2. SYNOPSIS

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Title of Study: A Phase 1, Single-center, Open-label, Fixed-sequence, 4-period, 3-part Study in Healthy Adult Subjects to Evaluate the Effect of an Acidic Formulation of Acalabrutinib (ACP-196), Acidic Beverage, or Grapefruit Juice on the Pharmacokinetics of Acalabrutinib Alone and Coadministered With Omeprazole

Investigator(s): PPD

Study Center(s):
Celerion
PPD
Lincoln, Nebraska 68502 US

Publication (Reference): Not applicable.

Studied Period: **PHASE OF DEVELOPMENT:** I
(date of first enrollment)
28 January 2016
(**date of last completed**)
15 March 2016

Objectives:

Part 1 (Acidic Formulation)

Primary: To compare the effect of an acidic formulation on the PK profile of acalabrutinib alone and coadministered with omeprazole.

Secondary: To evaluate the safety and tolerability of an acidic formulation of acalabrutinib alone and coadministered with omeprazole.

Part 2 (Acidic Beverage – Orange Drink)

Primary: To compare the effect of a prototypical acidic beverage (orange drink) on the PK profile of acalabrutinib alone and coadministered with omeprazole.

Secondary: To evaluate the safety and tolerability of acalabrutinib alone and coadministered with omeprazole, administered with and without an acidic beverage.

Part 3 (Grapefruit Juice)

Primary: To compare the effect of grapefruit juice on the PK profile of acalabrutinib alone and coadministered with omeprazole.

Secondary: To evaluate the safety and tolerability of acalabrutinib alone and coadministered with omeprazole, administered with and without grapefruit juice.

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Methodology: This was a 3-part, Phase 1 study. Each part was conducted as an open-label, single-center, 4-period, fixed-sequence study to compare the effect of an acidic formulation of acalabrutinib, acidic beverage (orange drink), or grapefruit juice on the PK profile of acalabrutinib alone and when coadministered with omeprazole. Subjects were enrolled into Part 1 of the study first and then subsequent subjects were randomized in a 1:1 ratio to either Part 2 or Part 3.

Number of Subjects (Planned and Analyzed): A total of 36 subjects were enrolled in the study (12 subjects per arm were dosed to ensure completion of 10 subjects per arm), and 35 subjects completed the study. All 36 subjects were included in the PK 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 study products were 100 mg ACP-196 acidic formulation (Lot no. various, compounded with tartaric acid, Lot no. CCI , and alginic acid, NF, Lot no. CCI), omeprazole delayed-release capsules 40 mg (Lot no. CCI), Ocean Spray® 100% grapefruit no sugar added (Lot no. CCI), and Capri Sun orange drink (Lot no. CCI).

Acalabrutinib and omeprazole were administered orally with approximately 240 mL of water or with 240 mL acidic beverage or with grapefruit juice.

Duration of Treatment: Subjects were housed from the day before dosing in Period 1, at the time indicated by the clinical research unit (CRU), until 24 hours after the Day 10 acalabrutinib dose. There was no washout between the acalabrutinib dose on Day 3 and the first dose of omeprazole on Day 4. The total study duration was approximately 8 weeks from Screening to end of study procedures.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The study product was 100 mg ACP-196 reference formulation capsules (Lot no. CCI) administered orally with approximately 240 mL of water, with 240 mL acidic beverage, or with grapefruit juice.

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Criteria for Evaluation:

Pharmacokinetics: Blood samples for the determination of plasma acalabrutinib and omeprazole concentrations and PK parameters were collected before dosing to 24 hours postdose on Parts 1, 2, and 3 (in each part, samples were collected during Days 1, 3, 8, and 10). Plasma samples of acalabrutinib and omeprazole were analyzed using a validated liquid chromatography/tandem mass spectrometry assay method. The analytical range for acalabrutinib was 1.00 to 1000 ng/mL. The analytical range for omeprazole was 10.0 to 1000 ng/mL.

A noncompartmental PK approach was used to analyze individual plasma acalabrutinib and omeprazole concentration-time data (using Phoenix® WinNonlin® Version 6.3). Actual sample times were used in the calculations of the PK parameters.

The following PK parameters were calculated for acalabrutinib: $AUC_{0\text{-last}}$, $AUC_{0\text{-inf,}}$ C_{max}, $AUC_{\%extrap}$, $AUC_{0\text{-6h,}}$ $AUC_{0\text{-12h}}$, T_{max}, λ_z, $t_{½}$,, CL/F, and Vz/F. The following PK parameters were calculated for omeprazole: $AUC_{0\text{-24}}$, $AUC_{0\text{-last}}$, C_{max}, T_{max}, CL/F, and Vz /F.

Safety: Safety was evaluated by clinical laboratory tests, physical examination, vital signs, and adverse events (AEs).

Statistical Methods:

Pharmacokinetics: All plasma acalabrutinib and omeprazole concentrations and PK parameters descriptive statistics were generated using SAS® Version 9.3. Plasma acalabrutinib and omeprazole concentrations were listed by study part, analyte, treatment and day (period). PK parameters were tabulated by study part, analyte, treatment and day (period) and listed by subject and parameter. 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 timepoints and individual PK parameters. In addition, geometric mean (geom. mean) and geometric CV% (geom. CV%) were presented for all PK parameters.

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Analysis of Variance (ANOVA):
For each part separately, an analysis of variance (ANOVA) was performed on the natural log (ln)-transformed) acalabrutinib PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} for each comparison of interest. The ANOVA model included treatment as a fixed effect and subject as a random effect. Each ANOVA included calculation of least-squares means (LSM), the difference between treatment LSM, and the standard error associated with this difference. The above statistical analyses were done for each part separately using SAS® PROC MIXED. Acalabrutinib ratios of LSM were calculated using the exponentiation of the difference between treatment LSM from the ANOVA on the ln-transformed $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. These ratios were expressed as a percentage of the reference treatment. Consistent with the two one-sided test, 90% confidence intervals (CIs) for the ratios were derived by exponentiation of the CIs obtained for the difference between treatment LSM resulting from the ANOVA on the ln-transformed $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The CIs were expressed as a percentage of the reference treatment.

In addition, an analysis of Treatment 1C, 2C, and 3C (N=36) versus Treatments 1A, 2A, and 3A (N=36) was done using data from all 3 parts of the study and only Treatments A and C, using SAS® PROC MIXED.

