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 Acalabrutinib		
NAME OF ACTIVE INGREDIENT Acalabrutinib		

Title of Study:	An Open-label, Fixed Sequence Study in Healthy Subjects to Assess the Pharmacokinetics of Acalabrutinib and its Active Metabolite, ACP-5862, when Administered Alone and in Combination with Moderate CYP3A4 Inhibitors Fluconazole or Isavuconazole
Investigator(s):	PPD, MD (Until PPD PPD, MD, MPH (Starting on PPD)
Study Center(s):	PPD PPD, USA
Publication (Reference):	Not applicable.
Studied Period: **(date of first enrollment)** 03 January 2020 **(date of last completed)** 15 April 2020	**PHASE OF DEVELOPMENT**: I

Objectives:

Primary:

To assess the effect of fluconazole and isavuconazole on the pharmacokinetics (PK) of acalabrutinib and the formation of its active metabolite, ACP-5862.

Secondary:

To assess the safety and tolerability of acalabrutinib in combination with fluconazole or with isavuconazole.

Exploratory:

- To determine bruton tyrosine kinase (BTK)-receptor occupancy (RO) in isolated peripheral blood mononuclear cells (PBMCs).
- To examine plasma samples for the determination of isavuconazole concentrations.
- To examine plasma samples for 4-beta-hydroxy (4β-OH) cholesterol as a cytochrome P450 (CYP)3A4 biomarker.
- To examine exploratory biomarker development.

The pharmacodynamic (PD) endpoints are discussed in a standalone PD report.

Methodology:
This was an open-label, randomized, 2-period study conducted at a single study center.

Twenty-eight (28) healthy, adult male and female (of non-childbearing potential only) subjects were initially enrolled. Two (2) subjects discontinued early and were replaced.

Screening of subjects occurred within 28 days before the first dosing.

On Day 1 of Period 1, subjects were randomized to 1 of 2 treatment sequences.

On Day 1 of Period 1, a single oral dose of 100 mg acalabrutinib (Treatment A) was administered to all subjects. Blood samples for plasma PK assessment of acalabrutinib and ACP-5862 were collected predose and through 24 hours postdose. A blood sample for plasma biomarker analysis was collected predose. Blood samples for PBMCs were collected predose through 168 hours postdose after acalabrutinib dosing.

In Period 2, the subjects who participated in Period 1 received either Treatment B (fluconazole) or Treatment C (isavuconazole), according to the assigned sequence as per the randomization scheme.

In Period 2 Treatment B (fluconazole), subjects received a single oral loading dose of 400 mg fluconazole on Day 1 one hour before a single oral dose of 100 mg acalabrutinib. Blood samples for plasma PK assessment of acalabrutinib and ACP-5862 were collected predose and through 24 hours postdose after acalabrutinib dosing.

In Period 2 Treatment C (isavuconazole), subjects received 200 mg isavuconazole three times daily (TID; approximately every 8 hours apart) on Day 1. On Days 2 through 5, subjects received 200 mg isavuconazole once daily (QD) with a single dose of 100 mg acalabrutinib coadministered on Day 5. Blood samples for plasma PK assessment of acalabrutinib and ACP-5862 were collected predose and through 24 hours postdose on Day 5. Blood samples for plasma concentration of isavuconazole were collected predose on Days 3 to 5. Blood samples for plasma biomarker analysis were collected predose on Day 5. Blood samples for PBMCs were collected predose on Days 1 to 5 and through 168 hours postdose after acalabrutinib dosing on Day 5.

There was a washout of at least 8 days between dosing in Period 1 and first dose in Period 2.

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

Number of Subjects (Planned and Analyzed):
A total of 30 subjects received at least one of the study treatments and were included in the safety analysis. Of the 28 subjects initially randomized, 2 subjects discontinued early (both randomized to Treatment Sequence AC) and were replaced. A total of 28 subjects completed the study. All of the available data from the 30 subjects enrolled were included in the PK analysis, with the exception of the analysis of variance (ANOVA) models conducted by treatment sequence (AB or AC), which only included the 28 subjects who completed the study.

