2 SYNOPSIS

Title of Study:	A 2-Part, Phase I, Open-label, Single-dose, Sequential Randomized Crossover Study of New Acalabrutinib Maleate Tablet in Healthy Subjects to Evaluate Relative Bioavailability, Proton Pump Inhibitor (Rabeprazole) Effect, Food Effect and Particle Size Effect	
Study Numbers:	Parexel Study No.: 247685 Sponsor Study No.: D8220C00018 (ACE-HV-115)	
Investigational Medicinal Products:	Part 1: CCI acalabrutinib maleate tablet (Variant 1), oral CCI acalabrutinib capsule, oral CCI rabeprazole tablet, oral Part 2: CCI acalabrutinib maleate tablet (Variant 1), oral CCI acalabrutinib maleate tablet (Variant 2), oral CCI acalabrutinib maleate tablet (Variant 3), oral CCI acalabrutinib solution, oral	
Indication Studied:	B-cell lymphoid cancer	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB PPD Södertälje Sweden	Acerta Pharma BV PPD PPD Oss The Netherlands *Acerta Pharma is a member of the AstraZeneca Group*
Principal Investigator:	PPD	
Study Center:	Parexel Early Phase Clinical Unit - Baltimore	
Publication:	None	
Study Duration:	First subject first visit: 24 Jun 2020	Last subject last visit: 20 Jan 2021

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Study Objectives:

Primary objectives:

Part 1:

- To assess the relative bioavailability of the acalabrutinib maleate tablet compared with acalabrutinib capsules in fasted state

Part 2:

- To assess the impact of drug substance particle size on the bioavailability of acalabrutinib maleate tablets

Secondary objectives:

Part 1:

- To assess the ACP-5862 PK profile of the acalabrutinib maleate tablet compared with acalabrutinib capsule in fasted state
- To evaluate the effects of proton pump inhibitor rabeprazole on acalabrutinib and its metabolite (ACP-5862) PK profiles obtained after dosing the acalabrutinib maleate tablet
- To evaluate the effect of food on acalabrutinib and its metabolite (ACP-5862) PK obtained after dosing the acalabrutinib maleate tablet
- To assess the safety and tolerability of single doses of acalabrutinib maleate tablet in healthy subjects
- To measure pharmacodynamic parameter BTK receptor occupancy for acalabrutinib maleate tablet and acalabrutinib capsule in isolated PBMCs

Part 2:

- To assess the impact of drug substance particle size on the ACP-5862 PK profile of acalabrutinib maleate tablets
- To compare PK of acalabrutinib maleate tablet versus acalabrutinib oral solution in healthy subjects
- To assess the safety and tolerability of single doses of acalabrutinib maleate tablets with various drug substance particle size distribution in healthy subjects
- To assess the safety, tolerability, taste, and smell of single doses of acalabrutinib oral solution in healthy subjects

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Study Design:

This study was a 2-part, open-label, single-center, relative bioavailability, PPI effect, food effect, particle size effect, randomized, crossover study of acalabrutinib maleate tablets in healthy male and female subjects. The study was divided in 2 parts; after review of the safety and PK data from Part 1, the study continued with Part 2.

Part 1

Part 1 of this study was an open-label, 3-treatment-period, 4-treatment, single-center, relative bioavailability, PPI effect, food-effect, randomized crossover study of a new acalabrutinib maleate tablet.

Part 1 comprised of:

- A Screening period of maximum of 28 days;
- Three treatment periods during which subjects were resident from prior to the evening meal the night before dosing with IMP (Day -1) until at least 48 hours after dosing; discharged on the morning of Day 3; and
- A Follow-up Visit within 7 to 10 days

There was a minimum CCI

Each subject received 3 of the following 4 treatments in 3 treatment periods under fasted or fed conditions. Subjects were randomized to receive a treatment sequence of either CCI

- Treatment A: CCI acalabrutinib capsule, CCI
- Treatment B: CCI acalabrutinib maleate tablet (Variant 1), CCI
- Treatment C: CCI acalabrutinib maleate tablet (Variant 1), CCI
- Treatment D: CCI rabeprazole CCI acalabrutinib maleate tablet (Variant 1) and CCI rabeprazole CCI

Part 2:

Part 2 of this study was an open-label, 4-treatment-period, 4-treatment, single-center, relative bioavailability, randomized, crossover study to determine the effect of particle size on the PK of a single dose of acalabrutinib maleate tablet.

