CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216387Orig1Orig2s000

CLINICAL REVIEW(S)

NDA Clinical Review – Formulation Change

Application	NDA 216387
Priority or Standard	Standard
Received Date	October 4, 2021
PDUFA Goal Date	August 4, 2021
Division/Office	Division of Hematologic Malignancies II / OOD
Clinical Team	Margret Merino, MD (primary reviewer) Yvette Kasamon, MD (clinical team lead) Nicole Gormley, MD (Division Director, DHM II)
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP
Review Completion Date	July 22, 2022
Established/Proper Name	Acalabrutinib maleate
Trade Name	Calquence
Applicant	AstraZeneca Pharmaceuticals
Dosage Form	Tablets
Applicant Proposed Dosing Regimen	100 mg orally approximately every 12 hours
Applicant Proposed Indication(s)/Population(s)	No new indication or population. Provides new dosage formulation for the indications currently approved for acalabrutinib capsules: For the treatment of adult patients with: • Mantle cell lymphoma (MCL) who have received at least one prior therapy (accelerated approval) • Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL)
Recommendation on Regulatory Action	Accelerated Approval (MCL indication) Regular Approval (CLL or SLL indication)

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1. Executive Summary

The clinical review team recommends approval of Calquence® (acalabrutinib maleate) 100 mg tablets for the same indications that are approved for the acalabrutinib capsule formulation. Labeling for the currently approved acalabrutinib capsules includes a recommendation to avoid co-administration with proton pump inhibitors (PPIs) and to stagger dosing with H2-receptor antagonists and antacids. The new acalabrutinib maleate tablet (AMT) formulation is intended to allow for use regardless of concomitant PPIs, H2-receptor antagonists and antacids.

This application provided CMC, clinical pharmacology and limited clinical data from two healthy volunteer studies evaluating bioequivalence and bioavailability. The recommendation for approval of the new AMT formulation is based primarily on pharmacokinetic and updated CMC data. There were no clinical efficacy or safety data from patients included in this submission. Refer to clinical pharmacology review and the CMC review for details.

1.1. Product Information

Acalabrutinib is a second generation, small-molecule inhibitor of Bruton Tyrosine Kinase (BTK) and is currently approved for the treatment of patients with mantle cell lymphoma (MCL) who have received one prior therapy (accelerated approval), and for patients with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL). Acalabrutinib is currently available as 100 mg capsules. The recommended dosage is 100 mg orally approximately every 12 hours.

The most common (≥ 30%) adverse reactions associated with acalabrutinib are anemia, neutropenia, upper respiratory tract infection, thrombocytopenia, headache, diarrhea, and musculoskeletal pain. The USPI includes warnings and precautions for:

- Serious and opportunistic infections
- Hemorrhage
- Cytopenias
- Second primary malignancies
- Atrial fibrillation and flutter.

The USPI for the current capsule formulation includes instructions to avoid co-administration with proton pump inhibitors (PPIs) and to stagger dosing with H2-receptor antagonists and antacids. Labeling for the new acalabrutinib maleate tablet does not include the recommendation regarding the concomitant use of PPIs, H2-receptor antagonists and antacids. This submission primarily pertains to clinical pharmacology and chemistry, manufacturing, and control (CMC) data.

1.2. Conclusions on Substantial Evidence of Effectiveness

No new clinical efficacy data were submitted with this supplement. The acalabrutinib maleate formulation is relevant to both of the current indications for patients who currently take capsules of acalabrutinib. Refer to complete clinical pharmacology review for analysis of drug-drug interaction data, bioequivalence, and bioavailability data provided with this supplement.

1.3. Benefit-Risk Assessment

Because there were no new clinical efficacy or safety data in patients included in this NDA and no updates to the indication, efficacy, or safety sections in the USPI, there is no new benefit-risk assessment for this application.

1.4. Patient Experience Data

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Regulatory Background

Acalabrutinib was granted orphan drug designation on May 13, 2015 for the treatment of chronic lymphocytic leukemia (CLL) and on September 21, 2015 for the treatment of mantle cell lymphoma (MCL).

