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 Study in Healthy Adult Subjects to Evaluate the Effect of Gastric pH on Acalabrutinib Pharmacokinetics

Investigator(s): PPD

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

Publication (Reference): Not applicable.

Studied Period: **PHASE OF DEVELOPMENT:** I
(date of first enrollment)
03 June 2016
(**date of last completed**)
11 July 2016

Objectives:
Primary:
- To evaluate the effect of gastric pH and emptying rate on acalabrutinib pharmacokinetics (PK).

Secondary:
- To evaluate inter- and intra-subject variability in AUC and C_{max} of acalabrutinib (100 mg) after single-dose administration on 2 different days.
- To evaluate the safety and tolerability of acalabrutinib.

Exploratory:
- To evaluate exposure differences by H. pylori breath test status.
- To evaluate exposure differences by select CYP3A5, GSTM1, or BCRP genotype.

Methodology: This was an open-label, fixed-sequence, 2-period study under fasting conditions. Subjects checked into the clinic on the day before dosing and checked out after the last 24-hour assessment.

Number of Subjects (Planned and Analyzed): A total of 12 subjects were enrolled in the study. All 12 subjects completed the study and were included in the PK and 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 study product was 100 mg ACP-196 (acalabrutinib) capsules (Lot no. CCI). SmartPill® capsule was used to monitor the pH (Lot no. CCI).

Acalabrutinib and the SmartPill were administered orally with approximately 240 mL of distilled water maintained at room temperature. Specifically, the SmartPill was administered with 120 mL of distilled water, followed by the acalabrutinib dose with 120 mL of distilled water.

Duration of Treatment: Subjects checked into the clinic on the day before dosing and checked out after the last 24-hour assessment in each period. A washout of 72 hours occurred after Day 1 dosing of each period.

Reference Product, Dose, Duration, Mode of Administration, and Batch Number: The same test products were administered in Period 2.

Criteria for Evaluation:

Pharmacokinetics: Blood samples for the determination of plasma acalabrutinib concentrations and PK parameters were collected before dosing to 24 hours postdose on Periods 1 and 2. Plasma samples of acalabrutinib were analyzed using a validated liquid chromatography/tandem mass spectrometry assay method. The analytical range for acalabrutinib was 1.00 to 1000 ng/mL.

A noncompartmental PK approach was used to analyze individual plasma acalabrutinib 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_{0-6}, AUC_{0-12}, AUC_{0-last}, AUC_{0-inf}, $AUC_{\%extrap}$, C_{max}, T_{max}, λ_z, $t_{½}$, CL/F, and V_z/F.

Gastric Parameters (SmartPill Data): The SmartPill is an ingestible capsule that assesses motility by measuring pressure, pH, and temperature throughout the entire gastrointestinal (GI) tract. As the SmartPill capsule passed through the GI tract, it wirelessly transmitted data to the recorder that the subject wore attached to his/her belt or clothing. The key gastric parameters collected from the SmartPill for this study were stomach pH measurements collected on initial entry of the SmartPill into the stomach (at the Ingestion Event Time [IET]) and at 3, 8, and 17 minutes post-IET; and the gastric residence time (which reflects the gastric emptying rate). The pH parameters were calculated for each subject over a 20-second averaging period. A maximum of 5 pH samples for each 20-second interval were collected.

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

Statistical Methods:

Pharmacokinetics: All plasma acalabrutinib concentrations and PK parameters descriptive statistics were generated using SAS® Version 9.3. Plasma acalabrutinib concentrations were tabulated by period and listed by nominal sample time for all subjects. Plasma PK parameters of acalabrutinib were tabulated by period and listed by parameter for all subjects.

Summary statistics, including sample size (n), arithmetic mean (mean), standard deviation (SD), coefficient of variation (CV%), median, minimum, maximum, geometric means (Geom Mean), and geometric CV% (Geom CV%) were calculated for all nominal concentration timepoints and PK parameters. In addition, a 90% lower confidence interval (90% LCI) and 90% upper confidence interval (90% UCI) were reported for all PK parameters.

Summary statistics, including n, mean, SD, CV%, median, minimum, maximum, Geom Mean, Geom CV%, 90% LCI, and 90% UCI, were calculated for all gastric parameters.