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:

- Acalabrutinib supplied as 100 mg capsules (Lot No.: CCI [redacted]) for oral administration
- Fluconazole supplied as 200 mg tablets (Lot No.: CCI [redacted]) for oral administration
- Isavuconazole supplied as 186 mg isavuconazonium sulfate capsules (Lot No.: CCI [redacted]) equivalent to 100 mg isavuconazole for oral administration

Treatments are described as follows:

Treatment A: A single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1

Treatment B: Single oral doses of 400 mg fluconazole (2 x 200 mg tablets) at Hour -1 and 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1

Treatment C: Multiple oral doses of 200 mg isavuconazole (2 x 186 mg isavuconazonium sulfate capsules) TID on Day 1 and QD on Days 2 to 5 with a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) coadministered at Hour 0 on Day 5

All study drugs were administered orally with approximately 240 mL of water. In Treatment B, fluconazole and acalabrutinib doses were administered 1 hour apart with a total of 240 mL of water (ie, fluconazole dose was administered with approximately 120 mL of water and acalabrutinib doses were administered with approximately 120 mL of water).

Duration of Treatment:
The total planned duration of participation for each subject, from screening until the last follow-up visit, was up to approximately 44 to 48 days, depending on treatment sequence assignment.

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

Criteria for Evaluation:

Pharmacokinetics:
Serial blood samples for the determination of acalabrutinib and ACP-5862 plasma concentrations were collected through 24 hours post acalabrutinib dose in each period (ie, Days 1 to 2 for Treatments A and B and Days 5 to 6 for Treatment C). The following noncompartmental PK parameters were calculated from the acalabrutinib and ACP-5862 plasma concentration-time data using Phoenix® WinNonlin® Version 8.1 (as applicable): AUC_{0-t}, AUC_{0-inf}, $AUC_{\%extrap}$, C_{max}, T_{max}, T_{last}, K_{el}, t½, CL/F, V_z/F, metabolite-to-parent molar ratio (MR)_AUC_{0-t}, MR_AUC_{0-inf}, and MR_C_{max}.

Blood samples for the determination of isavuconazole were collected at predose on Days 3, 4, and 5 in Treatment C and were stored for potential future analysis.

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

Statistical Methods:

Pharmacokinetics:
Plasma concentrations and PK parameters of acalabrutinib and ACP-5862 were tabulated by treatment and listed by subject and nominal sample time, or parameter as appropriate, for all subjects in the PK Population. Summary statistics, including sample size (n), arithmetic mean (Mean), standard deviation (SD), coefficient of variation (CV%), standard error of the mean (SEM), minimum, median, and maximum were calculated for all nominal concentration timepoints and PK parameters. Geometric mean and geometric CV% were also presented for PK parameters. Mean and individual concentration-time profiles were presented on linear and semi-log scales.

A comparison of natural-log (ln)-transformed acalabrutinib and ACP-5862 PK parameters $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, and C_{max} was made to evaluate the relative bioavailability of acalabrutinib with fluconazole or isavuconazole (Treatments B and C; test) versus acalabrutinib alone (Treatment A; reference), by performing an ANOVA model using PROC MIXED of SAS®. The ANOVA model included treatment and sequence as fixed effects and subject within sequence as a random effect. The inferential results (least-squares means [LSMs], difference between LSMs, and 90% CIs of the difference) were exponentiated to the original scale. Geometric LSMs, 2-sided 95% confidence intervals (CIs), geometric mean ratios (GMRs), and 90% CIs were presented.

Additional ANOVA models were conducted by treatment sequence (AB or AC), with treatment as a fixed effect and subject as a random effect. The models conducted by treatment sequence only included subjects who completed both treatment periods.

Safety:
All AEs that occurred during this clinical trial were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), Version 23.0. Treatment-emergent AEs (TEAEs) were tabulated by System Organ Class (SOC) and Preferred Term. Summary tables included the number of subjects reporting the AE and as a percent of the number of subjects dosed by treatment. The number of AEs was also tabulated in a similar manner. Descriptive statistics were presented for clinical laboratory values, vital sign parameters, and ECG parameters by assessment timepoint and treatment. Change from baseline for these safety parameters was also summarized. All concomitant medications recorded during the study, if any, were coded with the World Health Organization (WHO) Dictionary and listed. All safety data results were presented in individual listings. No inferential statistics were performed on safety data.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

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

Summary of Plasma Acalabrutinib Pharmacokinetic Parameters (Pharmacokinetic Population)

