CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number (SDN)	216387 (SDN 0001)
Link to EDR	\\CDSESUB1\evsprod\NDA216387\0001
Submission Date	October 4, 2021
Submission Type	Standard
Brand Name	CALQUENCE®
Generic Name	Acalabrutinib
Dosage Form and Strengths	Tablet, 100 mg
Route of Administration	Oral
Proposed Indications	• Mantle cell lymphoma (MCL) who have received at least one prior therapy. • Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL).
Applicant	AstraZeneca
OCP Review Team	Catharine Bulik, PharmD; Nan Zheng, PhD (TL)
OCP Final Signatory	Brian Booth, PhD

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1. EXECUTIVE SUMMARY

CALQUENCE® (acalabrutinib) capsules were approved in 2017 for the treatment of adult patients with mantel cell lymphoma (MCL) who have received at least one prior therapy, and in 2019 for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The recommended dose for CALQUENCE® capsules is 100 mg every 12 hours, swallowed whole with water and with or without food. The product label for CALQUENCE® capsule includes the recommendations of avoiding co-administration with proton pump inhibitors and that dosing should be staggered by 2 hours with H2-receptor antagonists and antacids. (b) (4)

AstraZeneca submitted a 505(b)(1) NDA to seek approval for CALQUENCE® as acalabrutinib maleate film-coated tablets for the same adult indications (MCL who have received at least one prior therapy and patients with CLL or SLL) as CALQUENCE® capsules. The Applicant references CALQUENCE® (acalabrutinib) capsules 100 mg (NDA 210259) as the listed drug for this application. CALQUENCE® tablets have the same active moiety, strength, and route of administration as the CALQUENCE® capsules. However, CALQUENCE® tablets contain (b) (4) (known as 'acalabrutinib maleate'), a salt form of acalabrutinib (b) (4). The recommended dose for the CALQUENCE® tablets is 100 mg every 12 hours for adult patients. This new CALQUENCE® dosage form of 100 mg (base equivalent) tablets is set to replace the capsule formulation in the United States.

AstraZeneca conducted two clinical pharmacology studies in healthy subjects: 1) to compare the bioequivalence of the proposed CALQUENCE® 100 mg tablets to CALQUENCE® 100 mg capsules (Study D8220C00013), and 2) to evaluate the effect of proton-pump inhibitors on the relative bioavailability of CALQUENCE® 100 mg tablets and the effect of food on the bioavailability of CALQUENCE® 100 mg tablets (Study D8220C00018).

The key review questions focused on establishment of bioequivalence between the proposed CALQUENCE® 100 mg tablets and CALQUENCE® 100 mg capsules, demonstration of a lack of a food effect on CALQUENCE® tablets, demonstration of a lack of pH effect on the bioavailability of the CALQUENCE® tablets, and the appropriateness of dose recommendations for the CALQUENCE® tablet labeling that is based on the CALQUENCE® capsule labeling for the same adult patient population.

1.1 Recommendations

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends approval of this NDA.

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	Based on the scientific bridge established through a bioequivalence study between CALQUENCE® tablets (test) and CALQUENCE® capsules (listed drug),

	and data from the food-effect study and the clinical drug-drug interaction study with rabeprazole.
General dosing instructions	Oral doses of 100 mg approximately every 12 hours (for adult patients with mantle cell lymphoma who have received at least one prior therapy; for adult patients with chronic lymphocytic leukemia or small lymphocytic leukemia). CALQUENCE® is to be swallowed whole with water and with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	The following dose recommendations for CALQUENCE® tablets are based on the clinical pharmacology studies for the tablet formulation: 1) CALQUENCE® tablets can be administered with or without food. 2) The restrictions related to co-administration with acid reducing agents are not warranted for CALQUENCE® tablets
Bridge between the "to-be-marketed" and listed drug formulations	Bioequivalence between the CALQUENCE® tablet and CALQUENCE® capsules was demonstrated.

1.2 Post-Marketing Requirements and Commitment

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Acalabrutinib is a small-molecule inhibitor of Bruton tyrosine kinase (BTK). The following is a summary of the clinical pharmacokinetics (PK) of acalabrutinib. The following PK parameters for acalabrutinib and its active metabolite, ACP-5862, are from the CALQUENCE® capsule label, and the food effect results and the drug-drug interaction study results for acid reducing agents are based the clinical pharmacology studies on the CALQUENCE® tablets:

Acalabrutinib and ACP-5862 exposures increase proportionally with dose across a dose range of 75 to 250 mg (0.75 to 2.5 times the approved recommended single dosage) in patients with B-cell malignancies.

Absorption: The geometric mean absolute bioavailability of acalabrutinib was 25%. The median (min, max) time to maximal concentrations (T_{max}) of acalabrutinib andACP-5862 occurred at 0.5 hours (0.2, 3.0) and 0.75 (0.5, 4.0) hours, respectively, after oral administration. Acalabrutinib and ACP-5862 are substrates of P-gp in vitro.

Effect of Food: In healthy subjects, co-administration of a single 100 mg dose of acalabrutinib with a high-fat, high-calorie meal (approximately 918 calories, 59 grams carbohydrate, 59 grams fat, and 39 grams protein) did not affect the mean exposure (AUC) as compared to dosing under fasted conditions. The resulting maximal plasma concentration (C_{max}) decreased by 54% and the T_{max} was delayed 1-2 hours.

Distribution: The geometric mean (% CV) steady-state volume of distribution (Vss) of acalabrutinib and ACP-5862 was approximately 101 (52%) L and 67 (32%) L, respectively. Human plasma protein of acalabrutinib and ACP-5862 were 97.5% and 98.6%, respectively. The blood-to-plasma ratios of acalabrutinib and ACP-5862 were 0.8 and 0.7, respectively.