Evaluation of the Effect of Gastric pH and Emptying Rate on Acalabrutinib PK:
The effect of initial gastric pH; mean gastric pH at 3, 8, and 17 minutes post-IET; and gastric residence time (reflecting the gastric emptying rate) on $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and T_{max} was explored graphically through separate scatter plots (one for each combination of PK [y-axis] and gastric parameter [x-axis]). The figures also include a simple regression line and 95% confidence interval (CI) (using the RLCLM95 option in SAS).

Statistical Model: An analysis of covariance (ANCOVA) with fixed effect for period, subject included as a random effect, and gastric pH at 8 minutes post-IET included as covariate, was used to analyze PK parameters ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and T_{max}) and thus to evaluate exposure differences by gastric pH. This model was repeated for other gastric parameters (eg, initial gastric pH, mean gastric pH at 3 minutes post-IET, gastric pH at 17 minutes post-IET, and gastric residence time) as sensitivity or exploratory analyses. The ANCOVA analysis was performed using SAS® PROC MIXED.

Evaluation of Inter- and Intra-subject Variability in AUC and Cmax of Acalabrutinib (100mg) After Single-dose Administration on 2 Different Days:
To determine the variability of the PK profile of acalabrutinib after single-dose administration on 2 different days, an analysis of variance (ANOVA) using PROC MIXED of SAS® Version 9.3 was performed on the natural log (ln)-transformed acalabrutinib PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, $AUC_{0\text{-6}}$, $AUC_{0\text{-12}}$, and C_{max}. The ANOVA model included period as a fixed effect and subject as a random effect. The least-squares means (LSMs) was determined for each parameter. These results (LSMs) were exponentiated to the original scale. Geometric LSMs, subject variance, residual variance, intra-subject and inter-subject CV% were presented. As described in the rationale for endpoints, the inter-subject and intra-subject variability of the 2 doses of acalabrutinib administered on different days were calculated. Inter-subject CV% was calculated from the subject variance using SAS® PROC MIXED. The subject and residual variances were also provided in the same table.

Evaluation of Exposure Differences by H. pylori Breath Test Status:
An H. pylori breath test was done on Day -1 of Period 1. The model used for the secondary analysis was also used for each subset of subjects based on their H. pylori status (variable PYLORI: P=positive, N=negative) using SAS® PROC MIXED. In addition, the effect of H.

pylori status on the PK parameters was evaluated using a repeated-measures ANOVA where period was considered a repeated variable on the subject. The analysis was performed using SAS® PROC MIXED.

Evaluation of Exposure Differences by Genotypes:
PK parameter table summaries by CYP3A5, GSTM1, and BCRP genotypes were provided for evaluation of exposure differences. Graphical exploration was also used to assess exposure differences.

Safety: Treatment-emergent AEs (TEAEs) were summarized. Vital sign results and safety laboratory parameters for serum chemistry, hematology and urinalysis were summarized and change from baseline results were presented. All safety data were listed individually. No inferential statistical analyses were performed on the safety data.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Mean plasma acalabrutinib AUC and C_{max} values were somewhat lower in Period 2 compared with Period 1, noting that PK parameter variability was high (49 - 64% Geom CV%). Median acalabrutinib T_{max} and mean $t_{1/2}$ values were similar between both periods at approximately 0.75 and 1.9 hours, respectively. Mean acalabrutinib CL/F and V_z/F were slightly higher in Period 2 compared with Period 1.

Based on Geometric CV%, individual AUC and C_{max} values were slightly more variable in Period 2 compared with Period 1. $AUC_{0\text{-last}}$ Geom CV% values were 50 and 54, respectively, in Period 1 and Period 2, while C_{max} Geom CV% values were 52 and 64, respectively, in Period 1 and Period 2.