Prior regulatory interaction regarding this supplement included:

- Type C CMC meeting on April 17, 2019
- Type C Guidance meeting on January 14, 2021
- Type B Pre-NDA meeting – written responses issued May 26, 2022

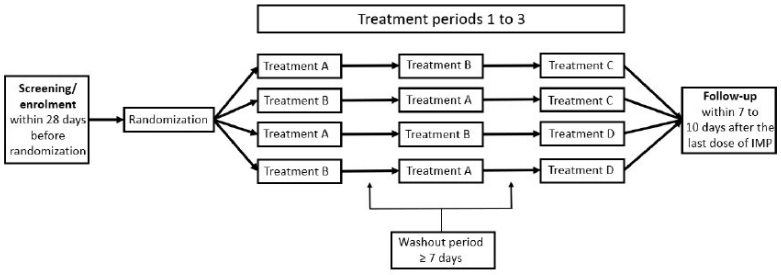
Refer to section 5 for regulatory background on Pediatric Research Equity Act (PREA) required studies.

3. Sources of Clinical Data and Review Strategy

Two healthy volunteer studies were submitted with this application. The clinical study report (CSR) and datasets were included for each study. Refer to the clinical pharmacology review for details regarding the study evaluations and PK results. Clinical review was limited to the safety data included for these studies.

Study D8220C00018 (ACE-HV-115): "A 2-Part, Phase 1, 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" included two parts. The primary objective of Part 1 of study D8220C00018 was to assess the relative bioavailability of the AMT compared with acalabrutinib capsules administered in a fasted state. In Part 1, participants received three single-dose treatments, each followed by a washout period of 7 days. The study schema is displayed in the figure below:

Figure 1: Study D8220c00018 Schema Part 1

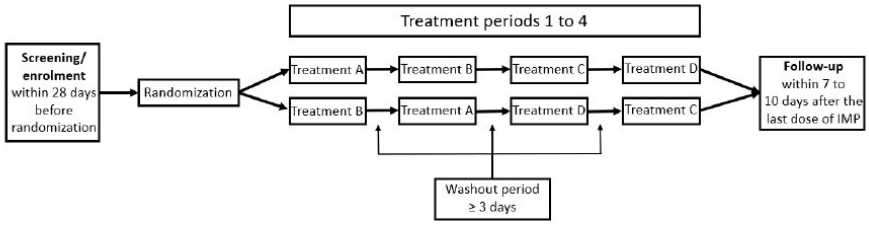


Subjects were randomized to one of 4 treatment sequences in a 4-sequence, 4-treatment, 3-period crossover: ABC, BAC, ABD, or BAD.
Treatment A = 100 mg acalabrutinib capsule, fasted state;
Treatment B = 100 mg acalabrutinib maleate tablet (Variant 1), fasted state;
Treatment C = 100 mg acalabrutinib maleate 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.

Source: Applicant CSR, page 37

The primary objective of Part 2 was to assess the impact of drug substance particle size of bioavailability of acalabrutinib maleate tablets. In Part 2 participants received four single-dose treatments, each followed by a washout period of three days. The study schema for part 2 is displayed in the figure below:

Figure 2: Study D8220c00018 Schema Part 2



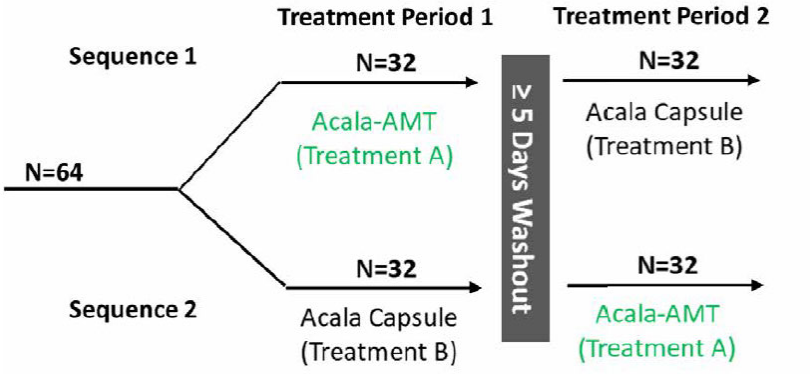
Subjects were randomized to one of 2 treatment sequences in a 2 × 4 crossover: ABCD or BADC.
Treatment A = 100 mg acalabrutinib maleate tablet (Variant 1), fasted state;
Treatment B = 100 mg acalabrutinib maleate tablet (Variant 2), fasted state;
Treatment C = 100 mg acalabrutinib maleate tablet (Variant 3), fasted state;
Treatment D = 100 mg acalabrutinib solution, fasted state.