Metabolism: Acalabrutinib is predominantly metabolized by CYP3A enzymes, and to a minor extent, by glutathione conjugation and amide hydrolysis, based on in vitro studies. ACP-5862 was identified as the major active metabolite in plasma with a geometric mean AUC value that was approximately 2- to 3-fold higher than the exposure of acalabrutinib. ACP-5862 is approximately 50% less potent than acalabrutinib with regard to BTK inhibition.

Elimination: The geometric mean (% CV) terminal elimination half-life ($t_{1/2}$) values of acalabrutinib and ACP-5862 were 1.4 (50%) hours and 6.4 (37%) hours, respectively. The geometric mean (%CV) apparent oral clearance (CL/F) values of acalabrutinib and ACP-5862 were 71 (35%) L/hr and 13 (42%) L/hr, respectively.

Excretion: Following administration of a single 100 mg radiolabeled acalabrutinib dose in healthy subjects, 84% of the dose was recovered in the feces (< 2% unchanged) and 12% of the dose was recovered in the urine (< 2% unchanged).

Hepatic Impairment: The AUC of acalabrutinib increased 1.9-fold in subjects with mild hepatic impairment (Child-Pugh class A), 1.5-fold in subjects with moderate hepatic impairment (Child-Pugh class B) and 5.3-fold in subjects with severe hepatic impairment (Child-Pugh class C) compared to subjects with normal liver function. No clinically relevant PK difference in ACP-5862 was observed in subjects with severe hepatic impairment (Child-Pugh Class C) compared to subjects with normal liver function. No clinically relevant PK differences in acalabrutinib and ACP-5862 were observed in patients with mild or moderate hepatic impairment (total bilirubin less and equal to the upper limit of normal [ULN] and AST greater than the ULN, or total bilirubin greater than the ULN and any AST) relative to patients with normal hepatic function (total bilirubin and AST within ULN).

Drug Interaction:

- Co-administration of acalabrutinib with itraconazole (strong CYP3A inhibitor) increased acalabrutinib C_{max} by 3.9-fold and AUC by 5.1-fold in healthy subjects.
- Co-administration of acalabrutinib with erythromycin (moderate CYP3A inhibitor), fluconazole (moderate CYP3A inhibitor), diltiazem (moderate CYP3A inhibitor) is predicted to increase acalabrutinib C_{max} and AUC values by approximately 2- to 3-fold.
- Co-administration of acalabrutinib with rifampin (strong CYP3A inducer) decreased the acalabrutinib Cmax by 68% and AUC by 77% in healthy subjects.
- No clinically significant differences in the pharmacokinetics of acalabrutinib were observed when co-administered with rabeprazole (proton pump inhibitor).
- Acalabrutinib is an inhibitor of CYP3A4/5, CYP2C8 and CYP2C9 *in vitro*. ACP-5862 is an inhibitor of CYP2C8, CYP2C9 and CYP2C19 *in vitro*.
- Acalabrutinib is an inducer of CYP1A2, CYP2B6, and CYP3A4 in vitro. ACP-5862 is an inducer of CYP3A4 *in vitro*.
- Acalabrutinib is an inhibitor of BCRP *in vitro*. ACP-5862 is an inhibitor of MATE1 *in vitro*. Acalabrutinib and ACP-5862 are substrates of P-gp and BCRP.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

For patients with MCL, CLL, or SLL, the recommended dosage of CALQUENCE® tablet is 100 mg taken orally approximately every 12 hours until disease progression or unacceptable toxicity.

CALQUENCE® tablets can be taken with or without food. This recommendation is based on the results of the food effect study with CALQUENCE® tablets, where the AUC of acalabrutinib and ACP-5862 were comparable, while the C_{max} of acalabrutinib and ACP-5862 decreased by 54% and 36%, respectively, in the presence of food. However, based on the review of the original acalabrutinib NDA (NDA 210259), no exposure-response relationships for safety or efficacy were identified with the C_{max} values of acalabrutinib or ACP-5862. As such, the decreases in the C_{max} values of acalabrutinib and ACP-5862 in the presence of food, are not expected to be clinically meaningful.

CALQUENCE® tablets can be taken concomitantly with proton-pump inhibitors (PPI). This recommendation is based on the results of the drug-drug interaction study with CALQUENCE® tablets and rabeprazole, where the AUC values of acalabrutinib, and ACP-5862 were not significantly different, and the C_{max} values of acalabrutinib and ACP-5862 decreased by 24% and 30%, respectively. As stated above, since no exposure-response relationships for safety or efficacy were identified with the C_{max} values of acalabrutinib or ACP-5862, the decreases in the C_{max} values of acalabrutinib and ACP-5862, that occurred after co-administration with rabeprazole, are not expected to be clinically meaningful.

2.2.2 Therapeutic individualization

- Avoid the coadministration of strong CYP3A4 inhibitors. If concomitant use of strong CYP3A4 inhibitors cannot be avoided, interrupt the use of CALQUENCE®. After discontinuation of a strong CYP3A inhibitor for at least 24 hours, resume the previous dosage of CALQUENCE.
- Avoid the concomitant use of moderate CYP3A4 inhibitors. If concomitant use of moderate CYP3A4 inhibitors cannot be avoided, reduce the CALQUENCE® 100 mg every 12 hours dosage to 100 mg once daily.
- Avoid the concomitant use of strong CYP3A inducers. If concomitant use of strong CYP3A4 inducers cannot be avoided, increase the CALQUENCE® dosage to 200 mg approximately every 12 hours.
- Avoid the use of CALQUENCE® in patients with severe hepatic impairment (Child-Pugh class C). No dosage adjustment of CALQUENCE® is recommended in patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment. The safety of CALQUENCE® has not been evaluated in patients with moderate or severe hepatic impairment.

2.3 Outstanding Issues

No outstanding issues.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

CALQUENCE®, as acalabrutinib capsules, was approved in 2017 for the treatment of adult patients with mantel cell lymphoma (MCL) who have received at least one prior therapy. Subsequently in 2019 CALQUENCE®, as acalabrutinib capsules, was approved for the treatment of adult patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). The recommended dose for CALQUENCE® is 100 mg every 12 hours.