Summary of Plasma Acalabrutinib Pharmacokinetic Parameters

Pharmacokinetic Parameters	Acalabrutinib in Period 1	n	Acalabrutinib in Period 2	n
Geometric Mean (GeomCV%)				
$AUC_{0\text{-}6}$ (ng•hr/mL)	721 (50.6)	12	519 (59.5)	12
$AUC_{0\text{-}12}$ (ng•hr/mL)	736 (49.7)	12	534 (56.7)	12
$AUC_{0\text{-last}}$ (ng•hr/mL)	734 (49.8)	12	541 (54.4)	12
$AUC_{0\text{-inf}}$ (ng•hr/mL)	738 (49.4)	12	588 (51.9)	9
C_{max} (ng/mL)	601 (52.6)	12	408 (63.5)	12
Arithmetic Mean (± SD)				
$AUC_{0\text{-}6}$ (ng•hr/mL)	799 (390)	12	592 (307)	12
$AUC_{0\text{-}12}$ (ng•hr/mL)	813 (393)	12	604 (306)	12
$AUC_{0\text{-last}}$ (ng•hr/mL)	812 (394)	12	608 (302)	12
$AUC_{0\text{-inf}}$ (ng•hr/mL)	816 (394)	12	652 (310)	9
$AUC_{\%extrap}$ (%)	0.586 (0.416)	12	0.668 (0.422)	9
C_{max} (ng/mL)	671 (334)	12	476 (274)	12
T_{max} (hr)[a]	0.751 (0.500, 2.01)	12	0.750 (0.500, 2.00)	12
λ_z (1/hr)	0.392 (0.128)	12	0.461 (0.204)	9
$t_{1/2}$ (hr)	1.94 (0.611)	12	1.90 (1.17)	9
CL/F (L/hr)	150 (72.4)	12	189 (86.8)	9
V_z/F (L)	436 (357)	12	538 (437)	9

Period 1: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Period 2: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
[a] T_{max} is presented as median (minimum, maximum)

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Gastric pH result difference between Period 1 versus Period 2:

Mean gastric pH results were comparable between both periods in subjects without stratification of H. pylori status with mean pH values of approximately 2.0 (Initial, 3, and 8 minutes Post-IET) and 1.6 at 17 minutes Post-IET.

Gastric pH results in H. pylori positive and negative subjects in Period 1 versus Period 2:

Overall, gastric pH levels in H. pylori positive subjects trended somewhat higher than in H. pylori negative subjects, with initial gastric pH of 1.5 and 1.7 in H. pylori negative subjects in Periods 1 and 2, respectively, compared with 2.5 and 2.3 in H. pylori positive subjects. Gastric pH levels were comparable between both periods in H. pylori negative subjects following Initial, 3, 8, and 17 minutes Post-IET with pH levels that ranged from 1.4 to 1.7 in Period 1 (maximum observed values ranged from 1.8 to 2.6) and 1.5 to 1.8 in Period 2 (maximum observed values ranged from 1.8 to 2.5). Gastric pH results were comparable between both periods in H. pylori positive subjects following Initial, 3, 8, and 17 minutes Post-IET with pH values that ranged from 1.7 to 2.5 (maximum observed values ranged from 2.6 to 4.1) in Period 1 and 1.6 to 2.9 in Period 2 (maximum observed values ranged from 2.0 to 6.1).

SmartPill Mean Gastric Residence Time:

Mean SmartPill gastric residence time was somewhat longer in H. pylori negative subjects (mean values of 1.52 and 1.94 hours in Periods 1 and 2, respectively) than in H. pylori positive subjects (mean values of approximately 1.18 and 0.981 hours in Periods 1 and 2, respectively). Mean SmartPill gastric residence time was comparable between subjects in Periods 1 and 2 with a mean value of approximately 1.5 hours.

Summary of Subject Gastric Parameters (SmartPill Data)