Part 2 comprised of:

- A Screening period of maximum 28 days;
- Four treatment periods during which subjects were resident prior to the evening meal the night before dosing with IMP (Day -1) until at least 48 hours after dosing; discharged on the morning of Day 3; and
- A Follow-up Visit within 7 to 10 days.

There was a minimum CCI

Each subject received the following treatments:

- Treatment A: CCI acalabrutinib maleate tablet (Variant 1), CCI
- Treatment B: CCI acalabrutinib maleate tablet (Variant 2), CCI
- Treatment C: CCI acalabrutinib maleate tablet (Variant 3), CCI
- Treatment D: CCI acalabrutinib solution, CCI

Subjects were randomized to either CCI

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Study Subjects:			
Planned for Inclusion:	**Randomized:**	**Completed Study:**	
Part 1: 28 Part 2: 24	Part 1: 30 Part 2: 24	Part 1: 29 Part 2: 22	
Main Inclusion Criteria: For both Parts 1 and 2, the study included healthy male and female subjects aged 18 to 55 (inclusive) years who had a body mass between 18.5 and 30.0 kg/m^2 (inclusive) and weighed at least 50 kg and no more than 100 kg (inclusive).			
Investigational Medicinal Products: Acalabrutinib tablet, capsule, and oral solution and Rabeprazole			
Part 1			

	Test Product (Variant 1)	**Reference Product**	**Interacting Product (Proton Pump Inhibitor, Rabeprazole)**
Supplier:	AstraZeneca	AstraZeneca	Parexel
Formulation:	Acalabrutinib maleate tablet (Variant 1)	Acalabrutinib capsule	Rabeprazole tablet
Strength/concentration:	CCI [redacted]		
Dose:			
Route of administration:	Oral	Oral	Oral
Regimen:	CCI [redacted]		
Special handling requirements:	CCI [redacted] The pharmacy at the site will need to dispense CCI [redacted] for each subject for dosing. AstraZeneca will generate Handling Instructions.	CCI [redacted] The pharmacy at the site will need to dispense CCI [redacted] for each subject for dosing. AstraZeneca will generate Handling Instructions.	Not applicable
Manufacturing Lot Number:	CCI [redacted]		
Expiry Date:	Oct 2020	Jan 2022	31 May 2022

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Part 2

	Variant 1 (Treatment A)	**Variant 2 (Treatment B)**	**Variant 3 (Treatment C)**	**Acalabrutinib Solution (Treatment D)**
Supplier:	AstraZeneca	AstraZeneca	AstraZeneca	Tablet: Acalabrutinib maleate tablet (Variant 1) AstraZeneca Deionized water: Parexel
Formulation:	Acalabrutinib maleate tablet (Variant 1)	Acalabrutinib maleate tablet (Variant 2)	Acalabrutinib maleate tablet (Variant 3)	Acalabrutinib solution prepared extemporaneously
Strength/concentration:	CCI [redacted]			
Dose:				
Route of administration:	Oral	Oral	Oral	Oral
Regimen:	CCI [redacted]			
Special handling requirements:	CCI [redacted] The pharmacy at the site will need to dispense CCI [redacted] for each subject for dosing. AstraZeneca will generate Handling Instructions.			The acalabrutinib solution for the study is prepared extemporaneously from the CCI [redacted] acalabrutinib maleate tablet Variant 1, CCI [redacted] according to the Handling Instructions.
Manufacturing Lot/Batch Number:	CCI [redacted]			
Expiry Date:	Oct 2020 Jul 2021	Oct 2020 Jul 2021	Oct 2020 Jul 2021	Oct 2020 Jul 2021

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Duration of Treatment:

In Part 1, each subject was expected to be involved in the study for approximately 7 to 8 weeks.