Source: Applicant CSR, page 37

Study D8223C00013: "A Phase 1, Open-Label, Randomized, 2-Treatment, 2-Period, Crossover Study in Healthy Subjects to Assess the Bioequivalence of Acalabrutinib Tablet and Acalabrutinib Capsule"

The primary objective of study D8223C00013 was to assess the relative bioavailability of the AMT compared with acalabrutinib capsules in a fasted state. Participants received two single-dose treatments, each followed by a 5 day washout period. The study schema is displayed in the figure below:

Figure 3: Study D8223C00013 Schema



Treatment A: Acalabrutinib maleate tablet, 100 mg, fasted state
Treatment B: Acalabrutinib capsule, 100 mg, fasted state

Acala, acalabrutinib; AMT, Acalabrutinib maleate tablet.

Source: Applicant CSR page 27

3.1. Table of Clinical Studies

Table 1: Table of Studies Supporting NDA 216387

Trial Identity/ NCT Number	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration	No. enrolled	Study Population
D8220C00018 ACE-HV-115 NCT04488016	2-part single-center, open label, randomized, crossover study	100 mg acalabrutinib capsule or 100 mg AMT or 100 mg solution orally	PK	Part 1 3 single-dose treatments Part 2 4 single-dose treatments	54	Male and female healthy volunteers
D8223C00013 NCT04768985	Multicenter, open label, randomized, 2-sequence, 2-treatment, 2-period, crossover study	100 mg AMT or 100 mg acalabrutinib capsule orally	PK	2 single-dose treatments	66	Male and female healthy volunteers

4. Safety Review

The safety population include all patients who received at least one dose of acalabrutinib. The total number of patients who received acalabrutinib for both studies was 120. All subjects were healthy volunteers.

In study D8223C00013, AE and SAE review occurred on day 2, 3 after each dose and 10 days after the last dose. Laboratory assessments occurred at screening and on day 1, 2 after each dose and 10 days after the last dose. Vitals and EKG were obtained prior to dosing and at 6 and 24 hours post dose.

In study D8220C00018, participants were in a residential center from the start of dose 1 through 48 hours after the last dose dose. AE and SAE review occurring occurred prior to treatment and on day 2, 3 after each dose and 10 days after the last dose. Laboratory assessments occurred at screening and on day 1, 2 after each dose and 7-10 days after the last dose. Vitals and EKG were obtained prior to dosing and at 6 and 24 hours post dose.

Treatment emergent AEs were reviewed and are summarized for each study separately. Exposure was limited based on the single dose nature of the studies.

A summary of AEs for each study is provided in the tables below.

Table 2: AE Summary for Part 1 of Study ACE-HV-115 /C8220C00018

	Part 1 N = 54				
Study Treatment	A Acalabrutinib 100 mg Capsule Fasted N = 30	B AMT 100 mg Fasted N = 29	C AMT 100 mg Fed N = 14	D Rabeprazole 20 mg QD 2 hours prior to AMT and on days -3, -2, -1 N = 14	Total Patients Randomized * N = 30
Any AE, n (%)	2 (6.7%)	5 (17.2%)	1 (7.1%)	1 (7.1%)	9 (30%)
Moderate AEs, n (%)	1 (3.3%)	2 (6.9%)	0	0	3 (10%)
Severe AEs, n (%)	0	0	0	0	0
SAEs, n (%)	0	0	0	0	0
AEs leading to discontinuation, n (%)	1 (3.3%)	1 (3.4%)	0	0	2 (6.7%)