In the current NDA, the Applicant is seeking approval for CALQUENCE® (acalabrutinib maleate) oral tablets via the 505(b)(1) approval pathway for the same adult indications as the current CALQUENCE® capsules. The Applicant references CALQUENCE® (acalabrutinib) capsules, 100 mg (NDA 210259) as the listed drug. CALQUENCE® tablets have the same active moiety, strength and route of administration as the CALQUENCE® capsules. However, CALQUENCE® tablets contain (b) (4), a salt form of acalabrutinib. Per the Applicant, the new salt form (b) (4)

The Applicant proposes CALQUENCE® tablet at doses of 100 mg every 12 hours for adult patients diagnosed with MCL who have received at least one prior therapy, and for adult patients diagnosed with CLL or SLL. The recommendations of the same doses for the CALQUENCE® tablets as the CALQUENCE® capsules were based on comparable bioavailability between CALQUENCE® 100 mg capsules and CALQUENCE® 100 mg tablets, as demonstrated in a bioequivalence study in the fasted state, a PPI effect study and a food effect study using CALQUENCE® tablets.

3.2 General Pharmacological and Pharmacokinetic Characteristics

Refer to Section 2.1 for the PK parameters.

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes. The CALQUENCE® tablets dose of 100 mg every 12 hours for adult patients who have been diagnosed with MCL who have received at least one prior therapy, and for adult patients with CLL or SLL, are based on the establishment of a scientific bridge through the demonstration of bioequivalence (refer to Section 3.3.2) between the CALQUENCE® capsules and the tablets.

3.3.2 Has a scientific bridge been established between the currently approved drug product(s) and the proposed drug product(s)?

Yes. A scientific bridge has been established between the CALQUENCE® capsule and the CALQUENCE® tablet to support the labeling recommendations.

Study D8223C00013 demonstrated that the bioavailability of the CALQUENCE® tablet, 100 mg, is comparable to the 100 mg strength of the CALQUENCE® capsule, in that the 90% confidence intervals (CI) of the geometric mean ratio (GMR) for the primary PK parameters C_{max}, AUC_{last},

and $AUC_{0-\infty}$ were within the bioequivalence limits of 80% to 125% (Table 1: Refer to Appendix 4.1 for details).

Table 1: Summary Statistics for the Bioequivalence Evaluation (Study D8223C00013)

Analyte	Parameter (unit)	CALQUENCE®, 100 mg tablet (Test)	CALQUENCE® 100 mg capsule (Reference)	Ratio of Test / Reference	90% Confidence Interval of Ratio
CALQUENCE® Capsules, 100 mg vs. CALQUENCE® tablets, 100 mg					
Acalabrutinib	AUC_{last} (h*ng/mL)	561.9	568.8	0.99	93.61, 104.24
	$AUC_{0-\infty}$ (h*ng/mL)	566.1	574.3	0.99	93.44, 103.96
	C_{max} (ng/mL)	535.4	533.5	1.00	90.78, 110.96
ACP-5862	AUC_{last} (h*ng/mL)	1398	1374	1.02	98.16, 105.48
	$AUC_{0-\infty}$ (h*ng/mL)	1490	1468	1.02	98.23, 104.96
	Cmax (ng/mL)	476.3	459.4	1.04	95.7, 112.32

3.3.3 Are there clinically relevant food-drug interactions and what is the appropriate management strategy?

No. While acalabrutinib and ACP-5862 C_{max} values decreased in the fed state, as observed in the original CALQUENCE® NDA (NDA 210259) a lack of exposure-response relationships for safety or efficacy were observed with $C_{max.}$ As such, the current decreases in the acalabrutinib and ACP-5862 C_{max} values are not expected to be clinically meaningful. Therefore, CALQUENCE® tablets can be administered with or without food.

In Study D8220C00018, the acalabrutinib and ACP-5862 AUC values were comparable while the C_{max} values decreased by 54% and 36%, respectively, when the CALQUENCE® tablet, 100 mg, was co-administered with a standard FDA high fat meal (FDA meal: 800-1000 total calories, with 500-600 calories from fat, ≥ 50% of the meal is fat, with 55-65 g fat; the actual breakfast consisted of 2 eggs fried in butter, 2 slices of bacon, 1 buttered English muffin, 112 g of hash-browned potatoes, and approximately 240 mL of whole milk) compared to the CALQUENCE® tablet, 100 mg, under fasted conditions (Table 2: Refer to Appendix 4.2 for details). Since the previous evaluation of acalabrutinib exposure-response relationships (NDA 210259) did not suggest a significant relationship between Cmax and efficacy endpoints, decreases in the acalabrutinib and ACP-5862 C_{max} values are not expected to be clinically meaningful. Therefore, CALQUENCE® tablets can be administered with or without food.

Table 2: Summary statistics for assessment of food effect (Study D8220C00018)

Analyte	Parameter (unit)	Fed (Test)	Fasted (Reference)	Ratio of Test / Reference	90% Confidence Interval of Ratio
CALQUENCE® tablets, 1 x 100 mg Fed vs. Fasting					
Acalabrutinib	AUC_{last}(h*ng/mL)	525.7	538.2	0.98	87.18, 109.5
	$AUC_{0-\infty}$ (h*ng/mL)	528.7	541.2	0.98	87.19, 109.5