Part 1: Effect of Acidic Formulation on Acalabrutinib PK in the Presence or Absence of Omeprazole: The comparisons of interest (test versus reference) were as follows:
Treatment 1B (Day 3/Period 2) versus Treatment 1A (Day 1/Period 1);
Treatment 1D (Day 10/Period 4) versus Treatment 1B (Day 3/Period 2);
Treatment 1D (Day 10/Period 4) versus Treatment 1C (Day 8/Period 3);
Treatment 1D (Day 10/Period 4) versus Treatment 1A (Day 1/Period 1);
Treatment 1C (Day 8/Period 3) versus Treatment 1A (Day 1/Period 1).

Part 2: Effect of Acidic Beverage on Acalabrutinib PK in the Presence or Absence of Omeprazole: The comparisons of interest (test versus reference) were as follows:
Treatment 2B (Day 3/Period 2) versus Treatment 2A (Day 1/Period 1);
Treatment 2D (Day 10/Period 4) versus Treatment 2B (Day 3/Period 2);
Treatment 2D (Day 10/Period 4) versus Treatment 2C (Day 8/Period 3);
Treatment 2D (Day 10/Period 4) versus Treatment 2A (Day 1/Period 1);
Treatment 2C (Day 8/Period 3) versus Treatment 2A (Day 1/Period 1).

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Part 3: Effect of Grapefruit Juice on Acalabrutinib PK in the Presence or Absence of Omeprazole: The comparisons of interest (test versus reference) were as follows:
Treatment 3B (Day 3/Period 2) versus Treatment 3A (Day 1/Period 1);
Treatment 3D (Day 10/Period 4) versus Treatment 3B (Day 3/Period 2);
Treatment 3D (Day 10/Period 4) versus Treatment 3C (Day 8/Period 3);
Treatment 3D (Day 10/Period 4) versus Treatment 3A (Day 1/Period 1);
Treatment 3C (Day 8/Period 3) versus Treatment 3A (Day 1/Period 1).

Pooled Data: Effect of Omeprazole on Acalabrutinib PK:
The following comparison was done on pooled subjects' data as described above. The comparison of interest (test versus reference) was as follows:

Treatments 1C, 2C, and 3C (Day 1 in all parts) versus Treatments 1A, 2A, and 3A (Day 8 in all parts).

Pooled Data: Effect of H. Pylori Status
The following comparison was done on pooled subjects' data as described above. The comparison of interest (test versus reference) was as follows:
H. pylori positive subjects in pooled Treatments 1A, 2A, and 3A (Day 1 in all parts) versus
H. pylori negative subjects in pooled Treatments 1A, 2A, and 3A (Day 1 in all parts).

Safety: All AEs that occurred during this clinical study were coded using the most current version of the Medical Dictionary for Regulatory Activities (MedDRA®), Version 18.1. Concomitant medications recorded during the study were coded with the World Health Organization (WHO) Dictionary Version 01SEP2015. AE summary tables were presented by severity and relationship to study drug and by number of subjects and number of AEs reported. Clinical laboratory and vital signs data were summarized and clinical laboratory data were also presented in shift tables. All safety data were listed by subject.

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SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Statistical comparisons of plasma acalabrutinib PK parameters in Part 1:
Treatment 1B (test) versus 1A (reference) – effect of acidic formulation: Combining acidic excipients with acalabrutinib granules (acidic formulation) resulted in a small decrease in acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$. Geometric mean $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, were approximately 0.79-fold lower (79% of acalabrutinib reference formulation) when acalabrutinib acidic formulation was administered. The decrease in C_{max} was 0.87-fold, 87 % of acalabrutinib reference formulation. One subject had a relatively high AUC ($AUC_{0\text{-last}}$ = 2560) in the reference formulation group relative to all other subjects, with a decrease to 0.66-fold compared with the reference formulation exposure ($AUC_{0\text{-last}}$ = 1680). The large decrease in exposure in this subject may have influenced the geometric mean 21% decrease in AUC to 0.79-fold that was measured in the entire treatment group.

Treatment 1C (test) versus 1A (reference) – effect of omeprazole: Adding omeprazole to the reference formulation given with water resulted in a decrease in acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}. The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.58-, 0.65-, and 0.27-fold lower, respectively (58%, 65%, and 27% of acalabrutinib reference formulation), after coadministration of omeprazole and acalabrutinib reference formulation (See also comparison of all Groups 1C, 2C, 3C versus 1A, 2A, 3A (N=36).

Treatment 1D (test) versus 1A (reference) – Does the acidic formulation overcome omeprazole to give exposure similar to acalabrutinib reference formulation given without omeprazole: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.76-, 0.76-, and 0.75-fold lower, respectively (76%, 76%, and 75% of acalabrutinib reference formulation), after coadministration of omeprazole and acalabrutinib acidic formulation compared with acalabrutinib reference formulation given alone.

Treatment 1D (test) versus 1B (reference) – effect of omeprazole on acidic formulation: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ were comparable after coadministration of omeprazole and acalabrutinib acidic formulation compared with acalabrutinib acidic formulation given alone, with GMRs of approximately 0.96 fold and 0.97 fold, respectively (96% and 97% of the acidic formulation). Mean acalabrutinib C_{max} was approximately 0.86-fold lower (86% of the acidic formulation) after coadministration of omeprazole and acalabrutinib acidic formulation.

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Treatment 1D vs 1C: In the presence of omeprazole, which formulation gives higher exposure: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 1.31-, 1.18-, and 2.82-fold higher, respectively (131%, 118%, and 282% of the reference formulation given with omeprazole), after coadministration of omeprazole and acalabrutinib acidic formulation.

Intra-subject variability between treatments was approximately 24%, 22%, and 71% for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, respectively.

Based on geometric LSM comparisons, combining acidic excipients with acalabrutinib granules (acidic formulation) resulted in a small decrease in AUC (0.79-fold), compared with the reference formulation. In the presence of omeprazole, the prototype acidic formulation afforded relatively higher exposure than the reference formulation given with omeprazole ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were 1.31-, 1.18-, and 2.82-fold higher, respectively. Therefore, in the presence of omeprazole, the acidic formulation restored acalabrutinib exposure to the level observed for the acidic formulation without omeprazole, but not back to level of the acalabrutinib reference formulation without omeprazole.