In Part 2, each subject was expected to be involved in the study for approximately 6 to 7 weeks.

Treatment Compliance:

Dosing took place at the study center (Parexel Early Phase Clinical Unit – Baltimore). Compliance was assured by direct supervision and witnessing of IMP administration.

Criteria for Evaluation:

Pharmacokinetic Parameters:

Part 1

- Primary PK parameters:
  Acalabrutinib - Cmax, AUClast, AUCinf
- Secondary PK parameters:
  Acalabrutinib – AUC(0-12), tmax, t1/2λz, CL/F, Vz/F
  ACP-5862 - Cmax, AUClast, AUCinf, AUC(0-12), tmax, t1/2λz , ACP-5862 (metabolite) to acalabrutinib (parent) ratio (M:P) for Cmax, and AUCinf

Part 2

- Primary PK parameters:
  Acalabrutinib - Cmax, AUClast, AUCinf
- Secondary PK parameters:
  Acalabrutinib – AUC(0-12), tmax, t1/2λz, CL/F, Vz/F
  ACP-5862 - Cmax, AUClast, AUCinf, AUC(0-12), tmax, t1/2λz, ACP-5862 (metabolite) to acalabrutinib (parent) ratio (M:P) for Cmax, and AUCinf

Pharmacodynamic Parameters:

BTK receptor occupancy for acalabrutinib was evaluated (Part 1 only)

Safety Variables:

Assessment of AEs, laboratory variables (haematology, clinical chemistry, coagulation, and urinalysis),

vital signs (systolic and diastolic BP, pulse, oxygen saturation levels), 12-lead ECGs, physical examination, and body temperature

Other Variables:

Taste and smell (Part 2 only)

Statistical Methods:

Analysis Populations:

- Randomized Set: the randomized set consisted of all subjects randomized into the study.
- Pharmacokinetic Analysis Set: the PK analysis set consisted of all subjects in the safety analysis set who had at least one quantifiable post-dose concentration with no important protocol deviations or AEs considered to have impacted on the analysis of the PK data. Data may have been excluded from the descriptive and inferential statistics for a specific treatment period as a result of the following: Data from subjects who experienced emesis during the course of the study, occurring at or before 2 times the median tmax of the affected treatment group. Data from subjects for whom the pre-dose concentration is > 5% of Cmax for acalabrutinib and ACP-5862 in a specific treatment period. The exclusion of any PK data or time points from the calculation of the PK parameters was documented by the PK Scientist including the reason(s) for exclusion.
- Pharmacodynamic Analysis Set: for Part 1 only, the PD analysis set consisted of all subjects in the safety analysis set who had at least one BTK-RO value post-dose.
- Safety Analysis Set: the safety analysis set for each study part included all subjects who received the dose in Treatment Period 1 and for whom any safety post-dose data were available. Unless otherwise stated the safety analysis set was used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP was also presented using the safety analysis set.
- CCI [redacted]

Presentation and Analysis of Pharmacokinetic Data:

Listings of individual PK blood sample collection times (against derived sampling time deviations), concentrations and parameters were presented for the safety analysis set. Individual PK concentration and parameter data for any subjects not included in the PK analysis set or excluded from the summary tables, figures and/or inferential statistical analyses was included in the listings and flagged with an appropriate footnote. Listings were presented by study Part and Treatment.

Summaries of reportable PK concentrations and parameters, and statistical analyses were presented for the PK analysis set, unless otherwise specified. PK concentrations and parameters for each analyte were summarized separately by study Part and Treatment using appropriate descriptive statistics.

Individual concentrations with collection time deviations of > ±10% from the protocol scheduled time, were used in the PK analysis but were flagged for exclusion from the summary tables and corresponding figures.

The available concentration data and PK parameter data for any subjects excluded from the descriptive and inferential statistics was listed and presented in the individual concentration-time figures.