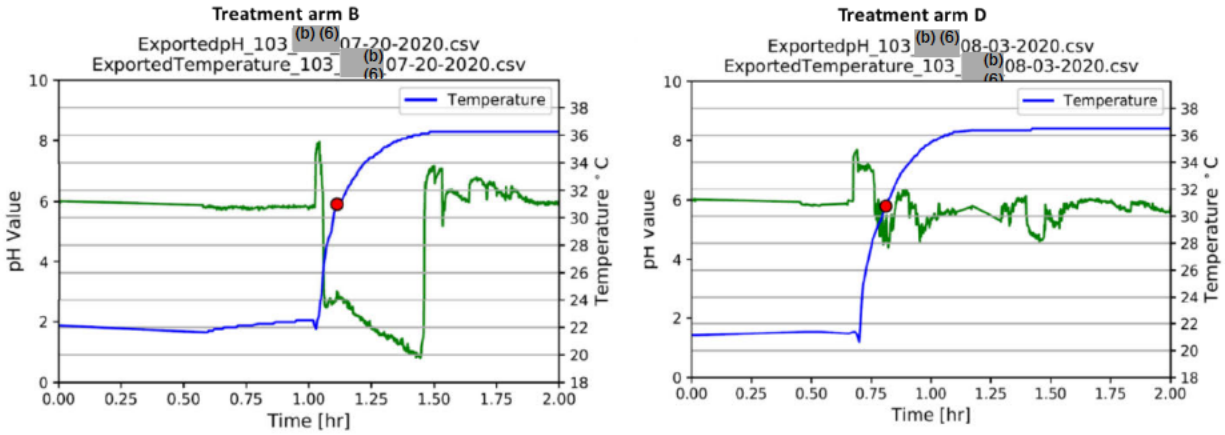
	C_{max} (ng/mL)	255.6	555.4	0.46	35.92, 58.95
ACP-5862	AUC_{last}(h*ng/mL)	1532	1531	1.00	95.47, 104.9
	$AUC_{0-\infty}$ (h*ng/mL)	1644	1617	1.02	96.90, 106.7
	C_{max} (ng/mL)	358.4	560.6	0.64	54.15. 75.49

3.3.4 Are there clinically relevant drug-drug interactions with acid reducing agents and what is the appropriate management strategy?

No. While there were potential study design issues with the clinical drug-drug interaction (DDI) study between the CALQUENCE® tablet and rabeprazole, data from the SmartPill® measurement mitigated these potential design issues. Additionally, while decreases were seen in acalabrutinib and ACP-5862 C_{max} values in the presence of rabeprazole, these changes are not expected to be clinically meaningful since, in the original CALQUENCE® NDA (NDA 210259), there were a lack of significant exposure-response relationships between safety or efficacy and C_{max}. Finally, in the presence of rabeprazole, acalabrutinib AUC_{last} and $AUC_{0-\infty}$ values increased. While the original CALQUENCE® NDA (NDA 210259) details that a positive exposure-safety relationship was established between acalabrutinib AUC_{0-24h} values and the probability to have Grade 2 + neutropenia, the actual percent increase in the AUC values are expected to cause no to minimal increases in the probability to have Grade 2 + neutropenia.

In Study D8220C00018, the clinical DDI study was conducted as follows: Treatment B, administration of a CALQUENCE® tablet, 1x 100 mg (fasted), vs. Treatment D, administration of 20 mg rabeprazole QD (fasted) at 2 hours before administration of a CALQUENCE® tablet, 1 x 100 mg and following prior administration of 20 mg rabeprazole BID (with meals) on Days -3, -2, and -1. In the same study, a SmartPill® was administered followed immediately by a single oral dose of the CALQUENCE® tablet. The design of this clinical DDI study was considered questionable due to the short duration of administration of rabeprazole (3 days) before co-administration with CALQUENCE® tablets. However, upon review of the SmartPill® data from individuals in the study (Figure 1; Refer to Appendix 4.2 for details), administration of rabeprazole resulted in sustained elevated pH values. As detailed in the data from a representative patient in Treatment B of Figure 1 (left panel), the SmartPill® was administered at the approximately 1-hour timepoint and passed into the intestine at the 1.5-hour timepoint as indicated by a drastic increase in pH measurement from between 1 and 2 to approximately 6. In the representative patient in the rabeprazole treatment arm (Treatment D, right panel), the SmartPill® was administered at the approximately 0.75-hour timepoint and the pH measurement was maintained at 5-6 during the passage of the SmartPill® from the stomach into intestine (i.e. within 0.5 hours after SmartPill® administration). The mean (SD) of measured gastric pH values are 2.9 (1.6) and 5.7 (1.2), in Treatment B and Treatment D, respectively. These data provide assurance that the rabeprazole administration increased pH adequately to assess the impact of the coadministration of a PPI on the pharmacokinetics of the CALQUENCE® tablet.

Figure 1. SmartPill® Data in Two Different Study Participants.



Treatment arm B = 100 mg CALQUENCE film-coated tablet, fasted; **Treatment arm D** = 20 mg rabeprazole QD (fasted) at 2 hours before administration of 100 mg CALQUENCE film-coated tablet and following prior administration of 20 mg rabeprazole twice daily (with meals) on Days -3, -2, and -1.

* The average stomach pH 2 minutes after dosing (red dot) was considered to correspond to the stomach pH conditions in which the CALQUENCE® tablets were dissolved.

The results of the clinical DDI study with rabeprazole demonstrated that the acalabrutinib and ACP-5862 C_{max} values decreased by ~24% and 30%, respectively when the CALQUENCE® tablet was co-administered with rabeprazole, compared to the CALQUENCE® tablet under fasted conditions alone (**Table 3**: Refer to **Appendix 4.2** for details).

Acalabrutinib AUC_{last} and $AUC_{0-\infty}$ increased by 14% and 17.4%, respectively when CALQUENCE® tablet was co-administered with rabeprazole compared to CALQUENCE® tablet under fasted conditions alone. (**Table 3**: Refer to **Appendix 4.2** for details).