Source: Sponsor CSR, verified by FDA review of ADAE dataset

*Total = number of patients randomized who received treatments A and B and followed by treatments C or D

Table 3: AE Summary for Part 2 of Study ACE-HV-115 /C8220C00018

	Part 2 N = 24				
Study Treatment 100 mg fasted	A AMT Variant 1 N = 24	B AMT Variant 2 N = 24	C AMT Variant 3 N = 24	D Acalabrutinib solution N = 24	Total Patients Randomized N = 24
Any AE, n (%)	0	4 (17%)	1 (4.2%)	4 (17%)	8 (33%)
Moderate AEs, n(%)	0	0	0	0	0
Severe AEs, n (%)	0	0	0	0	0
SAEs, n(%)	0	0	0	0	0
AEs leading to discontinuation, n(%)	0	0	0	0	0

Source: Sponsor CSR, verified by FDA review of ADAE dataset

In study D8220C00018, intensity of AEs was defined as mild, moderate or severe based on the following criteria specified in the protocol:

Mild: aware of the sign or symptom but easily tolerated
Moderate: discomfort sufficient to cause interference with normal activities
Severe: incapacitating, with inability to perform normal activities

In study D8223C00018, in Part 1, there were two subjects who experienced AEs resulting in discontinuation of study therapy. One subject receiving the acalabrutinib capsule experienced a non-serious pruritic rash 5 days after receiving treatment. Acalabrutinib was discontinued and the rash resolved after 2 days after treatment with hydroxyzine. A second patient receiving AMT variant 1 in treatment period 1 and acalabrutinib capsule in treatment period 2 experienced non-serious ALT increase 2 days after receiving acalabrutinib capsule in treatment period 2 and discontinued study therapy. The ALT elevation had been observed at the study period 2 pre-dose assessment, and resolved on follow-up at 23 days after onset. In Part 2, the only AE preferred term reported in more than one patient was headache, which occurred in 2 (6.7%) of patients.

In study D8223C00018, in Part 2, there were no AEs resulting in discontinuation of study therapy. In Part 2, the only AEs by preferred term reported in more than one patient was constipation, which occurred in 2 (8.3%) of patients.

In both parts of the study, there were no fatal or serious AEs.

Reviewer comment: This study was not designed to evaluate comparative safety between the AMT variants or between AMT and the acalabrutinib capsule. Exposure is limited due to study design which involved single dose administration. The AEs observed were consistent with the known safety profile for acalabrutinib. Overall there were no new signals identified.

Table 4: AE Summary for Study C8223C00013

	Treatment A Acalabrutinib Maleate Tablet N = 65	Treatment B Acalabrutinib Capsule N = 63	Total Patients Randomized N = 66
Any AE, n (%)	10 (15.4%)	3 (4.8%)	11 (16.7%)
AEs leading to discontinuation, n (%)	0	0	0
Grade 2 AE, n (%)	1 (1.5%)	0	1
Grade ≥ 3 AE, n (%)	0	0	0
SAEs, n (%)	0	0	0

Source: Sponsor CSR, verified by FDA review of ADAE dataset

In study D8223C00013, AEs were grade 1 with the exception of one grade 2 event of dizziness following administration of AMT (treatment A).

The most comment AE in treatment A (AMT) by preferred term was headache 5 (8%). Additional AEs (1 patient each) were abdominal pain, TSH increased, bowel movement irregularity, cough, contact dermatitis, diarrhea, dizziness, and flank pain.

In Treatment B (acalabrutinib capsule) the most common AEs by preferred term (1 patient each) were erythema, sluggishness, and toothache.

There were no significant changes in laboratory parameters, vitals signs or EKG findings observed in either healthy volunteer study.

Reviewer comment: This study was not designed to evaluate comparative safety between the acalabrutinib maleate tablet and the acalabrutinib capsule. Exposure is limited due to study design which involved single dose administration. The AEs observed were all grade 1 except for one grade 2 event and were consistent with the known safety profile for acalabrutinib. Overall there were no new signals identified.