All figures were based on the PK analysis set, with the exception of individual plots by subject which were based on the safety analysis set.

Data permitting, the following figures were presented as appropriate:

- Gmean [values taken from concentration summary table] plasma concentrations vs scheduled time post-dose presented by analyte on both linear (with ±gSD) and semi-logarithmic (no ±gSD) scales with all treatments overlaid on the same plot.
- Individual subject plasma concentration-time data graphically presented on both linear and semi-logarithmic scales by analyte using actual time post-dose as:
  - By subject with all treatments for the same subject overlaid on the same plot.
  - By treatment combined (spaghetti) individual plots with all subjects overlaid on the same plot for each Treatment.
- Scatter plots of individual and summary PK parameters against Treatment by analyte and by study Part.

Part 1

To assess the relative bioavailability of the acalabrutinib maleate tablet compared with acalabrutinib capsule in fasted state, the primary PK parameters of acalabrutinib and its metabolite, ACP-5862, was compared between

Treatment B (acalabrutinib maleate tablet) versus A (acalabrutinib capsule). The analyses were performed using a linear mixed effects analysis of variance model using the natural logarithm of Cmax, AUCinf and AUClast as the response variables, sequence, period, treatment as fixed effect and subject nested within sequence as random effect. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for Cmax, AUCinf, and AUClast were estimated and presented. Also, ratios of geometric means together with CIs (2 sided 90%) were estimated and presented.

To evaluate the effect of proton pump inhibitor rabeprazole on acalabrutinib and its metabolite (ACP-5862) PK profiles obtained after dosing the acalabrutinib maleate tablet, the primary PK parameters of acalabrutinib and its metabolite, ACP-5862, were compared between Treatment D (acalabrutinib plus rabeprazole) versus B (acalabrutinib maleate tablet), from the same ANOVA model.

To evaluate the effect of food on acalabrutinib and its metabolite (ACP-5862), PK obtained after dosing the acalabrutinib maleate tablet, the primary PK parameters of acalabrutinib and its metabolite, ACP-5862, were compared between Treatment C (fed) versus B (fasted) from the same ANOVA model.

If AUCinf was not determined for all subjects or all treatments, an alternative AUC measure, such as AUC to a fixed time point, may have been used in the evaluation of bioavailability, food effect/drug-drug interaction.

Part 2

To assess the impact of drug substance particle size on the bioavailability of acalabrutinib maleate tablets, the primary PK parameters of acalabrutinib and its metabolite, ACP-5862, were compared between Treatment B (Variant 2 - smaller than target) vs A (Variant 1 - target), C (Variant 3 - larger than target) vs A (Variant 1 - target), and C (Variant 3 - larger than target) vs B (Variant 2 - smaller than target) and the analyses were performed using a linear mixed effects analysis of variance model using the natural logarithm of Cmax, AUCinf and AUClast as the response variables, sequence, period, treatment as fixed effect and subject nested within sequence as random effect. Transformed back from the logarithmic scale, geometric means together with CIs (2-sided 95%) for Cmax, AUCinf, and AUClast were estimated and presented. Also, ratios of geometric means together with CIs (2 sided 90%) were estimated and presented.

To compare PK of acalabrutinib maleate tablet to acalabrutinib oral solution, the primary PK parameters of acalabrutinib and its metabolite, ACP-5862, were compared between treatments D (solution) versus A (Variant 1 - target), from the same ANOVA model.

If AUCinf was not determined for all subjects or all treatments, an alternative AUC measure, such as AUC to a fixed time point, may have been used in the evaluation of bioavailability, drug-drug interaction.

Part 1 and 2

Additionally, the 90% CI for the difference in median tmax were planned to be calculated and presented, using the same comparisons from the ANOVAs.

The median differences and 90% CIs were planned to be tabulated for each comparison and analyte.

Presentation and Analysis of Pharmacodynamic Data:

For Part 1, sample collections for BTK occupancy from the peripheral blood samples were listed for each applicable treatment. The BTK occupancy data is provided in a PD report as an appendix to the CSR and was not generated by Parexel Biostatistics.