	Acalabrutinib in Period 1				Acalabrutinib in Period 2			
Gastric Parameters	H. Pylori Negative	n	H. Pylori Positive	n	H. Pylori Negative	n	H. Pylori Positive	n
Arithmetic Mean (± SD ; %CV)								
Initial Gastric pH	1.5 (0.46 ; 30)	6	2.5 (0.97 ; 39)	6	1.7 (0.55 ; 33)	6	2.3 (1.1 ; 49)	6
Gastric pH 3 min post-IET	1.7 (0.65 ; 37)	6	2.5 (0.85 ; 33)	6	1.8 (0.44 ; 24)	6	2.9 (2.0 ; 68)	6
Gastric pH 8 min post-IET	1.6 (0.47 ; 29)	6	2.3 (0.63 ; 28)	6	1.8 (0.31 ; 17)	6	2.7 (1.7 ; 62)	6
Gastric pH 17 min post-IET	1.4 (0.30 ; 22)	5	1.7 (0.52 ; 31)	6	1.5 (0.26 ; 17)	6	1.6 (0.48 ; 30)	5
Gastric Residence Time	1.52 (1.41 ; 92.4)	6	1.18 (0.728 ; 61.5)	6	1.94 (0.967 ; 49.8)	6	0.981 (0.972 ; 99.1)	6
Minimum/Maximum								
Initial Gastric pH	0.98/2.1	6	1.6/4.1	6	1.1/2.5	6	0.91/4.4	6
Gastric pH 3 min post-IET	0.96/2.6	6	1.6/3.7	6	1.2/2.5	6	0.76/6.1	6
Gastric pH 8 min post-IET	1.1/2.4	6	1.5/3.3	6	1.4/2.2	6	0.92/5.5	6
Gastric pH 17 min post-IET	1.0/1.8	5	1.1/2.6	6	1.2/1.8	6	0.96/2.0	5
Gastric Residence Time	0.200/3.80	6	0.340/2.50	6	0.960/3.50	6	0.260/2.80	6

Period 1: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Period 2: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule

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The Effect of Gastric pH and Emptying Rate on Acalabrutinib PK Parameters:

No clear relationship was observed between acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and T_{max} parameters versus gastric pH.

No clear relationship was observed between acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} parameters versus SmartPill gastric residence time. An apparent trend was observed that T_{max} values may increase with increasing SmartPill gastric residence time, however, the CI of the regression slope included zero.

Analysis of Covariance (ANCOVA):

The wide 95% CIs indicated a high variability in the AUC and C_{max} PK parameters. The negative slope might indicate a trend in the PK parameters using gastric pH at 8 minutes as a covariate. However, this was not significant since 0 was included in the wide 95% CI.

Covariate Regression Estimates

Covariate	Parameter	Estimate of Slope	Standard Error	95% Confidence Interval for Slope
Gastric pH 8 min post-IET	$AUC_{0\text{-inf}}$	-12.5028	97.6179	-231.07 - 206.06
	$AUC_{0\text{-last}}$	-11.7961	84.9290	-201.03 - 177.44
	C_{max}	-25.8141	70.3332	-182.53 - 130.90

Period 1: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Period 2: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Tmax result is not generated due to too many likelihood evaluations.
Model is using gastric pH at 8 minutes as the covariate.
Sensitivity and exploratory results are not presented as none is significant.

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Evaluation of Inter- and Intra-subject variability in AUC and C_{max}:

For all subjects, the inter-subject CV% values following Periods 1 and 2 were approximately 44% and 32% for AUC and C_{max}, respectively. The intra-subject CV% ranged from approximately 22% to 30% for AUC and was 46% for C_{max}.

The inter-subject CV% in H. pylori negative subjects was approximately 44% for AUC and 33% for C_{max}. The inter-subject CV% results indicated more variability in H. pylori positive subjects (for AUC) compared with that in H. pylori negative subjects with a CV% that ranged from approximately 45% to 51% for AUC and was 32% for C_{max}.

The intra-subject CV% values in H. pylori negative subjects were approximately 20% for AUC and 22% for C_{max}. The intra-subject CV% was higher in H. pylori positive subjects compared with H. pylori negative subjects with a CV% that ranged from approximately 27% to 33% for AUC and was 66% for C_{max}. The variability in H. pylori positive subjects was mainly observed in Period 1 and was due to Subjects [8259] and [7620] who had high C_{max} values (ie, can be considered outliers) compared to other subjects in the same period; however, C_{max} values for these 2 subjects were comparable to those of other subjects in Period 2.

Overall, it appeared that the PK parameters in H. pylori positive subjects were more variable than those observed in H. pylori negative subjects.