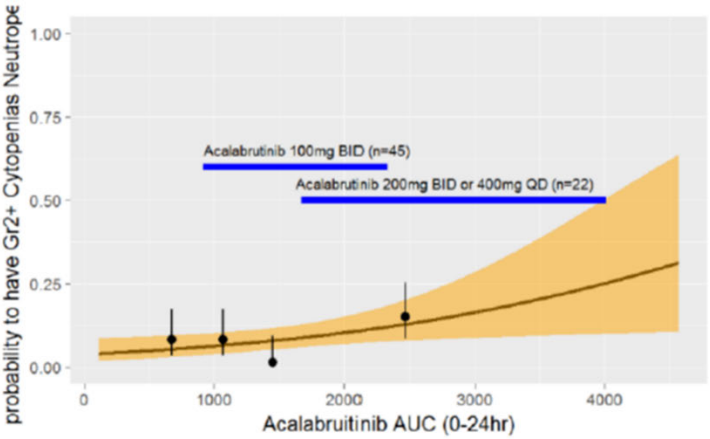
No exposure-response relationships for safety or efficacy were observed for C_{max} in the original CALQUENCE® NDA review, and the increases in C_{max} in the presence of a PPI are not clinically meaningful. However, a positive relationship between AUC_{0-24h} and the probability to have Grade 2+ neutropenia was determined in the original CALQUENCE® NDA review, where increasing the dose from 100 mg BID to 200 mg BID was associated with the probability of increased Grade 2+ neutropenia of 7.5% (95% CI: 4.9%, 11.2%) to 13 % (95% CI: 7.9%, 20.8%). In the current study the actual increases in the AUC values, in the presence of rabeprazole, will not significantly increase the probability to have Grade 2 + neutropenia (**Figure 2**, source: NDA 210259, page 65-66, DARRTs reference ID: 4173186).

Table 3: Summary Statistics for the Assessment of PPI Effect on CALQUENCE® Tablets (Study D8220C00018)

Analyte	Parameter (unit)	With rabeprazole (Test)	Fasted (Reference)	Ratio of Test / Reference	90% Confidence Interval of Ratio
CALQUENCE® tablets, 1 x 100 mg Fasted vs. 20 mg rabeprazole QD (fasted) at 2 hours before administration of CALQUENCE® tablet, 1 x 100 mg and following prior administration of 20 mg rabeprazole BID (with meals) on Days -3, -2, and -1					

Acalabrutinib	AUC_{last}(h*ng/mL)	669.7	587.8	113.9	101.4, 128.0
	$AUC_{0-\infty}$ (h*ng/mL)	694.1	591.1	117.4	105.4, 130.8
	C_{max} (ng/mL)	371.9	486.9	76.4	54.88, 106.3
ACP-5862	AUC_{last}(h*ng/mL)	1656	1666	99.4	90.81, 108.8
	$AUC_{0-\infty}$ (h*ng/mL)	1783	1770	100.7	93.26, 108.8
	C_{max} (ng/mL)	365.3	523.6	70.0	51.31, 94.86

Figure 2. Exposure-Response Relationship for AUC_{0-24h} versus the Incident Rate of Neutropenia by Logistic Regression.



Source: FDA's Analysis. Solid line is the logistic regression of the predicted probability of Grade 2+ Cytopenias Neutropenia. The yellow area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as circle and error bar vs the mean concentration. The blue bar is 5% to 95% quantile of exposure of Acalabrutinib in the pivotal at dosing regimen of 100mg BID (upper) and a subgroup patients in ACE-CL-001 at dosing regimen of 200mg BID or 400mg QD.

3.3.5 What is the appropriate timeframe in which to restart acalabrutinib therapy after the discontinuation of a strong CYP3A4 inhibitor?

The PBPK models evaluated in the NDA 210259 review were applied to simulate acalabrutinib exposures after discontinuation of a 7-day treatment with itraconazole 200 mg twice daily. The original acalabrutinib AUC value after treatment with itraconazole was predicted to be 5-fold of the exposure at the recommended CALQUENCE® dose of 100 mg every 12 hours. After a 24-hour washout period, the acalabrutinib exposure was predicted to decrease to approximately 4-fold of the exposure at the recommended dose level. Following this prediction, a washout period of 3-4 days would result in an acalabrutinib exposure that is less than 2-fold of the exposure at the recommended dose level. Based on an assessment of enzyme turnover rate, the elimination half-life and the recovery half-life of index strong CYP3A4 inhibitors, and assuming a 4x safety margin for short term exposure and 2x safety margin for longer exposure, a minimum washout period of 24 hours is proposed to account for the carryover effect in the enzyme inhibition and to avoid potential toxicity due to high acalabrutinib exposures.

4. APPENDICES

4.1 Bioequivalence Study

The Applicant conducted a Phase 1 open label, randomized, two-treatment, two-period, crossover study to assess the bioequivalence of CALQUENCE® tablets, 100 mg (test) against the approved CALQUENCE® 1 x 100 mg capsule (reference) under fasting conditions (Table 4).

Table 4: Design of Study D8223C00013

Purpose	Bioequivalence of CALQUENCE® tablets, 100 mg (test) against the approved CALQUENCE® capsules, 100 mg (reference)
Study Design	Open-label, randomized, two-treatment, two-sequence, two-period, crossover. Washout period of at least 5 days between period 1 and period 2. Subject fasted overnight for at least 10 hours prior to dosing until 4 hours post dose.
Study Population	Sixty-six (66) subjects were randomized into the study. Sixty-four (64) subjects completed the study.
Proposed Dose	A single oral dose CALQUENCE® 1 x 100 mg tablet or CALQUENCE® Capsules, 1 x 100 mg was administered with 240 mL of non-carbonated water at room temperature.
Instruction for Concomitant Medication (DDI Potential)	Apart from paracetamol/acetaminophen (up to 2 g per day), no concomitant medication or therapy was allowed.
PK Sampling Schedule	Pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0, 24.0, and 48.0 hours post dose (16 samples per treatment period)
ECG Monitoring Schedule	1.0, 6.0, and 24.0 hours post-dose in each treatment period

Subjects (b) (6) and (b) (6) were withdrawn from the study due to lost to follow-up or by subject decision. Data from these subjects were included in the PK analysis dataset, however, some PK parameters (e.g. terminal elimination half-life of the metabolite) cannot be calculated due to incomplete PK profiles and therefore were not included in the summary statistics.