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Summary of Plasma Acalabrutinib Pharmacokinetic Parameters After Treatments 1A, 1B, 1C, and 1D

	Acalabrutinib on Day 1		**Acalabrutinib on Day 3**		**Acalabrutinib on Day 8**		**Acalabrutinib on Day 10**	
Pharmacokinetic Parameters	**Treatment 1A**	**n**	**Treatment 1B**	**n**	**Treatment 1C**	**n**	**Treatment 1D**	**n**
Geometric Mean								
AUC_{0-6} (ng*hr/mL)[a]	735.46 (81.8%)	12	586.30 (50.3%)	12	338.75 (123.1%)	12	559.05 (59.6%)	12
AUC_{0-12} (ng*hr/mL)[a]	752.71 (80.0%)	12	595.47 (50.6%)	12	388.69 (97.2%)	12	572.21 (59.2%)	12
AUC_{0-last} (ng*hr/mL)[a]	750.61 (79.9%)	12	593.15 (50.8%)	12	434.14 (75.3%)	12	569.15 (59.8%)	12
AUC_{0-inf} (ng*hr/mL)[a]	755.73 (79.5%)	12	596.75 (50.7%)	12	489.32 (57.6%)	12	576.11 (58.8%)	12
C_{max} (ng/mL)[a]	621.92 (94.1%)	12	541.37 (48.8%)	12	164.98 (237.5%)	12	464.61 (54.6%)	12
Arithmetic Mean								
AUC_{0-6} (ng*hr/mL)[b]	906.33 ± 602.59 (66.5%)	12	654.02 ± 354.59 (54.2%)	12	459.31 ± 284.87 (62.0%)	12	641.59 ± 357.39 (55.7%)	12
AUC_{0-12} (ng*hr/mL)[b]	923.87 ± 617.56 (66.8%)	12	665.44 ± 365.79 (55.0%)	12	492.13 ± 288.64 (58.7%)	12	656.25 ± 367.75 (56.0%)	12
AUC_{0-last} (ng*hr/mL)[b]	921.63 ± 618.83 (67.1%)	12	663.59 ± 367.30 (55.4%)	12	517.36 ± 284.67 (55.0%)	12	654.25 ± 369.71 (56.5%)	12
AUC_{0-inf} (ng*hr/mL)[b]	926.58 ± 620.23 (66.9%)	12	667.19 ± 368.21 (55.2%)	12	552.80 ± 275.65 (49.9%)	12	660.18 ± 370.61 (56.1%)	12
$AUC_{\%extrap}$ (%)[c]	0.67670 ± 0.38568	12	0.60367 ± 0.27345	12	9.9037 ± 14.832	12	1.2026 ± 1.0859	12
C_{max} (ng/mL)[b]	773.83 ± 438.41 (56.7%)	12	594.33 ± 259.94 (43.7%)	12	298.08 ± 246.03 (82.5%)	12	520.33 ± 253.24 (48.7%)	12
T_{max} (hr)[d]	0.63 (0.50, 1.00)	12	0.65 (0.50, 2.01)	12	0.89 (0.50, 4.03)	12	0.81 (0.47, 1.50)	12
λ_z (1/hr)[c]	0.42 ± 0.12	12	0.48 ± 0.19	12	0.22 ± 0.21	12	0.32 ± 0.14	12
$t_{1/2}$ (hr)[c]	1.79 ± 0.60	12	1.64 ± 0.53	12	7.66 ± 6.88	12	2.55 ± 1.17	12
CL/F (L/hr)[c]	168.28 ± 135.55	12	184.86 ± 83.491	12	234.16 ± 134.53	12	197.77 ± 103.29	12
Vz/F (L)[c]	441.20 ± 458.73	12	404.21 ± 192.06	12	3054.8 ± 3992.4	12	782.56 ± 761.51	12

[a]: Presented as Geometric Mean(GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (CV%)
[c]: Presented as Arithmetic Mean ± SD
[d]: Presented as Median (Minimum, Maximum)
Treatment 1A: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 1
Treatment 1B: Single oral dose of acalabrutinib 100 mg (acidic formulation) with 240 mL water on Day 3
Treatment 1C: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 8 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of water on Day 8
Treatment 1D: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 10 and a single oral dose of acalabrutinib
100 mg (acidic formulation) with 240 mL of water on Day 10
SD = Standard Deviation; GeomCV% = Geometric Coefficient of Variation
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Statistical Comparisons of Plasma Acalabrutinib Pharmacokinetic Parameters – Part 1

		Geometric LSM						
		First		Second				
Parameter	**Comparison**	**(Test)**	**n**	**(Reference)**	**n**	**GMR (%)**	**90% Confidence Interval (p-value)**	**Intra-subject CV%**
$AUC_{0\text{-last}}$ (ng*hr/mL)	1B vs 1A	593.15	(12)	750.61	(12)	79.02	67.28 - 92.81 (0.0185)	23.60
	1C vs 1A	434.14	(12)	750.61	(12)	57.84	49.24 - 67.93 (<.0001)	23.60
	1D vs 1A	569.15	(12)	750.61	(12)	75.83	64.56 - 89.06 (0.0064)	23.60
	1D vs 1B	569.15	(12)	593.15	(12)	95.95	81.70 - 112.70 (0.6667)	23.60
	1D vs 1C	569.15	(12)	434.14	(12)	131.10	111.62 - 153.98 (0.0075)	23.60
$AUC_{0\text{-inf}}$ (ng*hr/mL)	1B vs 1A	596.75	(12)	755.73	(12)	78.96	68.01 - 91.68 (0.0115)	21.87
	1C vs 1A	489.32	(12)	755.73	(12)	64.75	55.76 - 75.18 (<.0001)	21.87
	1D vs 1A	576.11	(12)	755.73	(12)	76.23	65.66 - 88.51 (0.0042)	21.87
	1D vs 1B	576.11	(12)	596.75	(12)	96.54	83.15 - 112.09 (0.6926)	21.87
	1D vs 1C	576.11	(12)	489.32	(12)	117.74	101.40 - 136.71 (0.0733)	21.87
C_{max} (ng/mL)	1B vs 1A	541.37	(12)	621.92	(12)	87.05	56.07 - 135.14 (0.5972)	70.70
	1C vs 1A	164.98	(12)	621.92	(12)	26.53	17.09 - 41.18 (<.0001)	70.70
	1D vs 1A	464.61	(12)	621.92	(12)	74.71	48.12 - 115.98 (0.2700)	70.70
	1D vs 1B	464.61	(12)	541.37	(12)	85.82	55.28 - 133.24 (0.5603)	70.70
	1D vs 1C	464.61	(12)	164.98	(12)	281.62	181.39 - 437.21 (0.0004)	70.70