Statistical Analysis of Plasma Acalabrutinib Pharmacokinetic Parameters Showing Subject Variance, Residual Variance, Inter- and Intra-subject CV%: Acalabrutinib in Periods 1 and 2

	Acalabrutinib in Period 2 (N=12)		Acalabrutinib in Period 1 (N=12)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	Subject Variance	Residual Variance	Inter-Subject CV%	Intra-Subject CV%
$AUC_{0\text{-last}}$ (ng*hr/mL)	540.9	12	733.8	12	0.1740	0.0664	43.59	26.21
$AUC_{0\text{-inf}}$ (ng*hr/mL)	604.5	9	738.1	12	0.1809	0.0493	44.52	22.47
$AUC_{0\text{-6}}$ (ng*hr/mL)	518.6	12	720.8	12	0.1780	0.0875	44.14	30.24
$AUC_{0\text{-12}}$ (ng*hr/mL)	533.6	12	735.5	12	0.1742	0.0757	43.62	28.05
C_{max} (ng/mL)	408.2	12	601.0	12	0.0962	0.1953	31.77	46.45
T_{max} (hr)	0.77	12	0.81	12	0.0000	0.1596	0.00	41.60

Period 1: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Period 2: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Intra-subject CV% = 100 x sqrt[exp(residual variance)-1]
Inter-subject CV% = 100 x sqrt[exp(between subject variance)-1]

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Statistical Analysis of Plasma Acalabrutinib Pharmacokinetic Parameters Showing Subject Variance, Residual Variance, Inter- and Intra-subject CV%: Acalabrutinib in Periods 1 and 2 - H. Pylori Negative Subjects

	Acalabrutinib in Period 2 (N=6)		Acalabrutinib in Period 1 (N=6)					
Parameter	Geometric LSMs	n	Geometric LSMs	n	Subject Variance	Residual Variance	Inter-Subject CV%	Intra-Subject CV%
$AUC_{0\text{-last}}$ (ng*hr/mL)	548.7	6	624.7	6	0.1717	0.0375	43.27	19.54
$AUC_{0\text{-inf}}$ (ng*hr/mL)	552.6	6	629.2	6	0.1684	0.0371	42.83	19.43
$AUC_{0\text{-6}}$ (ng*hr/mL)	540.9	6	613.4	6	0.1763	0.0405	43.91	20.32
$AUC_{0\text{-12}}$ (ng*hr/mL)	550.5	6	626.6	6	0.1710	0.0378	43.19	19.64
C_{max} (ng/mL)	392.5	6	514.3	6	0.1025	0.0478	32.85	22.12
T_{max} (hr)	0.87	6	0.78	6	0.0000	0.2332	0.00	51.24

Period 1: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Period 2: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Intra-subject CV% = 100 x sqrt[exp(residual variance)-1]
Inter-subject CV% = 100 x sqrt[exp(between subject variance)-1]

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Statistical Analysis of Plasma Acalabrutinib Pharmacokinetic Parameters Showing Subject Variance, Residual Variance, Inter- and Intra-subject CV%: Acalabrutinib in Periods 1 and 2 - H. Pylori Positive Subjects

	Acalabrutinib in Period 2 (N=6)		Acalabrutinib in Period 1 (N=6)					
Parameter	**Geometric LSMs**	**n**	**Geometric LSMs**	**n**	**Subject Variance**	**Residual Variance**	**Inter-Subject CV%**	**Intra-Subject CV%**
$AUC_{0\text{-last}}$ (ng*hr/mL)	533.2	6	862.0	6	0.2166	0.0718	49.18	27.28
$AUC_{0\text{-inf}}$ (ng*hr/mL)	641.6	3	865.9	6	0.1813	0.0850	44.59	29.78
$AUC_{0\text{-6}}$ (ng*hr/mL)	497.2	6	847.0	6	0.2315	0.1023	51.04	32.83
$AUC_{0\text{-12}}$ (ng*hr/mL)	517.2	6	863.3	6	0.2242	0.0848	50.13	29.75
C_{max} (ng/mL)	424.4	6	702.5	6	0.0944	0.3656	31.47	66.44
T_{max} (hr)	0.69	6	0.83	6	0.0575	0.0436	24.33	21.10

Period 1: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Period 2: A single oral dose of 100 mg acalabrutinib and 1 SmartPill capsule
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs derived from the ANOVA.
Intra-subject CV% = 100 x sqrt[exp(residual variance)-1]
Inter-subject CV% = 100 x sqrt[exp(between subject variance)-1]

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Statistical Comparisons of Plasma Acalabrutinib PK Parameters - The Effect of H. pylori Status on Plasma Acalabrutinib PK:

The geometric LSMs for the acalabrutinib PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} were approximately 16%, 30%, and 22% higher in H. pylori positive subjects relative to H. pylori negative subjects. However, in Period 1, two H. pylori positive subjects exhibited $AUC_{0\text{-last}}$ and C_{max} levels that could be considered outliers. Mean plasma acalabrutinib AUC and C_{max} values in H. pylori positive subjects were comparable with those in H. pylori negative subjects in Period 2. Thus the LSMs comparison may be biased by the presence of outliers.

