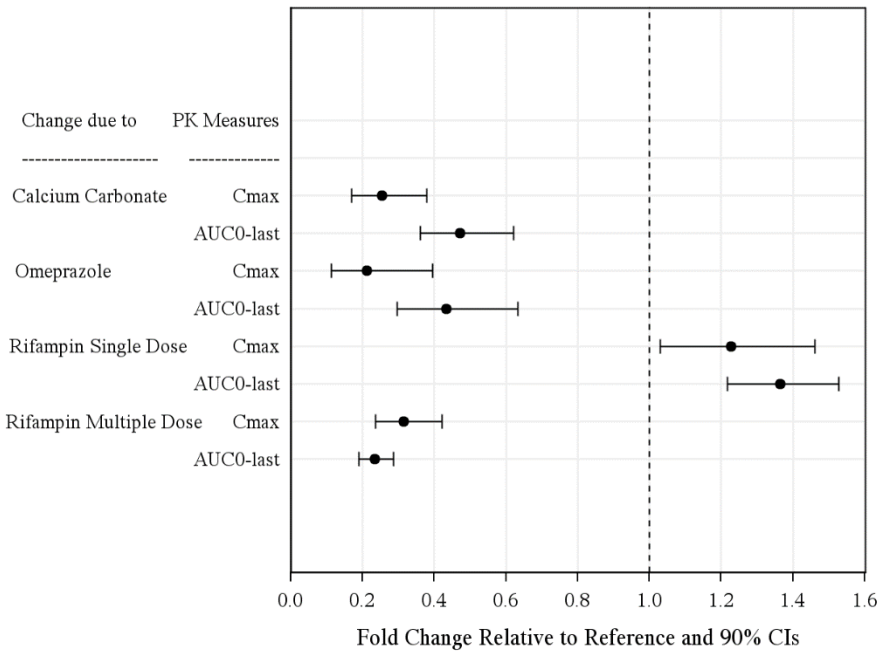
coadministered on Day 1 and at a median $T_{max,ss}$ value of 1 hour after multiple oral doses of rifampin administered daily for 9 days with a single oral dose of ACP-196 coadministered on Day 9.

The mean extent of exposure to rifampin, as measured by $AUC_{0\text{-last}}$, was approximately 40% lower on Day 9 after multiple daily oral doses, compared with a single oral dose of rifampin on Day 1.

Summary (Parts 1, 2, 3)

The summary of plasma ACP-196 statistical analyses of Parts 1, 2, and 3 is presented in the figure below:

Summary Forest Plot of Plasma ACP-196 After Single Dose Administration of Calcium Carbonate, Multiple Oral Doses of Omeprazole, or Rifampin as Displayed as 90% Confidence Interval of Geometric Mean Ratios for C_{max} and $AUC_{0\text{-last}}$



In all study parts, the 90% CIs around the GMRs exclude 100% ratio for $AUC_{0\text{-last}}$ and C_{max}, indicating that coadministration of calcium carbonate (Part 1), omeprazole (Part 2), or rifampin (Part 3) resulted in a PK drug interaction with ACP-196.

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Pharmacodynamic Results (Part 3):

6β-hydroxycortisol were measurable in urine for all subjects on all sampling days (Days 1, 4, 7, and 9) and free cortisol was measurable in urine for all subjects on all sampling days with the exception of 2 subjects on Day 1 (Subjects PPD and PPD and 1 subject on Day 4 (Subject PPD

Increasing mean concentrations of 6β-hydroxycortisol in urine were observed when multiple oral doses of rifampin were administered daily for 9 days while free cortisol concentrations remained relatively constant throughout the sampling days. Mean urine 6β-hydroxycortisol increased by approximately 4-fold between Day 1 and Day 4, 6-fold between Day 1 and Day 7, and 8-fold between Day 1 and Day 9.

The summary of urine ratios is presented in the following table.

Summary of Urine Ratios of 6β-hydroxycortisol to Free Cortisol (Treatment F) (Part 3)

Sampling Days (Predose)	Mean Ratio of 6ß-hydroxycortisol to Free Cortisol[a]	Mean of Change from Day 1[b]	P-Value
Day 1	5.895 (62.4) N=22		
Day 4	30.77 (64.3) N=23	21.79 N=21	<.0001
Day 7	35.05 (87.7) N=24	28.70 N=22	0.0003
Day 9	41.12 (51.9) N=24	34.46 N=22	<.0001

[a]: Presented as Arithmetic Mean (CV%)

[b]: The mean changes (Mean Ratio Day X - Mean Ratio Day 1) and corresponding p-values, based on a paired t-test, are provided for each time point. The null hypothesis was that the mean change was zero.

Treatment F (Period 2): A single oral dose of 600 mg rifampin with a single oral dose of 100 mg ACP-196 coadministered on Days 1 and 9.

CV% = Coefficient of Variation

Mean ratio of 6β-hydroxycortisol to free cortisol in urine increased by 5-fold, 6-fold, and 7-fold after 3, 6, and 8 days of rifampin daily administration, respectively. Statistical analyses demonstrated that this observed increase in mean ratio of 6β-hydroxycortisol to free cortisol in urine was statistically significant at nominal 0.05 level from Day 1 to Days 4, 7, and 9 after multiple daily doses of rifampin (p-values < 0.05).

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Safety Results: No deaths or SAEs were reported during this study. One subject was discontinued from the study due to an AE of viral gastroenteritis after treatment with ACP-196; the event was not related to the study treatment. AEs were reported by a total of ≤ 2 (8%) subjects each study part, with the exception of chromaturia, which is related to rifampin administration. Most events were mild (Grade 1) in intensity. Single events of dyspepsia (Part 1) and abdominal pain and generalized pruritus (Part 3) were considered to be related to ACP-196 alone. No remarkable findings were observed in the remaining assessments for clinical laboratory parameters, vital signs, ECGs, or physical examinations. No safety concerns were observed in the AE data or other remaining safety assessments when ACP-196 was coadministered with calcium carbonate, omeprazole, or rifampin.

Conclusions: Coadministration of ACP-196 with the gastric pH modifiers, calcium carbonate or omeprazole, decreased mean exposure to ACP-196.

Coadministration of ACP-196 with a multiple dose regimen of the strong CYP enzyme inducer, rifampin, decreased mean exposure to ACP-196. Rifampin dosed at 600 mg daily for 9 days, resulted in moderate induction of ACP-196 metabolism.

No safety concerns for ACP-196 were identified in this study.

Date of Report: 18 June 2015