Pharmacokinetic Parameters	Treatment A	Treatment B	Treatment C
AUC0-t (ng*hr/mL)	712.9 (34.5) [n=30]	1476 (39.7) [n=14]	1113 (33.0) [n=14]
AUC0-inf (ng*hr/mL)	709.3 (34.3) [n=29]	1564 (34.4) [n=13]	1121 (32.2) [n=14]
AUC%extrap (%)	0.5390 ± 0.70225 [n=29]	0.2896 ± 0.086382 [n=13]	0.7249 ± 1.6030 [n=14]
Cmax (ng/mL)	546.5 (62.0) [n=30]	848.8 (69.8) [n=14]	710.6 (59.2) [n=14]
Tmax (hr)	0.748 (0.50, 3.00) [n=30]	0.753 (0.50, 2.01) [n=14]	0.738 (0.49, 2.00) [n=14]
Tlast (hr)	8.004 (6.00, 24.09) [n=30]	12.001 (10.00, 24.01) [n=14]	10.001 (7.99, 24.04) [n=14]
t½ (hr)	1.366 ± 1.0054 [n=29]	1.943 ± 0.3191 [n=13]	1.971 ± 1.4374 [n=14]
CL/F (L/hr)	148.6 ± 48.717 [n=29]	67.31 ± 22.745 [n=13]	93.33 ± 29.377 [n=14]
Vz/F (L)	308.3 ± 327.57 [n=29]	186.5 ± 66.369 [n=13]	280.9 ± 297.48 [n=14]

Treatment A: a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1
Treatment B: single oral doses of 400 mg fluconazole (2 x 200 mg tablets) at Hour -1 and 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1
Treatment C: multiple oral doses of 200 mg isavuconazole (2 x 186 mg isavuconazonium sulfate capsules) TID on Day 1 and QD on Days 2 – 5 with a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) coadministered at Hour 0 on Day 5
AUCs and Cmax values are presented as geometric mean (geometric CV%) [n].
Tmax and Tlast values are presented as median (minimum, maximum) [n].
Other parameters are presented as arithmetic mean ± SD [n].
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The statistical comparisons of acalabrutinib PK parameters after acalabrutinib with fluconazole (Treatment Sequence AB) or isavuconazole (Treatment Sequence AC) versus acalabrutinib alone are summarized in the following tables.

Summary of Statistical Comparisons of Plasma Acalabrutinib Pharmacokinetic Parameters: Acalabrutinib With Fluconazole (Treatment B) Versus Acalabrutinib Alone (Treatment A) (Pharmacokinetic Population – Sequence AB Only)

Parameter	Treatment B (Test)			Treatment A (Reference)			GMR (%)	90% Confidence Interval	Intra-subject CV%
	Geometric LSMs	95% Confidence Interval	n	Geometric LSMs	95% Confidence Interval	n			
AUC0-t (ng*hr/mL)	1476	1194.00 - 1825.09	14	738.0	596.90 - 912.40	14	200.03	169.24 - 236.42	25.36
AUC0-inf (ng*hr/mL)	1564	1263.68 - 1936.85	13	725.9	586.34 - 898.69	13	215.52	193.64 - 239.87	15.40
Cmax (ng/mL)	848.8	628.31 - 1146.73	14	574.3	425.10 - 775.85	14	147.80	110.19 - 198.25	46.07

Treatment B: single oral doses of 400 mg fluconazole (2 x 200 mg tablets) at Hour -1 and 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 (test)
Treatment A: a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (B [test]/A [reference])
Intra-subject CV% = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA
The ANOVA model using PROC MIXED of SAS® includes treatment as a fixed effect and subject as a random effect.
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Summary of Statistical Comparisons of Plasma Acalabrutinib Pharmacokinetic Parameters: Acalabrutinib With Isavuconazole (Treatment C) Versus Acalabrutinib Alone (Treatment A) (Pharmacokinetic Population – Sequence AC Only)

Parameter	Treatment C (Test)			Treatment A (Reference)			GMR (%)	90% Confidence Interval	Intra-subject CV%
	Geometric LSMs	95% Confidence Interval	n	Geometric LSMs	95% Confidence Interval	n			
AUC0-t (ng*hr/mL)	1113	926.94 - 1336.66	14	696.4	579.92 - 836.26	14	159.84	144.59 - 176.70	15.07
AUC0-inf (ng*hr/mL)	1121	937.23 - 1341.69	14	700.8	585.75 - 838.54	14	160.00	144.77 - 176.84	15.03
Cmax (ng/mL)	710.6	495.53 - 1019.06	14	519.6	362.30 - 745.07	14	136.77	114.09 - 163.97	27.60