First = First treatment in the comparison
Second = Second treatment in the comparison
Parameters were ln-transformed before analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (test/reference)
Intra-subject CV% = 100 x (square root (exp[MSE]-1))
CV% = Coefficient of variation.
MSE = Residual variance from ANOVA.
Treatment 1A: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 1
Treatment 1B: Single oral dose of acalabrutinib 100 mg (acidic formulation) with 240 mL water on Day 3
Treatment 1C: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 8 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of water on Day 8
Treatment 1D: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 10 and a single oral dose of acalabrutinib
100 mg (acidic formulation) with 240 mL of water on Day 10
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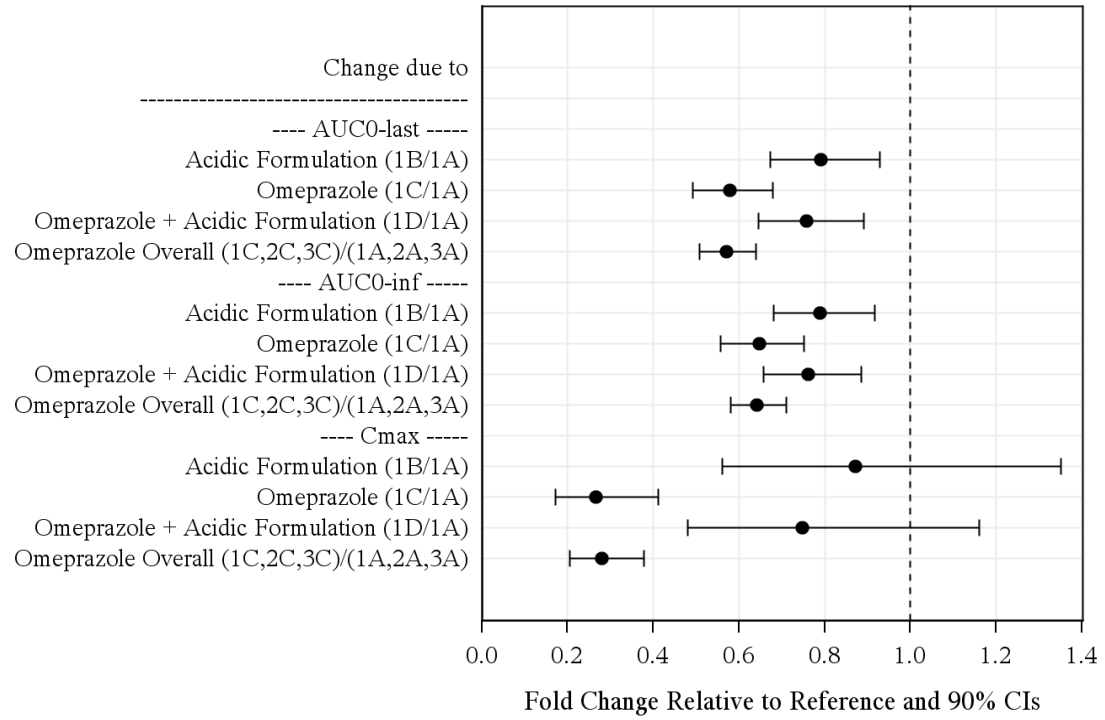
Part 1: Effect of Acidic Formulation: Summary Forest Plot of Plasma Acalabrutinib After Single Dose Administration (Acidic or Reference Formulation) Administered With Water, With or Without Omeprazole. Displayed as 90% Confidence Interval of Geometric Mean Ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}



Geometric Mean Ratio and 90% CI bars are presented
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Statistical comparisons of plasma acalabrutinib PK parameters in Part 2:
Treatment 2B (test) versus 2A (reference) – effect of acidic beverage: Combining acalabrutinib reference formulation with an acidic beverage (orange drink) resulted in a decrease in acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The geometric mean plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.60-, 0.62-, and 0.44-fold lower, respectively (60%, 62%, and 44%, of acalabrutinib with water), when acalabrutinib reference formulation was given with the acidic beverage, compared with acalabrutinib reference formulation given with water. One subject had a relatively late T_{max} (4 hours) in the reference group relative to all other subjects (median T_{max} = 0.5 hour).

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Treatment 2C (test) versus 2A (reference) – effect of omeprazole: Adding omeprazole to the reference formulation given with water resulted in a decrease in acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}. The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.51-, 0.59-, and 0.24-fold lower, respectively (51%, 59%, and 24% of acalabrutinib reference formulation), after coadministration of omeprazole and acalabrutinib reference formulation. (See also comparison of all Groups 1C, 2C, 3C versus 1A, 2A, 3A [N=36]).

Treatment 2D (test) versus 2A (reference) – Does the acidic beverage overcome omeprazole to give exposure similar to acalabrutinib reference formulation given without omeprazole: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.54-, 0.57-, and 0.29-fold lower, respectively (54%, 57%, and 29% of acalabrutinib with water), after coadministration of acalabrutinib reference formulation with an acidic beverage and omeprazole compared with acalabrutinib reference formulation with water.

Treatment 2D (test) versus 2B (reference) – effect of omeprazole on acalabrutinib reference formulation given with an acidic beverage: The geometric mean plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were not different after coadministration of omeprazole, acalabrutinib reference formulation and acidic beverage compared with acalabrutinib reference formulation and acidic beverage, with GMRs of approximately 0.89-, 0.92-, and 0.66-fold, (89%, 92%, and 66% of acalabrutinib with acidic beverage).

Treatment 2D versus 2C: In the presence of omeprazole, does acalabrutinib reference formulation administration with water or an acidic beverage give higher exposure: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were not different at approximately 1.05-, 0.98-, and 1.21-fold, respectively (105%, 98%, and 121% of acalabrutinib reference formulation with water), in the presence of omeprazole after administration with acidic beverage compared with administration with water.

Intra-subject variability between treatments was approximately 28%, 23%, and 91% for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, respectively.

Taken together, these acalabrutinib exposure comparisons showed that when acalabrutinib reference formulation was taken with an acidic beverage, $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, respectively, were 0.60-, 0.62-, and 0.44-fold lower (60%, 62%, and 44%), relative to acalabrutinib reference formulation taken with water. In the presence of omeprazole, the acidic beverage did not increase acalabrutinib exposure, compared with the exposure observed for acalabrutinib reference formulation and omeprazole given with water.