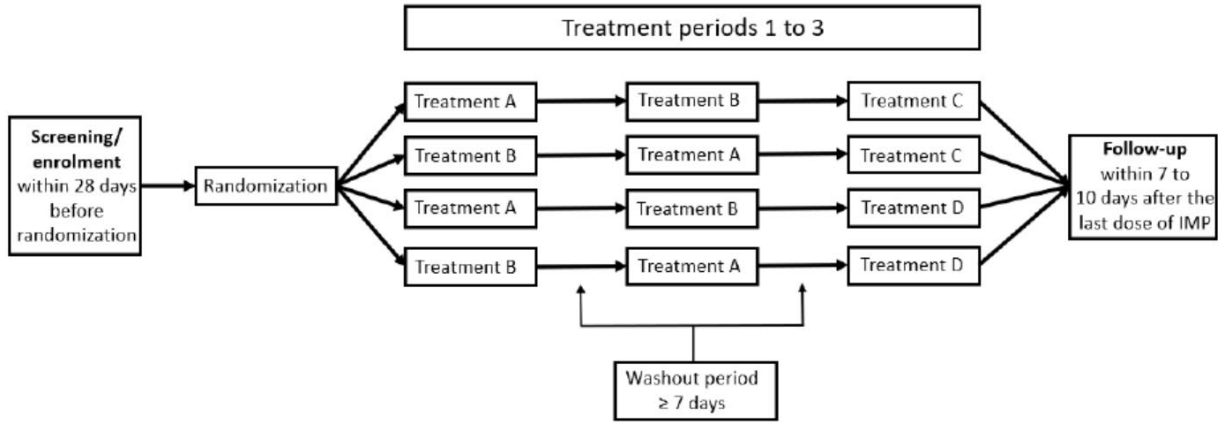
The 90% confidence intervals of the GMR for C_{max}, AUC_{last}, and $AUC_{0\text{-}inf}$ were within the acceptable BE limits of 80% to 125% when comparing the CALQUENCE® 100mg tablets (T) to the approved CALQUENCE® 100 mg capsules (R) under fasting conditions (Table 1). Therefore, the CALQUENCE® 100 mg tablets and the CALQUENCE® 100 mg capsules are bioequivalent.

The reviewers conducted an independent analysis on the submission. The results of the reviewer's analysis are numerically the same as the sponsor's and support the sponsor's conclusions.

4.2 Food Effect Study and Clinical DDI Study

The Applicant conducted 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 (Figure 3, Table 5).

Figure 3: Study D8220C00018 Flow Chart – Part 1.



Subjects were randomized to one of 4 treatment sequences in a 4-sequence, 4-treatment, 3-period crossover: ABC, BAC, ABD, or BAD.
Treatment A = 100 mg acalabrutinib capsule, fasted state;
Treatment B = 100 mg acalabrutinib maleate tablet (Variant 1), fasted state;
Treatment C = 100 mg acalabrutinib maleate tablet (Variant 1), fed state;
Treatment D = 20 mg rabeprazole QD (fasted) at 2 hours before administration of 100 mg acalabrutinib maleate tablet (Variant 1) and following prior administration of 20 mg rabeprazole BID (with meals) on Days -3, -2, and -1.

Table 5: Design of Study D8220C00018 – Food Effect

Purpose	To evaluate the impact of food and impact of proton-pump inhibitors on the exposures of acalabrutinib and ACP-5862
Study Design	Single dose, open-label, 3-treatment-period, 4-treatment, single-center, relative bioavailability, PPI effect, food-effect, randomized crossover study of CALQUENCE® 100 mg capsule (reference) and CALQUENCE® 100 mg tablet (test). Minimum washout period of 7 days between each acalabrutinib administration. 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 ABC, BAC, ABD, or BAD: • Treatment A: 100 mg acalabrutinib capsule, fasted state (> 10 h) • Treatment B: 100 mg acalabrutinib maleate tablet (Variant 1), fasted state (> 10 h) • Treatment C: 100 mg acalabrutinib maleate tablet (Variant 1), fed state • Treatment D: 20 mg rabeprazole × 1 (fasted) at 2 hours before administration of 100 mg acalabrutinib maleate tablet (Variant 1) and following prior administration of 20 mg rabeprazole BID (with meals) on Days -3, -2, and -1
Study Population	Thirty (30) were randomized into the study. Twenty-nine (29) subjects completed the study.
Proposed Dose	Food effect: A single oral dose, CALQUENCE® tablet, 100 mg was administered with 240 mL of water. Treatment B: A single oral dose after an overnight fast of at least 10 hours, and no food 4 hours post-dose. Treatment C: a single oral dose of after an overnight fast of at least 10 hours and 30 minutes after the start of a standardized FDA high-fat high-calorie breakfast (non-vegetarian breakfast, comprising of 800-1000 Kcal). Subject consumed this breakfast within 30 minutes of serving in each period. PPI Effect:

	Treatment B: A single oral dose, CALQUENCE® tablet, 100 mg was administered with 240 mL of water in the fasted state Treatment D: 20 mg rabeprazole QD (fasted) at 2 hours before administration of 100 mg CALQUENCE® tablet and following prior administration of 20 mg rabeprazole BID (with meals) on Days -3, -2, and -1. ALL PATIENTS: SmartPill® administration with 120 mL of still water followed immediately by a single 100 mg oral dose of CALQUENCE® tablet
Instruction for Concomitant Medication (DDI Potential)	Apart from paracetamol/acetaminophen no concomitant medication or therapy will be allowed.
PK Sampling Schedule	Pre-dose and at 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, 12.0, and 24.0 hours post dose
ECG Monitoring Schedule	24 hours pre-dose and 24 hours post-dose in each period

Subject (b) (6) treatment sequence ABC, received all treatments but was lost to follow-up.