Treatment C: multiple oral doses of 200 mg isavuconazole (2 x 186 mg isavuconazonium sulfate capsules) TID on Day 1 and QD on Days 2 – 5 with a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) coadministered at Hour 0 on Day 5 (test)
Treatment A: a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (C [test]/A [reference])
Intra-subject CV% = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA
The ANOVA model using PROC MIXED of SAS® includes treatment as a fixed effect and subject as a random effect.
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Coadministration of the strong-moderate CYP3A4/5 inhibitor fluconazole and weak-moderate CYP3A4/5 inhibitor isavuconazole resulted in an increase in exposure to acalabrutinib. Geometric LSM acalabrutinib total exposure (based on AUC_{0-t} and AUC_{0-inf}) was approximately 2.0- to 2.2-times higher and peak exposure (based on C_{max}) was approximately 1.5-fold higher after acalabrutinib with fluconazole versus acalabrutinib alone. Geometric LSM acalabrutinib total exposure was approximately 1.6-times higher and peak exposure was approximately 1.4-fold higher after acalabrutinib with isavuconazole versus acalabrutinib alone. The results for each of the comparisons were comparable for the ANOVA models including the data for all 30 subjects. Corresponding increases in mean $t_{½}$ values and decreases in mean CL/F values were observed for the combination treatments relative to acalabrutinib alone. Rate of absorption of acalabrutinib (based on T_{max}) was comparable across treatments.

The summary of plasma ACP-5862 PK parameters is presented in the following table.

Summary of Plasma ACP-5862 Pharmacokinetic Parameters (Pharmacokinetic Population)

Pharmacokinetic Parameters	Treatment A	Treatment B	Treatment C
AUC0-t (ng*hr/mL)	1839 (21.4) [n=30]	1656 (40.9) [n=14]	1572 (29.1) [n=14]
AUC0-inf (ng*hr/mL)	1949 (20.4) [n=30]	1968 (19.9) [n=13]	1769 (23.0) [n=13]
AUC%extrap (%)	5.601 ± 2.2935 [n=30]	7.751 ± 2.3084 [n=13]	7.067 ± 2.6917 [n=13]
Cmax (ng/mL)	520.9 (36.7) [n=30]	348.7 (78.7) [n=14]	352.2 (66.5) [n=14]
Tmax (hr)	1.017 (0.50, 4.01) [n=30]	1.499 (0.75, 2.04) [n=14]	1.248 (0.74, 4.03) [n=14]
Tlast (hr)	24.057 (12.01, 24.14) [n=30]	24.006 (24.00, 24.01) [n=14]	24.034 (24.00, 24.06) [n=14]
t½ (hr)	8.084 ± 1.1684 [n=30]	8.850 ± 1.6363 [n=13]	8.937 ± 1.3087 [n=14]
MR_AUC0-t	2.592 ± 0.74474 [n=30]	1.141 ± 0.39001 [n=14]	1.422 ± 0.43551 [n=14]
MR_AUC0-inf	2.764 ± 0.78779 [n=29]	1.271 ± 0.40621 [n=13]	1.540 ± 0.46942 [n=13]
MR_Cmax	0.9858 ± 0.35978 [n=30]	0.4289 ± 0.15639 [n=14]	0.5117 ± 0.19641 [n=14]

Treatment A: a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1
Treatment B: single oral doses of 400 mg fluconazole (2 x 200 mg tablets) at Hour -1 and 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1
Treatment C: multiple oral doses of 200 mg isavuconazole (2 x 186 mg isavuconazonium sulfate capsules) TID on Day 1 and QD on Days 2 – 5 with a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) coadministered at Hour 0 on Day 5
For Treatment B, the t½, AUC0-inf, AUC%extrap, and MR_AUC0-inf for Subject PPD were excluded from the summary statistics because t½ > half the sampling interval and AUC%extrap > 20%.
For Treatment C, the AUC0-inf, AUC%extrap, and MR_AUC0-inf for Subject PPD were excluded from the summary statistics because AUC%extrap was > 20%.
AUCs and Cmax values are presented as geometric mean (geometric CV%) [n].
Tmax and Tlast values are presented as median (minimum, maximum) [n].
Other parameters are presented as arithmetic mean ± SD [n].
Source: Tables 14.2.2.1.4, 14.2.2.1.5a and 14.2.2.1.6a
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The statistical comparisons of ACP-5862 PK parameters after acalabrutinib with fluconazole (Treatment Sequence AB) or isavuconazole (Treatment Sequence AC) versus acalabrutinib alone are summarized in the following tables.