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Summary of Plasma Acalabrutinib Pharmacokinetic Parameters After Treatments 2A, 2B, 2C, and 2D

	Acalabrutinib on Day 1		**Acalabrutinib on Day 3**		**Acalabrutinib on Day 8**		**Acalabrutinib on Day 10**	
Pharmacokinetic Parameters	**Treatment 2A**	**n**	**Treatment 2B**	**n**	**Treatment 2C**	**n**	**Treatment 2D**	**n**
Geometric Mean								
AUC_{0-6} (ng*hr/mL)[a]	740.28 (51.4%)	12	418.37 (52.7%)	12	305.60 (87.6%)	12	363.86 (77.8%)	12
AUC_{0-12} (ng*hr/mL)[a]	755.65 (51.3%)	12	441.53 (44.4%)	12	347.37 (73.4%)	12	389.33 (67.3%)	12
AUC_{0-last} (ng*hr/mL)[a]	753.80 (51.5%)	12	451.96 (40.5%)	12	385.10 (59.6%)	12	404.22 (57.9%)	12
AUC_{0-inf} (ng*hr/mL)[a]	758.30 (51.1%)	12	467.99 (39.0%)	12	452.38 (49.6%)	10	459.47 (42.3%)	11
C_{max} (ng/mL)[a]	679.78 (55.0%)	12	296.34 (87.0%)	12	162.55 (170.4%)	12	196.89 (117.9%)	12
Arithmetic Mean								
AUC_{0-6} (ng*hr/mL)[b]	816.26 ± 349.49 (42.8%)	12	464.95 ± 216.86 (46.6%)	12	380.38 ± 227.96 (59.9%)	12	434.77 ± 235.48 (54.2%)	12
AUC_{0-12} (ng*hr/mL)[b]	832.75 ± 354.21 (42.5%)	12	480.39 ± 211.98 (44.1%)	12	412.28 ± 224.00 (54.3%)	12	452.07 ± 235.39 (52.1%)	12
AUC_{0-last} (ng*hr/mL)[b]	831.05 ± 353.98 (42.6%)	12	486.19 ± 203.57 (41.9%)	12	437.04 ± 213.25 (48.8%)	12	457.17 ± 226.80 (49.6%)	12
AUC_{0-inf} (ng*hr/mL)[b]	834.99 ± 354.17 (42.4%)	12	500.41 ± 198.43 (39.7%)	12	494.90 ± 204.37 (41.3%)	10	495.67 ± 206.41 (41.6%)	11
$AUC_{\%extrap}$ (%)[c]	0.59224 ± 0.54440	12	3.0364 ± 8.2734	12	6.9427 ± 10.714	10	3.0737 ± 7.1069	11
C_{max} (ng/mL)[b]	759.17 ± 345.69 (45.5%)	12	355.88 ± 180.39 (50.7%)	12	264.82 ± 234.10 (88.4%)	12	256.57 ± 142.05 (55.4%)	12
T_{max} (hr)[d]	0.50 (0.50, 4.00)	12	0.88 (0.50, 1.54)	12	1.27 (0.50, 3.02)	12	1.29 (0.76, 2.02)	12
λ_z (1/hr)[c]	0.46 ± 0.20	12	0.52 ± 0.23	12	0.23 ± 0.27	10	0.35 ± 0.14	11
$t_{1/2}$ (hr)[c]	1.92 ± 1.30	12	2.28 ± 3.30	12	7.27 ± 6.23	10	3.17 ± 4.06	11
CL/F (L/hr)[c]	147.74 ± 80.044	12	227.15 ± 79.020	12	245.62 ± 127.71	10	233.85 ± 90.010	11
Vz/F (L)[c]	460.81 ± 537.91	12	704.73 ± 1020.4	12	3158.4 ± 4209.5	10	1284.1 ± 2199.7	11

[a]: Presented as Geometric Mean(GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (CV%)
[c]: Presented as Arithmetic Mean ± SD
[d]: Presented as Median (Minimum, Maximum)
Treatment 2A: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 1
Treatment 2B: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of acidic beverage on Day 3
Treatment 2C: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 8 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of water on Day 8
Treatment 2D: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 10 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of acidic beverage on Day 10
SD = Standard Deviation; GeomCV% = Geometric Coefficient of Variation
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Statistical Comparisons of Plasma Acalabrutinib Pharmacokinetic Parameters – Part 2

		Geometric LSM						
		First		Second				
Parameter	**Comparison**	**(Test)**	**n**	**(Reference)**	**n**	**GMR (%)**	**90% Confidence Interval (p-value)**	**Intra-subject CV%**
$AUC_{0\text{-}last}$ (ng*hr/mL)	2B vs 2A	451.96	(12)	753.80	(12)	59.96	49.69 - 72.34 (<.0001)	27.69
	2C vs 2A	385.10	(12)	753.80	(12)	51.09	42.34 - 61.64 (<.0001)	27.69
	2D vs 2A	404.22	(12)	753.80	(12)	53.62	44.44 - 64.70 (<.0001)	27.69
	2D vs 2B	404.22	(12)	451.96	(12)	89.44	74.13 - 107.91 (0.3218)	27.69
	2D vs 2C	404.22	(12)	385.10	(12)	104.96	86.99 - 126.65 (0.6652)	27.69
$AUC_{0\text{-}inf}$ (ng*hr/mL)	2B vs 2A	467.99	(12)	758.30	(12)	61.72	52.84 - 72.08 (<.0001)	22.69
	2C vs 2A	444.44	(10)	758.30	(12)	58.61	49.69 - 69.13 (<.0001)	22.69
	2D vs 2A	433.43	(11)	758.30	(12)	57.16	48.71 - 67.06 (<.0001)	22.69
	2D vs 2B	433.43	(11)	467.99	(12)	92.62	78.93 - 108.67 (0.4217)	22.69
	2D vs 2C	433.43	(11)	444.44	(10)	97.52	82.28 - 115.59 (0.8040)	22.69
C_{max} (ng/mL)	2B vs 2A	296.34	(12)	679.78	(12)	43.59	25.46 - 74.65 (0.0134)	91.30
	2C vs 2A	162.55	(12)	679.78	(12)	23.91	13.96 - 40.95 (<.0001)	91.30
	2D vs 2A	196.89	(12)	679.78	(12)	28.96	16.91 - 49.60 (0.0004)	91.30
	2D vs 2B	196.89	(12)	296.34	(12)	66.44	38.80 - 113.78 (0.2073)	91.30
	2D vs 2C	196.89	(12)	162.55	(12)	121.13	70.73 - 207.43 (0.5507)	91.30