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings. Continuous variables were summarized using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment. Categorical variables were summarized in frequency tables (frequency and proportion) by treatment. The analysis of the safety variables was based on the safety analysis set.

Adverse events were summarized by Preferred Term and SOC using MedDRA vocabulary. Listings of SAEs and adverse events that led to withdrawal were made. The number of subjects who had any AE, SAEs, AEs that

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led to withdrawal, and AEs with severe intensity were summarized. Adverse events which occur from time of informed consent before dosing are reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests and ECGs (listings only) were presented. Any new or aggravated clinically relevant abnormal medical physical examination finding compared with the baseline assessment was reported as an AE. Data was summarized for the observed values at each scheduled assessment, together with the corresponding changes from the baseline when baseline is defined. Clinical laboratory data was reported in Système International units in the CSR.

Out-of-range values for safety laboratory were flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (e.g., AZ, program, or laboratory ranges).

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Determination of Sample Size:

A sample size of 24 evaluable healthy subjects was chosen based on the desire to gain adequate information while exposing as few healthy subjects as possible to the study procedures. In Part 1 of the study, 28 heathy subjects (7 per sequence group) were randomized into the study in order to have at least 24 evaluable healthy subjects complete the study (allowing for an approximate 20% dropout rate). In Part 2 of the study, 24 heathy subjects (12 per sequence group) were randomized into the study in order to have at least 20 evaluable healthy subjects complete the study (allowing for an approximate less than 25% dropout rate).

Protocol Deviations:

No important protocol deviations were identified in this study.

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Pharmacokinetic Results:

Part 1

- Mean PK exposures (Cmax and AUCs) of acalabrutinib and metabolite ACP-5862 were similar following oral administration of acalabrutinib maleate tablet (Variant 1) versus acalabrutinib capsule under fasted state; relative bioavailability was approximately 91% and 98% for acalabrutinib Cmax and AUCs, respectively, and was approximately 100% and 103% to 104% for ACP-5862 Cmax and AUCs, respectively.
- Co-administration of PPI (rabeprazole) with acalabrutinib maleate tablet (Variant 1) had no apparent effect on the PK exposures of acalabrutinib and metabolite ACP-5862; Cmax was slightly lower (~24% difference in geometric means) and AUCs were slightly higher (~14 to 17% difference in geometric means) for acalabrutinib. Cmax of ACP-5862 was approximately 30% lower, with comparable AUCs in the presence versus absence of PPI.
- For acalabrutinib maleate tablet (Variant 1), food reduced the Cmax of acalabrutinib and ACP-5862 by approximately 54% and 36%, respectively, and had no effect on AUCs.

Part 2

- Mean PK exposures (Cmax and AUCs) of acalabrutinib and metabolite ACP-5862 were similar following oral administration of acalabrutinib maleate tablet with different particle sizes (Variant 1, 2, and 3); 90% CIs for geometric mean ratios were nearly or well within the 80% to 125% margin.
- Acalabrutinib solution had a higher Cmax and comparable AUCs versus acalabrutinib maleate tablet (Variant 1); relative bioavailability was approximately 122% and 102% for acalabrutinib Cmax and AUCs, respectively, and was approximately 124% and 106% to 107% for ACP-5862 Cmax and AUCs, respectively.

Pharmacodynamic Results:

No differences in BTK receptor occupancy across all treatment groups were observed.

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Safety Results:

Part 1

The CCI acalabrutinib capsule, CCI acalabrutinib maleate tablet, and CCI acalabrutinib maleate tablet CCI rabeprazole were safe and well tolerated in this study.