Summary of Statistical Comparisons of Plasma ACP-5862 Pharmacokinetic Parameters: Acalabrutinib With Fluconazole (Treatment B) Versus Acalabrutinib Alone (Treatment A) (Pharmacokinetic Population – Sequence AB Only)

Parameter	Treatment B (Test)			Treatment A (Reference)			GMR (%)	90% Confidence Interval	Intra-subject CV%
	Geometric LSMs	95% Confidence Interval	n	Geometric LSMs	95% Confidence Interval	n			
AUC0-t (ng*hr/mL)	1656	1393.79 - 1968.15	14	1942	1634.09 - 2307.49	14	85.29	72.97 - 99.70	23.63
AUC0-inf (ng*hr/mL)	1956	1752.10 - 2182.91	13	2060	1846.65 - 2297.51	14	94.95	90.64 - 99.45	6.66
Cmax (ng/mL)	348.7	261.14 - 465.66	14	536.0	401.36 - 715.70	14	65.06	48.57 - 87.16	45.85

The AUC0-inf for Subject PPD was excluded from the comparison for Treatment B, because t½ > half the sampling interval and AUC%extrap > 20%.
Treatment B: single oral doses of 400 mg fluconazole (2 x 200 mg tablets) at Hour -1 and 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 (test)
Treatment A: a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (B [test]/A [reference])
Intra-subject CV% = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA
The ANOVA model using PROC MIXED of SAS® includes treatment as a fixed effect and subject as a random effect.
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Summary of Statistical Comparisons of Plasma ACP-5862 Pharmacokinetic Parameters: Acalabrutinib With Isavuconazole (Treatment C) Versus Acalabrutinib Alone (Treatment A) (Pharmacokinetic Population – Sequence AC Only)

Parameter	Treatment C (Test)			Treatment A (Reference)			GMR (%)	90% Confidence Interval	Intra-subject CV%
	Geometric LSMs	95% Confidence Interval	n	Geometric LSMs	95% Confidence Interval	n			
AUC0-t (ng*hr/mL)	1572	1357.51 - 1819.52	14	1790	1546.47 - 2072.79	14	87.78	82.42 - 93.49	9.43
AUC0-inf (ng*hr/mL)	1737	1530.29 - 1971.35	13	1900	1675.40 - 2154.05	14	91.43	86.20 - 96.97	8.44
Cmax (ng/mL)	352.2	260.37 - 476.43	14	489.9	362.15 - 662.68	14	71.90	62.75 - 82.37	20.54

The AUC0-inf for Subject PPD was excluded from the comparison for Treatment C, because AUC%extrap > 20%.
The data for Subjects PPD and PPD were excluded from the comparisons for Treatment A, because the subjects did not complete Treatment C.
Treatment C: multiple oral doses of 200 mg isavuconazole (2 x 186 mg isavuconazonium sulfate capsules) TID on Day 1 and QD on Days 2 – 5 with a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) coadministered at Hour 0 on Day 5 (test)
Treatment A: a single oral dose of 100 mg acalabrutinib (1 x 100 mg capsule) at Hour 0 on Day 1 (reference)
Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (C [test]/A [reference])
Intra-subject CV% = 100 x (square root (exp[MSE]-1)), where MSE = Residual variance from ANOVA
The ANOVA model using PROC MIXED of SAS® includes treatment as a fixed effect and subject as a random effect.
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Coadministration of the CYP3A4/5 inhibitors fluconazole and isavuconazole resulted in a decrease in peak exposure to ACP-5862, while total exposure to ACP-5862 was similar to slightly lower relative to the acalabrutinib alone. Geometric LSM ACP-5862 peak exposure after acalabrutinib with fluconazole was approximately 35% lower than after acalabrutinib alone. Geometric LSM ACP-5862 total exposure was comparable (5% lower) to slightly lower (15% lower) after acalabrutinib with fluconazole relative to acalabrutinib alone, for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$, respectively. Geometric LSM ACP-5862 peak exposure after acalabrutinib with isavuconazole was approximately 28% lower than after acalabrutinib alone. Geometric LSM ACP-5862 total exposure was comparable (9% lower) to slightly lower (12% lower) after acalabrutinib with isavuconazole relative to acalabrutinib alone, for $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$, respectively. Mean $t_{½}$ values were similar across treatments and median T_{max} values were approximately 1.0, 1.25, and 1.5 hours after acalabrutinib alone, acalabrutinib with isavuconazole, and acalabrutinib with fluconazole, respectively. Mean metabolite-to-parent ratios ($MR\_AUC_{0\text{-}t}$, $MR\_AUC_{0\text{-}inf}$, and MR_C_{max}) were approximately 54% to 56% lower after acalabrutinib with fluconazole and 44% to 48% lower after acalabrutinib with isavuconazole relative to acalabrutinib alone. Thus, the increases in exposure to acalabrutinib were generally mirrored by decreases in exposure observed for ACP-5862, suggesting no meaningful change in total AUC of the active components in the presence of a strong-moderate or weak-moderate CYP3A4/5 inhibitor.

