2 SYNOPSIS

Title of Study:	A Phase I, Open-Label, Randomized, 2-Treatment, 2-Period, Crossover Study in Healthy Subjects to Assess the Bioequivalence of Acalabrutinib Tablet and Acalabrutinib Capsule	
Study Numbers:	Parexel: 252879 Sponsor: D8223C00013	
Investigational Medicinal Products (IMP):	Test Product: Acalabrutinib maleate tablet (AMT), 100 mg Reference Product: Acalabrutinib capsule, 100 mg	
Indication Studied:	B-cell lymphoid cancer	
Development Phase:	Phase I	
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden	Acerta Pharma B.V. PPD The Netherlands *Acerta Pharma B.V. is a member of the AstraZeneca group of companies*
National Coordinating Investigator:	PPD	
Study Center (National Coordinating Investigator):	Parexel Early Phase Clinical Unit – Baltimore, USA	
Publication:	None	
Study Duration:	First subject first visit: 25 Feb 2021	Last subject last visit: 10 May 2021

Study Objective(s):

Primary objective(s):

To demonstrate the bioequivalence of AMT and acalabrutinib capsule, administered in the fasted state.

Secondary objective(s):

- To compare the pharmacokinetic (PK) profile of ACP-5862, the active metabolite of acalabrutinib, following administration of AMT and acalabrutinib capsule.
- To compare the safety and tolerability of single doses of AMT and acalabrutinib capsule.

Exploratory objective(s):

To measure the pharmacodynamics (PD) of acalabrutinib.

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Study Design:

This study was a multicenter, Phase I, open-label, randomized, 2-sequence, 2-treatment, 2-period, crossover, bioequivalence study with single doses of acalabrutinib administered orally in healthy subjects at 3 study centers in the US.

The study was designed to demonstrate the bioequivalence of AMT (Treatment A) compared with the marketed acalabrutinib capsule (Treatment B) in the fasted state.

The study comprised:

- Visit 1: A screening period of up to 28 days before first dosing.
- Visit 2: Two treatment periods:
  - Subjects were admitted to the study center on Day -2 of Treatment Period 1 to confirm eligibility before first dosing. Eligibility criteria were reconfirmed on Day -1 of each treatment period.
  - On Day 1 of Treatment Periods 1 and 2, subjects were administered the assigned treatment (A or B) as randomized, followed by a washout of at least 5 days between Treatment Periods 1 and 2.
  - Subjects were discharged from the study center on the morning of Day 3 of Treatment Period 2 after the scheduled study assessments had been completed.
- Visit 3: A Follow-up Visit/Early Termination Visit was conducted 7 to 10 days after last administration of IMP.

Subjects were randomized to receive either treatment sequence 1 (AB) or treatment sequence 2 (BA).

Study Subjects:

Planned for Inclusion:	**Randomized:**	**Completed Study:**
64 subjects	66 subjects	64 subjects

Main Inclusion Criteria:

Healthy male subjects, and female subjects of non-childbearing potential, 18 to 55 years of age (inclusive), with a body mass index (BMI) between 18.5 to 30 kg/m^2 inclusive and weighed at least 50 kg and no more than 100 kg inclusive at Screening, and who were non-smokers.

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Investigational Medicinal Product(s):

	Test Formulation	**Reference Formulation**
Supplier:	AstraZeneca	
Formulation:	Acalabrutinib maleate tablet (AMT)	Acalabrutinib capsule
Strength/concentration:	100 mg	
Dose:	100 mg CCI [redacted]	100 mg
Route of administration:	Oral	
Regimen:	Single dose	
Availability:	IMP was provided upon regulatory and ethical approval of the study	
Batch/manufacturing Lot Number:	CCI [redacted]	CCI [redacted]
Expiry date:	31 Jul 2021	31 Mar 2022

Duration of Treatment:

It was planned that each subject would be involved in the study for approximately 6 weeks.

Treatment Compliance:

Dosing took place at the study centers. Administration of the IMP was recorded in the database. Compliance was assured by direct supervision and witnessing of IMP administration. After oral administration, a check of the subject's mouth and hands was performed.

Criteria for Evaluation:

Pharmacokinetic Parameters:

- Primary PK parameters:
  Acalabrutinib - AUCinf, AUClast, Cmax.
- Secondary PK parameters:
  Acalabrutinib - tmax, t1/2λz, MRT, λz, CL/F, Vz/F.
  Metabolite ACP-5862 - AUCinf, AUClast, Cmax, tmax, t1/2λz, MRT, λz, M:P[AUC], M:P[Cmax].

Safety Variables:

- Adverse events (AEs)/serious AEs (SAEs).
- Laboratory assessments (hematology, coagulation, clinical chemistry, urinalysis).
- Physical examination.
- Standard 12-lead electrocardiogram (ECG).
- Vital signs (systolic and diastolic blood pressure [BP], pulse, respiratory rate, tympanic temperature).

Exploratory Variables:

- Blood sampling for bruton tyrosine kinase (BTK) receptor occupancy in PBMCs.

Statistical Methods:

Analysis Populations:

- Randomized Set: all subjects randomized into the study.
- Pharmacokinetic Analysis Set: all subjects in the safety analysis set who had at least 1 quantifiable post-dose acalabrutinib concentration with no important protocol deviations or AEs considered to impact the analysis of the PK data.
- Safety Analysis Set: all subjects who received at least 1 dose of IMP in Treatment Period 1 and for whom any post dose safety data were available.

Presentation and Analysis of Pharmacokinetic Data:

Listings of PK blood sample collection times, as well as derived sampling time deviations were provided. For each analyte, plasma concentrations and PK parameters were summarized by treatment. Diagnostic PK parameters were summarized and listed. Tabulations were based on the PK analysis set. Data from subjects excluded from the PK analysis set were included in the data listings, but not in the descriptive statistics or in the inferential statistics.