Statistical Analysis of Plasma Acalabrutinib Pharmacokinetic Parameters - the Effect of H. Pylori Status

	H. Pylori Geometric LSM					
Parameter	**Positive**	**n**	**Negative**	**n**	**GMR (%)**	**90% Confidence Interval (p-value)**
$AUC_{0\text{-last}}$ (ng*hr/mL)	677.9	(12)	585.4	(12)	115.80	70.77 - 189.48 (0.6010)
$AUC_{0\text{-inf}}$ (ng*hr/mL)	763.7	(9)	589.7	(12)	129.52	79.77 - 210.31 (0.3563)
C_{max} (ng/mL)	546.0	(12)	449.3	(12)	121.54	75.96 - 194.48 (0.4693)
T_{max} (hr)	0.79	(12)	0.92	(12)	86.07	54.12 - 118.03 (0.4480)

AUC and C_{max} parameters were ln-transformed before analysis. T_{max} was untransformed.
Geometric least-squares means (LSMs) were calculated by exponentiating the LSM from a repeated-measures ANOVA which included fixed effects for period and H. pylori status. Period was considered a repeated variable on the subject.

Parameters were ln-transformed before analysis.
Geometric Mean Ratio (GMR) = 100 x (positive/negative)

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The Effect of Genotype on Plasma Acalabrutinib PK

No clear trend was observed in acalabrutinib $AUC_{0\text{-last}}$ values when classified by GST-M1 (null mutation) and CYP3A5 (6986A>G) or BCRP (421C>A) polymorphisms, although few subjects were represented in some genotypes.

Safety Results: No deaths, serious adverse events (SAEs), or subject discontinuations due to AEs occurred in this study. Overall, a total of 12 TEAEs were experienced by 4 (33%) subjects in this study. All TEAEs were reported by 1 (8%) subject each. Of the 12 events reported overall, 10 AEs were Grade 1 severity and 2 AEs were Grade 2 severity. The principal investigator (PI) considered all AEs to be unrelated to study treatment.

Conclusions:
Overall, gastric pH was consistently low (approximately 2.0) in this study. No clear relationship was observed between acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, C_{max}, and T_{max} parameters versus gastric pH, suggesting acalabrutinib PK exposure is not significantly impacted when gastric pH falls within the generally low range.

No clear relationship was observed between acalabrutinib $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} parameters versus SmartPill gastric residence time.

Mean plasma acalabrutinib AUC and C_{max} values trended higher in H. pylori positive subjects compared with H. pylori negative subjects in Period 1. However, in Period 1, two H. pylori positive subjects exhibited $AUC_{0\text{-last}}$ and C_{max} levels that could be considered outliers. Mean plasma acalabrutinib AUC and C_{max} values in H. pylori positive subjects were comparable with those in H. pylori negative subjects in Period 2.

The inter-subject CV% values (for all subjects without regard to H. pylori status) were approximately 44% and 32% for AUC and C_{max}, respectively. The intra-subject CV% ranged from approximately 22% to 30% for AUC and was 46% for C_{max}.

PK parameters in H. pylori positive subjects were more variable than in H. pylori negative subjects. Inter-subject CV% in H. pylori negative subjects was approximately 44% for AUC and 33% for C_{max}. Inter-subject CV% in H. pylori positive subjects ranged from approximately 45% to 51% for AUC and was 32% for C_{max}. Intra-subject CV% in H. pylori negative subjects was approximately 20% for AUC and 22% for C_{max}. Intra-subject CV% in H. pylori positive subjects ranged from approximately 27% to 33% for AUC and was 66% for C_{max}.

A single oral dose of 100 mg acalabrutinib, coadministered with SmartPill, was safe and generally well tolerated by the healthy subjects in this study.

Date of Report: 13 April 2017