CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216387Orig1Orig2s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 216387
Supporting document/s:	1, 3
Applicant's letter date:	10/4/2021
CDER stamp date:	10/4/2021; 11/30/2021
Product:	Calquence (acalabrutinib maleate)
Indication:	Mantle cell lymphoma and chronic lymphocytic leukemia or small lymphocytic lymphoma
Applicant:	AstraZeneca UK Ltd.
Review Division:	Division of Hematology Oncology Toxicology (DHOT) for the Division of Hematologic Malignancies 2 (DHM2)
Reviewer:	Simon Williams, PhD
Supervisor:	Brenda Gehrke, PhD
Division Director:	John Leighton, PhD (DHOT), Nicole Gormley, MD (DHM2)
Project Manager:	Denise Felluca, PharmD, MBA

Disclaimer
Except as specifically identified, all data and information discussed below and necessary for approval of NDA 216387 are owned by AstraZeneca or are data for which AstraZeneca has obtained a written right of reference. Any information or data necessary for approval of NDA 216387 that AstraZeneca does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 216387.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

The Applicant, AstraZeneca UK Ltd, is seeking marketing approval for acalabrutinib maleate 100 mg tablets for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy and chronic lymphocytic leukemia or small lymphocytic lymphoma.

1.2 Brief Discussion of Nonclinical Findings

For the current NDA, the Applicant submitted toxicology studies to support the proposed impurity specifications. Since the proposed specifications for the impurities are above the qualification threshold as per ICH Q3B (R2), toxicology assessments included 2 repeat-dose comparative toxicology studies in rats and 2 bacterial reverse mutation assays. The bacterial reverse mutation assays were negative with and without external metabolic activation systems at up to (b) (4) µg/plate of the impurities tested.
In the 4-week repeat-dose toxicology studies, Wistar rats (n=10/sex) were administered 100 mg/kg of acalabrutinib maleate spiked with (b) (4) % impurities by oral gavage. The observed toxicities were limited, non-adverse, and comparable between the groups. Based on the levels of the impurities in the animal studies, the proposed specification limits are justified from a Pharmacology/Toxicology perspective.

1.3 Recommendations

1.3.1 Approvability

Recommended for approval. There are no Pharmacology/Toxicology concerns with the proposed acalabrutinib maleate drug product.

1.3.2 Additional Non-Clinical Recommendations

None.

1.3.3 Labeling

There are no nonclinical changes to the proposed label.

2.5 Comments on Impurities/Degradants of Concern

The Applicant has proposed and justified the following specification limits for the impurities:

Table 1: Proposed specification limits (excerpted from the Applicant's submission)

	Acceptance criteria
(b) (4)	NMT (b) (4) w/w
	NMT w/w
	NMT w/w
	NMT w/w
Individual unspecified	NMT w/w
Total	NMT w/w

The proposed limits of up to (b) (4) for the individual impurities would result in daily intakes of up to (b) (4), based on an acalabrutinib clinical daily dose of 3.4 mg/kg (200 mg daily dose for a 60 kg patient).

(b) (4)

This impurity was qualified in a repeat-dose rat study where it was (b) (4)% of the 100 mg/kg daily dose (b) (4). This dose resulted in no notable toxicological findings in the rats. The human equivalent dose of (b) (4) mg/kg suggests that the proposed limit is qualified.

(b) (4)

This impurity was qualified in a repeat-dose rat study where it was (b) (4)% of the 100 mg/kg daily dose (b) (4) This dose resulted in no notable toxicological findings in the rats. The human equivalent dose of (b) (4) mg/kg suggests that the proposed limit is qualified.

(b) (4)

This impurity was qualified in a repeat-dose rat study where it was (b) (4)% of the 100 mg/kg daily dose (b) (4). This dose resulted in no notable toxicological findings in the rats. The human equivalent dose of (b) (4) mg/kg suggests that the proposed limit is qualified.

(b) (4)

This impurity was qualified in a repeat-dose rat study where it was (b) (4)% of the 100 mg/kg daily dose (b) (4). This dose resulted in no notable toxicological findings in the rats. The human equivalent dose of (b) (4) mg/kg suggests that the proposed limit is qualified.