This conclusion is based on the following results:

- Overall, 9 (30.0%) subjects had at least 1 AE.
- The only AE reported by more than 1 subject in any treatment group was headache (2 [6.7%] subjects).
- Overall, 2 (6.7%) subjects had at least 1 AE considered related to IMP according to Investigator's causality assessment.
- The majority of AEs were mild in intensity and there were no severe AEs.
- There were no fatal events or other SAEs.
- Overall, 5 subjects had elevated ALT values: Of these, 1 subject reported the AE of ALT increased that was mild in intensity and possibly related to IMP as per Investigator's assessment. This subject had also elevated AST values with normal bilirubin and alkaline phosphatase.
- There were 2 AEs leading to treatment discontinuation (moderate rash pruritic and mild ALT increased).
- No clinically relevant findings were observed for laboratory results (other than ALT increase), vital signs, and ECGs and no safety concerns were raised.
- There was no impact on study conduct or safety of subjects due to COVID-19.

Part 2

The Variants 1, 2, and 3 of the CCI acalabrutinib maleate tablet and CCI acalabrutinib solution were safe and well tolerated in this study. With regard to smell and taste, the smell of the acalabrutinib solution tested in this study does not need to be artificially modified to be acceptable to subjects; future formulations to be dosed as oral solution should be taste-masked to improve palatability.

These conclusions are based on the following results:

- Overall, 8 (33.3%) subjects experienced at least 1 AE.
- There were no AEs reported by more than 1 subject in either Treatment.
- Overall, 2 (8.3%) subjects experienced the AE of constipation.
- Overall, 1 (4.2%) subject had 1 AE considered related to IMP according to Investigator's causality assessment.
- All AEs were mild in intensity.
- There were no AEs leading to treatment discontinuation or with outcome of death or SAEs.
- No clinically relevant findings were observed for laboratory results, vital signs, and ECGs and no safety concerns were raised.
- There was no impact on study conduct or safety of subjects due to COVID-19.
- The majority of subjects (20 out of 24 [83.3%]) did not experience a smell to the acalabrutinib solution. The taste scores (intensity scale from 0 [low] to 10 [maximum]) were 5.8 points [bitter] and below 3 points for the other main taste scores (sour, metallic, salty, sweet, hot and spicy).

Discussion and Conclusion:

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Pharmacokinetics

Part 1

- Acalabrutinib maleate tablet (Variant 1) had similar bioavailability as acalabrutinib capsule, based on the comparable exposures of acalabrutinib and ACP-5862 observed following oral administration of acalabrutinib maleate tablet versus acalabrutinib capsule.
- Co-administration of PPI (rabeprazole) with acalabrutinib maleate tablet (Variant 1) had no apparent effect on the PK exposures of acalabrutinib and ACP-5862.
- For acalabrutinib maleate tablet (Variant 1), food reduced the Cmax but had no effect on AUCs of acalabrutinib and ACP-5862.
- Acalabrutinib CCI capsule, acalabrutinib CCI maleate tablet, and acalabrutinib CCI maleate tablet CCI rabeprazole CCI were safe and well tolerated in this study.

Part 2

- Acalabrutinib maleate tablet particle size had no effect on the PK of acalabrutinib and ACP-5862, based on the comparable exposures observed following oral administration of acalabrutinib maleate tablet with different particle sizes (Variant 1, 2, and 3).
- Acalabrutinib oral solution had higher Cmax and comparable AUCs for acalabrutinib and ACP-5862 compared to acalabrutinib maleate tablet (Variant 1).
- Acalabrutinib CCI maleate tablet (Variant 1) acalabrutinib CCI maleate tablet (Variant 2), acalabrutinib CCI maleate tablet (Variant 3), and CCI acalabrutinib solution were safe and well tolerated in this study.
- The smell of the acalabrutinib solution tested in this study does not need to be artificially modified to be acceptable to subjects.

Pharmacodynamics

- No differences in BTK receptor occupancy across all treatment groups were observed.

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Safety

- Overall, no new safety concerns were found with acalabrutinib maleate formulation and the new formulation was tolerated well.
- The smell of the acalabrutinib solution tested in this study does not need to be artificially modified to be acceptable to subjects.

COVID-19 Pandemic

The COVID-19 pandemic was not judged to meaningfully impact the overall quality of the study, including the conduct, data, and interpretation of results.

Version and Date of Report: Final 1.0, dated 31 May 2021

This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.