First = First treatment in the comparison
Second = Second treatment in the comparison
Parameters were ln-transformed before analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (test/reference)
Intra-subject CV% = 100 x (square root (exp[MSE]-1))
CV% = Coefficient of variation.
MSE = Residual variance from ANOVA.
Treatment 2A: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 1
Treatment 2B: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of acidic beverage on Day 3
Treatment 2C: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 8 and a single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 8
Treatment 2D: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 10 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of acidic beverage on Day 10
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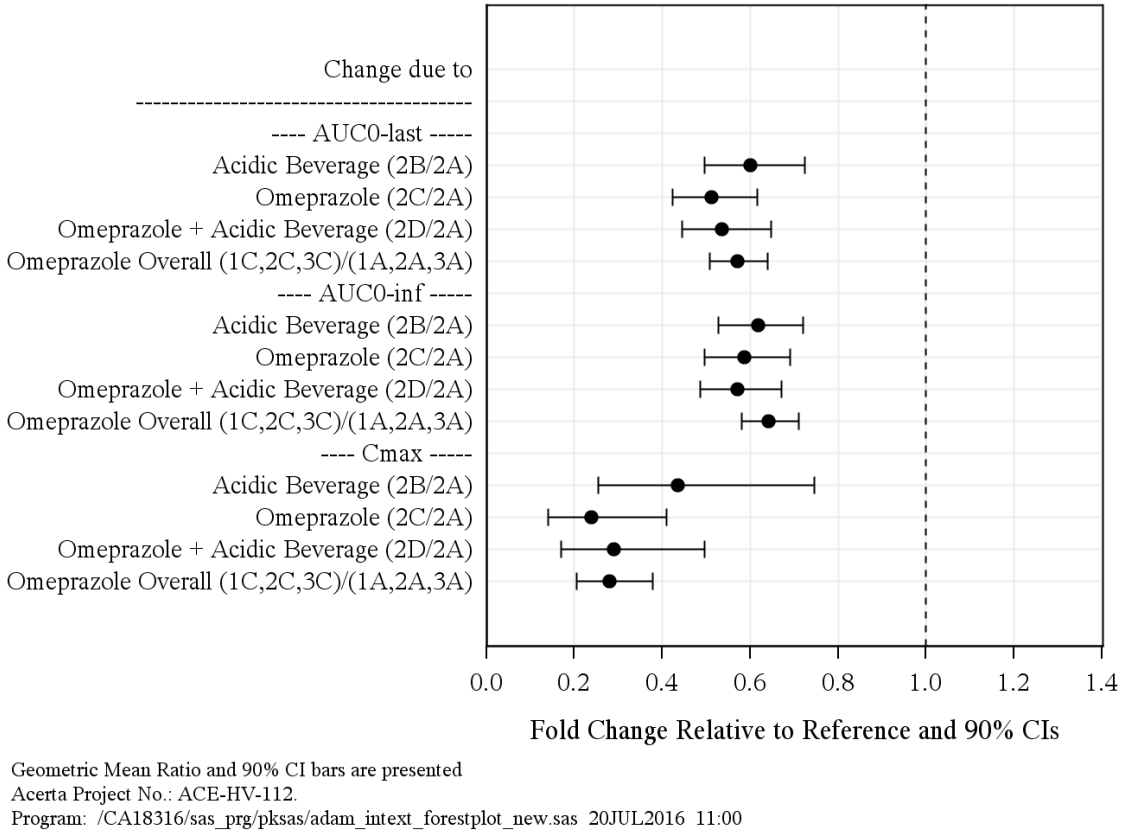
Part 2: Effect of Acidic Beverage (Orange Drink): Summary Forest Plot of Plasma Acalabrutinib After Single Dose Administration (Reference Formulation) Administered With Water or Acidic Beverage, With or Without Omeprazole. Displayed as 90% Confidence Interval of Geometric Mean Ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}



Geometric Mean Ratio and 90% CI bars are presented
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Statistical comparisons of plasma acalabrutinib PK parameters in Part 3:
Treatment 3B (test) versus 3A (reference) – effect of grapefruit juice: Combining grapefruit juice with acalabrutinib reference formulation resulted in a small decrease in acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.83-, 0.84-, and 0.65-fold lower, respectively (83%, 84%, and 65 % of acalabrutinib with water), when acalabrutinib reference formulation was given with grapefruit juice, compared with acalabrutinib reference formulation given with water.

Treatment 3C (test) versus 3A (reference) – effect of omeprazole: Adding omeprazole to the acalabrutinib reference formulation given with water resulted in a decrease in acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}. The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and

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C_{max} were approximately 0.63-, 0.67-, and 0.34-fold lower, respectively (63%, 67%, and 34% of acalabrutinib without omeprazole), when the reference formulation, water and omeprazole were combined. (See also comparison of all Groups 1C, 2C, 3C versus 1A, 2A, 3A (N=36)).

Treatment 3D (test) versus 3A (reference) – Does grapefruit juice overcome omeprazole i.e. to give exposure similar to acalabrutinib given without omeprazole: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.84-, 0.85-, and 0.56-fold lower, respectively (84%, 85%, and 56% of acalabrutinib and water), after coadministration of acalabrutinib reference formulation with grapefruit juice and omeprazole compared with acalabrutinib reference formulation with water.

Treatment 3D (test) versus 3B (reference) – effect of omeprazole on acalabrutinib given with grapefruit juice: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were comparable after coadministration of omeprazole, acalabrutinib reference formulation and grapefruit juice compared with acalabrutinib reference formulation and grapefruit juice, with GMR of approximately 1.01-, 1.01- and 0.87-fold, respectively (101%, 101%, and 87% of acalabrutinib with grapefruit juice), after omeprazole was added to acalabrutinib reference formulation given with grapefruit juice.

Treatment 3D versus 3C: In the presence of omeprazole, does coadministration with water or grapefruit juice give higher exposure: The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were approximately 1.34-, 1.26-, and 1.64-fold higher, respectively (134%, 126%, and 164% of acalabrutinib reference formulation given with omeprazole and water), in the presence of omeprazole after administration with grapefruit juice compared with administration with water.

Intra-subject variability between treatments was approximately 22%, 19%, and 56% for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, respectively.

Taken together, these comparisons showed that acalabrutinib reference formulation taken with grapefruit juice resulted in a small decrease in acalabrutinib exposure relative to acalabrutinib reference formulation taken with water. The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.83-, 0.84-, and 0.65-fold lower, respectively (83%, 84%, and 65 %, of acalabrutinib with water).

In the presence of omeprazole, grapefruit juice resulted in relatively higher exposure compared with acalabrutinib reference formulation given with omeprazole and water. $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were 1.34-, 1.26-, and 1.64-fold higher, respectively. Overall, in the presence of omeprazole, grapefruit juice restored acalabrutinib exposure to the level observed for grapefruit juice without omeprazole, but not back to level of the acalabrutinib reference formulation given with water.