6 General Toxicology

6.2.1 Repeat-Dose Toxicity

Study title: Acalabrutinib maleate: One Month Oral (Gavage) Toxicity Study in the Rat for Impurity Qualification

Study no.:	1974-043
Study report location:	4.2.3.7.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	04/30/2020
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Acalabrutinib maleate spiked with impurity (b) (4) Acalabrutinib base, 19600T9004, 99.2%

Key Study Findings

The 100 mg/kg dose was selected for this study because it was determined to be the no observable adverse effect level (NOAEL) for a previous 28-day repeat-dose study. The toxicities related to acalabrutinib base or acalabrutinib maleate with impurities (b) (4) administered to Han Wistar rats were non-adverse and no difference in the toxicity profile was observed between the two groups. The comparability of the acalabrutinib maleate and the acalabrutinib base was established in toxicological study 508985.

Methods

Doses:	100 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	Hydroxypropyl methylcellulose (b) (4) (b) (4) / polysorbate 80 (Tween 80) 0.4/0.2% w/v in water for injection
Species/Strain:	Rat/Wistar
Number/Sex/Group:	13 (10 main study + 3 toxicokinetics)
Age:	12 weeks
Weight:	168 to 351 grams
Satellite groups:	3 animals per group
Unique study design:	All animals received acalabrutinib. This is acceptable for qualification of the impurity.
Deviation from study protocol:	None that impacted the study results.

Observations and Results

Mortality

None.

Clinical Signs

Three acalabrutinib base-dosed animals showed excessive salivation.

Body Weights

Unremarkable.

Feed Consumption

Unremarkable.

Ophthalmoscopy

Unremarkable.

Hematology

Unremarkable.

Clinical Chemistry

Unremarkable.

Urinalysis

Unremarkable.

Gross Pathology

Unremarkable.

Organ Weights

Unremarkable.

Histopathology

Adequate Battery: Yes
Peer Review: Yes
Histological Findings
Microscopic findings for the control and impurity-spiked conditions were limited to the pancreas in males. The number of animals affected and the severity of the findings were higher in control animals.

Table 2: Microscopic findings for acalabrutinib base (control) and acalabrutinib maleate (impurity-spiked) in the pancreas (excerpted from the Applicant's submission)

Dose	100 mg/kg/day acalabrutinib maleate	100 mg/kg/day acalabrutinib base	100 mg/kg/day acalabrutinib maleate	100 mg/kg/day acalabrutinib base
Number of animals	10	10	10	10
Sex	Males		Females	
Pancreas (No. examined)	10	10	10	10
Hemorrhage/pigment/inflammation/fibrosis, islets	1	4	0	0
Minimal	1	0	0	0
Mild	0	2	0	0
Moderate	0	2	0	0

Special Evaluation

None.

Toxicokinetics

The peak serum concentrations (C_{max}) and overall exposure levels (AUC) were generally comparable between the 2 conditions, although the levels in the impurity-spiked groups (acalabrutinib maleate) tended to be lower with less variation.

Table 3: Summary of the toxicokinetic findings (excerpted from the Applicant's submission)

Analyte	Acalabrutinib			
Dose level	100 mg/kg/day acalabrutinib maleate		100 mg/kg/day acalabrutinib base	
Day	1	28	1	28
Males				
T_{max} median (range) (h)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.5)	0.25 (0.25-0.25)
Mean C_{max} (± SD) (ng/mL)	1210 (±376)	2240 (±280)	1580 (±175)	3060 (±976)
Mean $AUC_{(0-24)}$ (± SD) (hr*ng/mL)	2690 (±744)	4300 (±1100)	2790 (±229)	5370 (±1030)
Females				
T_{max} median (range) (h)	0.25 (0.25-0.25)	0.25 (0.25-0.25)	0.25 (0.25-0.5)	0.25 (0.25-0.25)
Mean C_{max} (± SD) (ng/mL)	2100 (±417)	3670 (±490)	3870 (±1370)	6330 (±2480)
Mean $AUC_{(0-24)}$ (± SD) (hr*ng/mL)	5010 (±976)	9460 (±3480)	5390 (±807)	10400 (±7510)

Dosing Solution Analysis

Dosing samples were analyzed by HPLC and were within 15% of the reference standards.