For ACP-5862, there were 2 profiles (Subject PPD after acalabrutinib with fluconazole and Subject PPD after acalabrutinib with isavuconazole) for which the extrapolation of $AUC_{0\text{-}t}$ to

$AUC_{0\text{-}inf}$ was >20%. In addition, for Subject PPD after acalabrutinib with fluconazole the $t_{½}$ was long relative to the sampling interval. The statistical summaries and comparisons of PK parameters were presented with and without the affected parameters. The statistical conclusions were the same regardless of whether or not the affected data were included. The results discussed in the text are based on the analysis with the affected parameters excluded.

The results discussed above were based on the ANOVA models conducted by treatment sequence (AB or AC). Analysis of variance models were also conducted including the data for all 30 subjects. The results for the ANOVA models run by sequence were comparable to the results for each ANOVA including data for all subjects, for both acalabrutinib and ACP-5862 (with or without the affected data for Subjects PPD and PPD for ACP-5862).

Safety Results:
There were no deaths, SAEs or subject discontinuation due to AEs in this study.

Overall, a total of 15 TEAEs were reported by 5 (17%) subjects in the study, with 2 subjects reporting AEs following acalabrutinib alone, 2 subjects reporting AEs following acalabrutinib with fluconazole, and 1 subject reporting AEs following isavuconazole alone. The most common AE in this study was constipation, which was reported by 2 (7%) subjects in the study. All 15 AEs reported in the study were mild (Grade 1) in severity and considered unrelated to study drugs, with the exception of 1 event of abdominal pain which was considered related to acalabrutinib. All AEs resolved by study completion. There were no significant trends noted in physical examination, vital sign, laboratory, or ECG data in this study.

Conclusions:
Total and peak exposures to acalabrutinib were higher when acalabrutinib was administered with the strong-moderate CYP3A4/5 inhibitor fluconazole compared to acalabrutinib alone. Geometric LSM $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were approximately 2.0- to 2.2-fold higher and C_{max} was approximately 1.5-fold higher after fluconazole coadministration. Peak exposure to the active metabolite ACP-5862 decreased by approximately 35% after fluconazole coadministration while total exposure was similar to slightly lower relative to the acalabrutinib alone. The mean metabolite-to-parent ratios were approximately 54% to 56% lower after acalabrutinib with fluconazole relative to acalabrutinib alone.

Total and peak exposures to acalabrutinib were higher when acalabrutinib was administered with the weak-moderate CYP3A4/5 inhibitor isavuconazole compared to acalabrutinib alone. Geometric LSM $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were approximately 1.6-fold higher and C_{max} was approximately 1.4-fold higher after isavuconazole coadministration. Peak exposure to the active metabolite ACP-5862 decreased by approximately 28% after isavuconazole coadministration while total exposure was similar to slightly lower relative to the acalabrutinib alone. The mean metabolite-to-parent ratios were approximately 44% to 48% lower after acalabrutinib with isavuconazole relative to acalabrutinib alone.

Administration of acalabrutinib alone and in combination with fluconazole or with isavuconazole appeared to be generally safe and well tolerated by the healthy adult subjects in this study.

Date of Report: 27 October 2020