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Summary of Plasma Acalabrutinib Pharmacokinetic Parameters After Treatments 3A, 3B, 3C, and 3D

	Acalabrutinib on Day 1		**Acalabrutinib on Day 3**		**Acalabrutinib on Day 8**		**Acalabrutinib on Day 10**	
Pharmacokinetic Parameters	**Treatment 3A**	**n**	**Treatment 3B**	**n**	**Treatment 3C**	**n**	**Treatment 3D**	**n**
Geometric Mean								
AUC_{0-6} (ng*hr/mL)[a]	802.22 (39.9%)	12	662.50 (45.2%)	12	434.57 (96.3%)	12	666.00 (47.4%)	12
AUC_{0-12} (ng*hr/mL)[a]	813.15 (39.9%)	12	677.92 (45.1%)	12	475.83 (79.7%)	12	685.94 (46.9%)	12
AUC_{0-last} (ng*hr/mL)[a]	809.93 (40.1%)	12	676.24 (45.3%)	12	508.89 (68.1%)	12	684.18 (47.1%)	12
AUC_{0-inf} (ng*hr/mL)[a]	814.28 (39.9%)	12	680.60 (45.1%)	12	546.47 (64.8%)	11	688.97 (46.8%)	12
C_{max} (ng/mL)[a]	798.38 (41.5%)	12	519.23 (51.7%)	12	273.48 (165.9%)	12	449.64 (62.1%)	12
Arithmetic Mean								
AUC_{0-6} (ng*hr/mL)[b]	855.65 ± 309.82 (36.2%)	12	722.51 ± 331.07 (45.8%)	12	562.00 ± 380.68 (67.7%)	12	729.06 ± 317.03 (43.5%)	12
AUC_{0-12} (ng*hr/mL)[b]	867.21 ± 313.27 (36.1%)	12	738.86 ± 336.69 (45.6%)	12	585.25 ± 373.45 (63.8%)	12	749.42 ± 322.19 (43.0%)	12
AUC_{0-last} (ng*hr/mL)[b]	864.25 ± 313.48 (36.3%)	12	737.55 ± 337.29 (45.7%)	12	601.94 ± 358.26 (59.5%)	12	747.91 ± 322.48 (43.1%)	12
AUC_{0-inf} (ng*hr/mL)[b]	868.40 ± 313.57 (36.1%)	12	741.70 ± 337.40 (45.5%)	12	636.65 ± 359.70 (56.5%)	11	752.42 ± 322.64 (42.9%)	12
$AUC_{\%extrap}$ (%)[c]	0.53498 ± 0.22878	12	0.63963 ± 0.29183	12	4.2574 ± 6.6267	11	0.69399 ± 0.34275	12
C_{max} (ng/mL)[b]	857.75 ± 337.11 (39.3%)	12	576.33 ± 268.17 (46.5%)	12	413.07 ± 299.61 (72.5%)	12	520.67 ± 287.00 (55.1%)	12
T_{max} (hr)[d]	0.63 (0.50, 1.01)	12	1.00 (0.75, 1.52)	12	0.78 (0.50, 3.01)	12	1.50 (0.75, 2.01)	12
λ_z (1/hr)[c]	0.43 ± 0.12	12	0.39 ± 0.15	12	0.29 ± 0.21	11	0.36 ± 0.07	12
$t_{1/2}$ (hr)[c]	1.69 ± 0.32	12	1.99 ± 0.70	12	4.71 ± 4.42	11	2.01 ± 0.40	12
CL/F (L/hr)[c]	131.79 ± 54.873	12	159.60 ± 67.870	12	213.81 ± 123.49	11	158.82 ± 70.354	12
Vz/F (L)[c]	310.30 ± 103.54	12	442.86 ± 216.47	12	1693.6 ± 2091.7	11	462.54 ± 223.93	12

[a]: Presented as Geometric Mean(GeomCV%)
[b]: Presented as Arithmetic Mean ± SD (CV%)
[c]: Presented as Arithmetic Mean ± SD
[d]: Presented as Median (Minimum, Maximum)
Treatment 3A: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 1
Treatment 3B: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of grapefruit juice on Day 3
Treatment 3C: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 8 and a single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 8
Treatment 3D: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 10 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of grapefruit juice on Day 10
SD = Standard Deviation; GeomCV% = Geometric Coefficient of Variation
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Statistical Comparisons of Plasma Acalabrutinib Pharmacokinetic Parameters – Part 3

		Geometric LSM						
		First		Second				
Parameter	**Comparison**	**(Test)**	**n**	**(Reference)**	**n**	**GMR (%)**	**90% Confidence Interval (p-value)**	**Intra-subject CV%**
$AUC_{0\text{-last}}$ (ng*hr/mL)	3B vs 3A	676.24	(12)	809.93	(12)	83.49	71.93 - 96.91 (0.0486)	21.83
	3C vs 3A	508.89	(12)	809.93	(12)	62.83	54.13 - 72.93 (<.0001)	21.83
	3D vs 3A	684.18	(12)	809.93	(12)	84.47	72.78 - 98.05 (0.0641)	21.83
	3D vs 3B	684.18	(12)	676.24	(12)	101.17	87.16 - 117.44 (0.8954)	21.83
	3D vs 3C	684.18	(12)	508.89	(12)	134.45	115.83 - 156.05 (0.0020)	21.83
$AUC_{0\text{-inf}}$ (ng*hr/mL)	3B vs 3A	680.60	(12)	814.28	(12)	83.58	73.28 - 95.33 (0.0275)	19.20
	3C vs 3A	547.66	(11)	814.28	(12)	67.26	58.74 - 77.01 (<.0001)	19.20
	3D vs 3A	688.97	(12)	814.28	(12)	84.61	74.18 - 96.50 (0.0390)	19.20
	3D vs 3B	688.97	(12)	680.60	(12)	101.23	88.75 - 115.46 (0.8759)	19.20
	3D vs 3C	688.97	(12)	547.66	(11)	125.80	109.87 - 144.05 (0.0072)	19.20
C_{max} (ng/mL)	3B vs 3A	519.23	(12)	798.38	(12)	65.04	45.30 - 93.38 (0.0523)	56.15
	3C vs 3A	273.48	(12)	798.38	(12)	34.26	23.86 - 49.18 (<.0001)	56.15
	3D vs 3A	449.64	(12)	798.38	(12)	56.32	39.23 - 80.86 (0.0112)	56.15
	3D vs 3B	449.64	(12)	519.23	(12)	86.60	60.32 - 124.33 (0.5054)	56.15
	3D vs 3C	449.64	(12)	273.48	(12)	164.41	114.51 - 236.05 (0.0263)	56.15