Food Effect:

The acalabrutinib and ACP-5862 C_{max} decreased by 54% and 36%, respectively when the CALQUENCE® 100 mg tablet was co-administered with a standard FDA high fat meal, compared to the CALQUENCE® 100 mg Capsule under fasted conditions (Table 2).

Clinical DDI Study – PPI Effect:

The acalabrutinib and ACP-5862 C_{max} values decreased by 24% and 30%, respectively when the CALQUENCE® tablet was co-administered with rabeprazole, compared to the CALQUENCE® tablet under fasted conditions alone (Table 3). In addition, acalabrutinib AUC_{last} and $AUC_{0-\infty}$ values increased by 14% and 17%, respectively, when the CALQUENCE® tablet was co-administered with rabeprazole compared to CALQUENCE® tablet under fasted conditions alone. (Table 3).

The reviewers conducted independent analysis on the submission. The results of the reviewer's analysis are numerically the same as the sponsor's results.

4.3 Bioanalytical Method

Acalabrutinib and ACP-5862 in human plasma were analyzed by protein precipitation and high-performance liquid chromatography tandem mass spectrometry. The assay validation parameters are as indicated in Table 6. The Office of Clinical Pharmacology review team has assessed the adequacy and acceptability of the following bioanalytical methods used in clinical studies.

Table 6: Summary of method performance of the bioanalytical method to measure acalabrutinib and ACP-5862 in human plasma.

Bioanalytical method validation report name, amendments, and hyperlinks	• Validation of a Method for the Determination of Acalabrutinib and ACP-5862 in Human Plasma by HPLC with MS/MS Detection. (b) (4) Study number: 8396-489 • Determination of Acalabrutinib and ACP-5862 in Human Plasma by HPLC with MS/MS Detection for Sponsor Reference Number D8223C00013. (b) (4) study number: 8460545

	• Determination of Acalabrutinib and ACP-5862 in Human Plasma Lithium Heparin by HPLC with MS/MS Detection for Sponsor Reference Number D8220C00018 (ACE-HV-115). (b) (4) study number: 8441039			
Method description	HPLC-MS/MS; ACACHPP			
Materials used for calibration curve & concentration	Acalabrutinib concentrations: 1.00, 2.50, 7.50, 20.0, 100, 500, 900, and 1000 ng/mL ACP-5862 concentrations: 5.00, 12.5, 37.5, 100, 500, 2500, 4500, 5000 ng/mL Lithium heparin plasma - Matrix			
Validated assay range	Acalabrutinib: 1.00 (LLOQ) to 1000 (ULOQ) ng/mL in human plasma ACP-5862: 5.00 (LLOQ) to 5000 (ULOQ) ng/mL in human plasma			
Material used for QCs & concentration	Acalabrutinib concentrations: 1.00 (LLOQ), 3.00 (Low), 50.0 (Mid), 400 (High), 800, and 8000 (ULOQ) ng/mL in human plasma ACP-5862 concentrations: 5.00 (LLOQ), 15.0 (Low), 250 (Mid), 2000 (High), 4000, and 40000 (ULOQ) ng/mL in human plasma			
Source & lot of reagents (LBA)	Acalabrutinib Batch no: AZ13829269-003 (b) (4) material ID: AU-20-FEB-2019-000059 Supplier: AstraZeneca Expiration date: 23Aug2020	ACP-5862 Batch no: AZ14028259-006 Material ID: AU-20-FEB-2019-000024 Supplier: AstraZeneca Expiration date: 11Nov2020	Acalabrutinib-d4 Batch no: $[^2H_4]$AZ13829269-010 Material ID: AU-06-NOV-2018-02555 Supplier: AstraZeneca Expiration Date: 23Aug2020	ACP-5912 Batch no: $[^2H_4]$AZ14028259-005 Material ID: AU-07-NOV-2018-000008 Supplier: AstraZeneca Expiration Date: 23Aug2019
Regression model & weighting	Regressions model: Linear regression Weighting factor: $1/x^2$			

Validation parameters	Method validation summary Report# 8396-489		Source location
Standard calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	8/analyte	Table 7.2, 7.3
	Cumulative accuracy (%bias) from LLOQ to ULOQ Acalabrutinib ACP-5862	 -2.5 to 1.7% -2.6 to 2.8%	Table 7.2, 7.3
	Cumulative precision (%CV) from LLOQ to ULOQ Acalabrutinib ACP-5862	 ≤ 4.1% ≤ 5.4%	Table 7.2, 7.3
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 4 QCs QCs: Acalabrutinib ACP-5862	 0 to 6.0% 0 to 6.2%	 Table 7.10, Table 7.11
	Inter-batch %CV QCs: Acalabrutinib ACP-5862	 ≤ 8.5% ≤ 9.3%	 Table 7.10, Table 7.11
Selectivity & matrix effect	Acalabrutinib: 6 lots of human plasma spiked at the LLOQ. All lots were within 20% accuracy. No interference noted ACP-5862: 6 lots of human plasma tested. All lots within 20% accuracy. No interference noted		Table 7.18-7.21
Interference & specificity	12 lots of blank human plasma were spiked with each analyte (acalabrutinib and ACP-5862) individually at the ULOQ without ISTD. In analytical run 3, Interference >20.0% of the peak area of the mean utilized LLOQ was observed from ACP-5862 to Acalabrutinib. This was retested with VAL-1 and no significant interference was noted between the two analytes.		Table 7.70-7.71
Hemolysis effect	Acalabrutinib: 6 replicates of low QC (3.00 ng/mL) and high QC (800 ng/mL) samples prepared in blank human plasma containing 2% lysed		Table 7.26-7.27