For each analyte, individual plasma concentration versus actual time were plotted in linear and semi-logarithmic scales with all treatments overlaid on the same plot and separate plots for each subject. Combined individual plasma concentration versus actual times were plotted in linear and semi-logarithmic scales with separate plots for each treatment and analyte. Geometric mean plasma concentration versus nominal sampling time were plotted in linear scale (+/-geometric standard deviation [SD]) and semi-logarithmic scale (no geometric SD presented) with all treatments overlaid on the same figure and separate figures for each analyte. Individual and geometric mean ratios between treatments for primary PK parameters (AUCinf, AUClast, and Cmax) were plotted using scatter plots for each analyte. All plots were based on the PK analysis set, with the exception of individual plots by subject which were based on the safety analysis set.

Bioequivalence was assessed between Treatment A: AMT (test) versus Treatment B: Acalabrutinib capsule (reference) following oral administration under fasted state based on the PK analysis set.

Analyses was performed using a linear mixed effects analysis of variance model using the natural logarithm of Cmax, AUClast, and AUCinf for acalabrutinib as the response variables, with sequence, period, treatment as fixed effects and subject nested within sequence as random effect. A similar analysis was also conducted for metabolite ACP-5862. Transformed back from the logarithmic scale, geometric means together with confidence intervals (CIs) (2-sided 95%) for Cmax, AUClast, and AUCinf were estimated and presented. Also, ratios of geometric means together with CIs (2-sided 90%) were estimated and presented. In addition, the inter- and intra-%CV were estimated and presented for Cmax, AUCinf, and AUClast for acalabrutinib and ACP-5862.

Presentation and Analysis of Safety Data:

All safety data (scheduled and unscheduled) were presented in the data listings and summarized descriptively as applicable. Adverse events were summarized by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) version 24.0. Tabulations and listings of data were presented for vital signs, clinical laboratory tests, and ECGs. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment were reported as an AE. Clinical laboratory data was reported in the units provided by the clinical laboratory, and in Système International units.

Presentation and Analysis of Exploratory Pharmacodynamic Data:

BTK receptor occupancy results were listed and summarized as appropriate, based on the PK analysis set.

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Determination of Sample Size:

Based on a bioequivalence range of 80 to 125% for Cmax and AUCinf for acalabrutinib, a within-subject coefficient of variation (CV) of 29.8% for Cmax and 15.1% for AUCinf (Study ACE-HV-115) and a "test/reference" mean ratio of 0.95, 52 evaluable subjects were needed to achieve a power of 90%. Approximately 64 subjects (~32 per treatment sequence) were to be randomized in order to have at least 52 evaluable subjects (26 per sequence) at the end of Treatment Period 2. Overall, a total of 64 subjects included in the study would provide at least 95% power to conclude bioequivalence with respect to each of Cmax and AUCinf, respectively.

Protocol Deviations:

Six (6) of the subjects reported an important protocol deviations. None of the reported important protocol deviations had an effect on the interpretation of the study results or led to exclusion of any subject from the analysis populations.

Pharmacokinetic Results:

- Bioequivalence was achieved between AMT and acalabrutinib capsule, based on the statistically equivalent PK exposures of acalabrutinib and metabolite ACP-5862 observed following oral administration of AMT versus acalabrutinib capsule.
  - Mean PK exposures (Cmax and AUCs) of acalabrutinib and metabolite ACP-5862 were similar following oral administration of AMT versus acalabrutinib capsule under fasted state; the 90%CIs for GMRs of Cmax and AUCs were well contained within the 80% to 125% bioequivalence margin.
- Between-subject variability (gCV%) in PK exposures was up to approximately 58% and 39% for acalabrutinib Cmax and AUCs, respectively, and up to approximately 45% and 32 % for ACP-5862 Cmax and AUCs, respectively; slightly lower following AMT than acalabrutinib capsule.

Pharmacodynamic Results:

BTK occupancy was observed to be similar (> 95%) between the AMT and acalabrutinib capsule formulations.

Safety Results:

- No AEs with outcome of death, SAEs, or AEs leading to discontinuation of IMP/withdrawal from study were reported during the study.
- Overall, 11 (16.7%) subjects experienced 16 AEs during the treatment periods. All reported AEs were of Grade 1 intensity with the exception of one Grade 2 intensity AE of dizziness following AMT (Treatment A). All AEs resolved by the end of the study. The most frequently reported AE was headache (5 [7.6%] subjects). Five (5) subjects had AEs possibly related to IMP: headaches (4 AEs), diarrhoea, dizziness, and sluggishness (one AE for each PT).
- The incidence of AEs in terms of occurrence and relatedness was higher following Treatment A compared to acalabrutinib capsule (Treatment B), but given the small number of AEs overall this did not raise any concerns for the AMT formulation.
- No clinically relevant trends were observed for laboratory results, vital signs, and ECGs.
- The COVID-19 pandemic did not impact the safety results of this study (no COVID-19 cases reported during the study).

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Discussion and Conclusion:	
Pharmacokinetics and Pharmacodynamics Bioequivalence was achieved between AMT and acalabrutinib capsule, based on the statistically equivalent PK exposures of acalabrutinib and metabolite ACP-5862 following oral administration of AMT and acalabrutinib capsule under fasted state. BTK target occupancy was similar between the AMT and acalabrutinib capsule formulations. **Safety** No safety or tolerability concerns were identified in this study following single doses of AMT and acalabrutinib capsule and the safety profile of the AMT formulation is considered acceptable. **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, dated 18 Aug 2021	
This study was conducted in compliance with International Council for Harmonisation Good Clinical Practice guidelines.	