First = First treatment in the comparison
Second = Second treatment in the comparison
Parameters were ln-transformed before analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100 x (test/reference)
Intra-subject CV% = 100 x (square root (exp[MSE]-1))
CV% = Coefficient of variation.
MSE = Residual variance from ANOVA.
Treatment 3A: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of water on Day 1
Treatment 3B: Single oral dose of acalabrutinib 100 mg (reference formulation) with 240 mL of grapefruit juice on Day 3
Treatment 3C: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 8 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of water on Day 8
Treatment 3D: Multiple oral doses of omeprazole 40 mg QD from Day 4 to Day 10 and a single oral dose of acalabrutinib
100 mg (reference formulation) with 240 mL of grapefruit juice on Day 10
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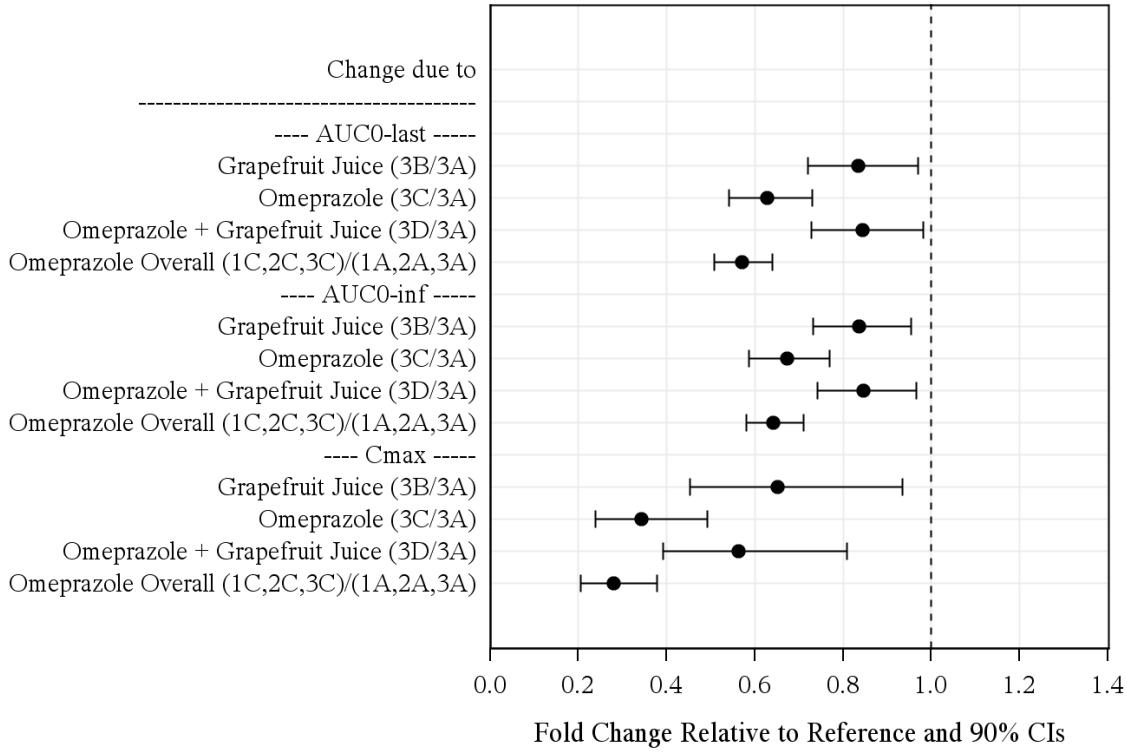
Part 3: Effect of Grapefruit Juice: Summary Forest Plot of Plasma Acalabrutinib After Single Dose Administration (Reference Formulation) Administered With Water or Grapefruit Juice, With or Without Omeprazole. Displayed as 90% Confidence Interval of Geometric Mean Ratios for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}



Geometric Mean Ratio and 90% CI bars are presented
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The Effect of Acalabrutinib on Omeprazole PK: The mean plasma omeprazole exposure (based on AUC and C_{max}) was not affected after coadministration of omeprazole and acalabrutinib reference formulation compared to omeprazole and acalabrutinib acidic formulation. In addition, the mean plasma omeprazole exposure was not affected after coadministration of omeprazole and acalabrutinib reference formulation with acidic beverage/grapefruit juice compared to omeprazole and acalabrutinib reference formulation.

The Effect of Omeprazole on Acalabrutinib PK (Pooled Treatments 1C, 2C, and 3C Versus Pooled Treatments 1A, 2A, and 3A): The geometric mean plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.57-, 0.64-, and 0.28-fold lower, respectively (57 %, 64%, and 28% of exposure in the absence of omeprazole), after coadministration of acalabrutinib (reference formulation and water) and omeprazole compared with acalabrutinib (reference formulation and water).

The Effect of H. Pylori Status (Pooled Treatments 1A, 2A, and 3A): After a single oral dose of acalabrutinib (reference formulation), the geometric LSMs for acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.59-, 0.59 and 0.75-fold lower, respectively (59%, 59%, and 75% of H. pylori negative subjects). The incidence of H. pylori positive and negative subjects was not balanced in the comparison, with 8 H. pylori positive subjects compared with 27 H. pylori negative subjects.

Safety Results: There were no deaths, serious adverse events (SAEs), or subject discontinuations due to AEs in this study. Overall, a total of 39 AEs were experienced by 19 (53%) of the 36 subjects in this study across all study parts. AEs were minimally reported throughout each study part. The most common events reported per study part were pruritus (Part 1, 3 [25%] subjects), vessel puncture site pain (Part 2, 2 [17%] subjects), and headache (Part 3, 2 [17%] subjects).

Across the 3 study parts, a total of 38 events were Grade 1 (mild) in intensity and 1 was Grade 2 (moderate, decreased appetite [Part 2]). The PI considered 27 events to be unrelated to the study treatment and 12 events to be related.

There were no remarkable observations in the remaining safety events for vital sign, physical examination, and laboratory assessments.

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Conclusion:

- In the pooled healthy subject population (N=36), geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.57-, 0.64-, and 0.28-fold lower after coadministration of acalabrutinib reference formulation, omeprazole and water, compared with acalabrutinib reference formulation and water.

- The acalabrutinib acidic formulation resulted in an overall small decrease in AUC compared with the reference formulation. In the presence of omeprazole, the acidic formulation restored acalabrutinib exposure to the level observed for the acidic formulation without omeprazole.

- Administration of acalabrutinib reference formulation with an acidic beverage (orange drink), resulted in an overall lower exposure ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max}, respectively, were 0.60-, 0.62-, and 0.44-fold lower), relative to acalabrutinib reference formulation taken with water. In the presence of omeprazole, the acidic beverage did not increase acalabrutinib exposure, compared with the exposure observed for acalabrutinib reference formulation and omeprazole taken with water.

- Acalabrutinib reference formulation taken with grapefruit juice resulted in a small decrease in acalabrutinib exposure relative to acalabrutinib reference formulation taken with water. The geometric LSM plasma acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 0.83-, 0.84-, and 0.65-fold lower, respectively.

- In the presence of omeprazole, grapefruit juice resulted in relatively higher exposure compared with acalabrutinib reference formulation given with omeprazole and water. $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were 1.34-, 1.26-, and 1.64-fold higher, respectively. In the presence of omeprazole, grapefruit juice restored acalabrutinib exposure to the level observed for grapefruit juice without omeprazole.

- Acalabrutinib was safe and well tolerated by the healthy subjects in this study.

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