	whole blood. %RSD values ≤15% for both low QC (5.8%) and high QC (1.8%). Mean bias values were within ±15.0% of the nominal concentration for each QC level. ACP-5862: 6 replicates of low QC (15.00 ng/mL) and high QC (4000 ng/mL) samples prepared in blank human plasma containing 2% lysed whole blood. %RSD values ≤15% for both low QC (3.5%) and high QC (1.2%). Mean bias values were within ±15.0% of the nominal concentration for each QC level.	
Lipemic effect	Not applicable	N/A
Dilution linearity	Acalabrutinib: 8000 ng/mL, (20X dilution); %RSD = 2%; the mean bias value was within ±15.0% of the nominal concentration. ACP-5862: 40000 ng/mL, (20X dilution); %RSD = 1.3%; the mean bias value was within ±15.0% of the nominal concentration.	Table 7.16-7.17
Bench-top/process stability	Analysis group 4 (Solution stability – bench-top; acalabrutinib and ACP-5862): Primary Stock solution RT stability: 6 Hours; High Intermediate solution RT stability: 6 Hours; Low Intermediate solution RT stability: 6 Hours Acalabrutinib (analysis group 6): Low QC (3.00 ng/mL) and high QC (800 ng/mL) stored 24 at room temperature. %RSD was 5.5% and 2.5%, respectively. All RE (%) values were within 15% of the low QC and the high QC. Accuracy 99.4% - 101.3% ACP-5862 (analysis group 6): Low QC (15.0 ng/mL) and high QC (4000 ng/mL) stored 24 at room temperature. %RSD was 7.4% and 2.9%, respectively. All RE (%) values were within 15% of the low QC and the high QC. Accuracy 96.7% - 98.0%	Table 7.1, 7.50-7.51
Freeze-Thaw stability	Acalabrutinib: 5 cycles (-10 to -30ºC): 97.9% to 101.0%; 5 cycles (-60 to -80ºC): 105.0% to 109.0% ACP-5862: 5 cycles (-10 to -30ºC): 97.3% to 103.3%; 5 cycles (-60 to -80ºC): 105.3% to 109.0%	Table 7.52 – 7.53
Long-term storage	Matrix LTS stability: 260 days at -10 to -30°C Matrix LTS stability: 228 days at -60 to -80°C	Table 7.1
Carry over	There was no evidence of carryover within the chromatographic regions of the analytes and ISTDs.	Figure 8.8
Validation Parameters	Method performance in study D8223C00013 Bioanalytical Report #8460545	Source location
Assay passing rate	Acalabrutinib: 31 (1.5% of total number of samples analyzed) ACP-5862: 16 (0.8% of total number of samples analyzed)	Table 9.16 – 9.17
Standard curve performance	Acalabrutinib • Cumulative bias range: -1.2 to 1.0% • Cumulative precision: ≤ 6% CV ACP-5862 • Cumulative bias range: -0.8 to 0.4% • Cumulative precision: ≤ 5.1% CV	Table 9.4-9.5
QC performance	Acalabrutinib • Cumulative bias range: -3.3 to -1.2% • Cumulative precision: ≤ 4.1% CV ACP-5862 • Cumulative bias range: -2 to -0.8% • Cumulative precision: ≤ 4.9% CV	Table 9.8-9.9
Method reproducibility	Acalabrutinib: Incurred sample reanalysis was performed in 166 study samples and 95.8 % of samples met the pre-specified criteria	Table 9.18 – 9.19

	ACP-5862: Incurred sample reanalysis was performed in 166 study samples and 98.5 % of samples met the pre-specified criteria	
Study sample analysis/ stability	• The total duration of sample storage was 50 days (from first sample collection on 23 March 2021 to the last sample analyzed on 12 May 2021). • Thus far, stability of human plasma QC samples after storage in a freezer set to maintain -60 to -80°C for 228 days was established and reported in the method validation, (b) (4) Study Number 8396489.	Section 4.4
Effect of rabeprazole	The presence of rabeprazole does not affect the quantification of acalabrutinib or ACP-5862 in human plasma. The blank samples spiked with rabeprazole did not contain any significant peaks at the retention time of acalabrutinib or ACP-5862 or ISTD.	Section 4.8
Validation Parameters	Method performance in study D8223C00018 Bioanalytical Report #8441039	Source location
Assay passing rate	Acalabrutinib: 116 (4.5% of total number of samples analyzed) ACP-5862: 101 (3.9% of total number of samples analyzed)	Table 9.10 – 9.1
Standard curve performance	Acalabrutinib • Cumulative bias range: -0.8 to 1.4% • Cumulative precision: ≤ 6.6% CV ACP-5862 • Cumulative bias range: -1.1 to 1.2% • Cumulative precision: ≤ 7.8% CV	Table 9.4-9.5
QC performance	Acalabrutinib • Cumulative bias range: -1.0 to 3.0% • Cumulative precision: ≤ 12.5% CV ACP-5862 • Cumulative bias range: 0.5 to 2.0% • Cumulative precision: ≤ 5.6% CV	Table 9.8-9.9
Method reproducibility	Acalabrutinib: Incurred sample reanalysis was performed in 196 study samples and 87.8 % of samples met the pre-specified criteria ACP-5862: Incurred sample reanalysis was performed in 196 study samples and 98.5 % of samples met the pre-specified criteria	Table 9.12 – 9.13
Study sample analysis/ stability	• The total duration of sample storage was 186 days (from first sample collection on 20 July 2020 to the last sample analyzed on 22 January 2021). • Thus far, stability of human plasma QC samples after storage in a freezer set to maintain -60 to -80°C for 228 days was established and reported in the method validation, (b) (4) Study Number 8396489.	Section 4.4

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/s/

NAN ZHENG on behalf of CATHARINE C BULIK
07/29/2022 04:15:10 PM

NAN ZHENG
07/29/2022 04:15:39 PM

BRIAN P BOOTH
08/02/2022 08:15:27 AM