5. Pediatrics and Assessment of Effects on Growth

An agreed iPSP was included in the submission which included a plan to request a full waiver for pediatric studies.

In May 2021, in the written response for the pre-NDA meeting, the Agency provided feedback to the Sponsor that since acalabrutinib maleate salt was considered a new active ingredient,

PREA as amended by FDARA applied and that an iPSP should be submitted to address the molecular target (BTK).

An iPSP was submitted 6/30/2021 and an Agreed iPSP was submitted on 9/9/2021. The agreed iPSP incudes a plan to request a full waiver for all pediatric age groups. The justification for the waiver included the rarity of the diseases for the approved adult indications in children and based on the lack of evidence for activity for a same in class agent. The division agrees that a waiver for all pediatric studies is justified based on data supporting that a drug with the same mechanism of action directed at the same molecular target expressed in the same cancer in children have failed to demonstrate evidence of activity.

6. Labeling changes

Labeling changes include the following:

In the Highlights of the USPI, the Initial U.S. Approval date was changed to 2017 rather than (b) (4) because 2017 is the year the active moiety was first approved. Section 2.2 (b) (4) was deleted (b) (4)

In section 2.3 Recommended Dosage for Drug Interactions, table 1 was modified to add a statement about resuming CALQUENCE® when dosing is held due to administration of a moderate CYP3A inhibitor. Text revised to read: "After discontinuation of strong CYP3A inhibitor for at least 24 hours, resume previous dosage of CALQUENCE."

Sections 7 Drug Interactions, and section 12.3 Pharmacokinetics, were updated to align with current labeling practice. See separate clinical pharmacology review for further details.

Section 8.3 Females and Males of Reproductive Potential was updated to align with current labeling practice for PLLR sections, including removing the phrase (b) (4) when describing duration for use of contraception.

Section 8.6 Hepatic Impairment was updated to add information that no dosage adjustment is recommending in patients with mild or moderate hepatic impairment.

In section 11 Description, a salt equivalency statement was added.

Section 12.3 Pharmacokinetics, removed the statement proposed by the Applicant that (b) (4)

Other minor changes were made throughout the label to align with current labeling practice.

7. Recommended Regulatory Action

The clinical review team recommends approval of this new formulation as outlined in this review, based primarily on the clinical pharmacology and CMC assessments.

8. Post Marketing Requirements and Commitments

One post marketing requirement will be included in this approval. This PMR is consistent with the confirmatory trial PMR issued with the 2017 accelerated approval for patients with relapsed or refractory mantle cell lymphoma. Refer to the approval letter for PMR milestones.

Rationale: ACE-LY-004 is a single-arm study of acalabrutinib (Calquence®) monotherapy in patients with relapsed or refractory mantle cell lymphoma, which was the basis for accelerated approval for this indication. The basis of accelerated approval was overall response rate (ORR) supported by duration of response. ORR is an intermediate endpoint that is reasonably likely to predict clinical benefit but is not a direct measure of clinical benefit. This PMR seeks to verify the clinical benefit of acalabrutinib as measured by progression-free survival (PFS) and overall survival (OS) in a randomized controlled clinical trial, in accordance with 21 CFR Subpart H. The same study under PMR 3291-1/NDA 210259 will be sufficient to confirm clinical benefit for this NDA involving the tablet formulation.

PMR:
Complete a randomized, double-blind, placebo-controlled clinical trial of acalabrutinib in combination with standard immunochemotherapy versus immunochemotherapy alone in patients with mantle cell lymphoma to obtain data on clinical efficacy and safety.

9. Appendices

9.1. Financial Disclosure

The Applicant submitted financial disclosure information from investigators and sub-investigators participating in trials D8220C00018 and D223C00013 indicating that none of the investigators reported disclosable financial interests or arrangements during the trials.

Was a list of clinical investigators provided:	Yes X	No ☐
Total number of investigators identified: 23		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐

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/s/

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