6.2.2 Repeat-Dose Toxicity

Study title: Acalabrutinib: 4 Week Oral Gavage Toxicity Study in the Rat

Study no.:	508985
Study report location:	4.2.3.7.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	04/24/2019
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Acalabrutinib maleate spiked with impurities, (b) (4) Acalabrutinib maleate, C697/2, 98.1%; Acalabrutinib base, C657/3, 98.3%

Key Study Findings

The 100 mg/kg dose was selected for this study because it was determined to be the no observable adverse effect level (NOAEL) for a previous 28-day repeat-dose study. The toxicities related to acalabrutinib base, acalabrutinib maleate, or acalabrutinib maleate with impurities (b) (4) administered to Han Wistar rats were non-adverse and no difference in the toxicity profile was observed between the groups.

Methods

Doses:	100 mg/kg
Frequency of dosing:	Daily
Route of administration:	Oral
Dose volume:	10 mL/kg
Formulation/Vehicle:	Hydroxypropyl methylcellulose (b) (4) (b) (4) / polysorbate 80 (Tween 80) 0.4/0.2% w/v in water for injection
Species/Strain:	Rat/Wistar
Number/Sex/Group:	13 (10 main study + 3 toxicokinetics)
Age:	9 to 10 weeks
Weight:	246 to 319 grams
Satellite groups:	2 animals per group
Unique study design:	All animals received acalabrutinib. This is acceptable for qualification of the impurity.
Deviation from study protocol:	None that impacted the study results.

Observations and Results

Mortality

None.

Clinical Signs

Salivation and ploughing behavior were noted in all groups.

Body Weights

Unremarkable.

Feed Consumption

Unremarkable.

Ophthalmoscopy

Unremarkable.

Hematology

Unremarkable.

Clinical Chemistry

Unremarkable.

Urinalysis

Unremarkable.

Gross Pathology

Discoloration of the thymus was noted in all groups.

Organ Weights

Unremarkable.

Histopathology

Adequate Battery: Yes

Peer Review: Yes

Histological Findings
Hemorrhage in the thymus was noted across all groups.

Toxicokinetics

The peak serum concentrations (C_{max}) and overall exposure levels (AUC) were generally comparable between the conditions.

Table 4: Summary of the toxicokinetic findings (excerpted from the Applicant's submission)

Dose level (mg/kg)	100 mg/kg ACP-196		100 mg/kg ACP-196 Maleate		100 mg/kg ACP-196 maleate with impurities	
Day	1	17	1	17	1	17
Males						
t_{max} (h)	0.5	1	0.5	0.5	0.5	0.5
C_{max} (± SE) (ng/mL)	741 (NA)	945 (245)	804 (NA)	1210 (80.0)	697 (NA)	1310 (94.9)
$AUC_{(0\text{-}24h)}$ (± SE) (h*ng/mL)	6480 (NA)	8510 (1970)	4590 (NA)	6150 (1600)	5070 (NA)	5600 (NA)
Females						
t_{max} (h)	1	0.5	0.5	0.25	0.25	0.25
C_{max} (± SE) (ng/mL)	1370 (NA)	4960 (NA)	1960 (NA)	4320 (755)	2930 (NA)	4430 (1400)
$AUC_{(0\text{-}24h)}$ (± SE) (h*ng/mL)	11200 (NA)	15200 (3190)	8560 (NA)	16700 (1960)	12500 (NA)	17700 (4900)

n is 1 for male and female groups on Day 1 and n is 3 for male and female groups on Day 17 (3 animals per sex per timepoint); one composite TK profile/sex/dose/day.

Dosing Solution Analysis

Dosing samples were analyzed by HPLC and were within 15% of reference standards.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: (b) (4): Genetic Toxicity Evaluation using a Bacterial Reverse Mutation Test with (b) (4): Genetic Toxicity Evaluation using a Bacterial Reverse Mutation Test with Salmonella typhimurium LT2 Strains TA1535, TA1537, TA98 and TA100, and Escherichia coli WP2 Strain uvrA/pKM101

Study no.:	AME01415
Study report location:	4.2.3.7.6
Conducting laboratory and location:	(b) (4)
Date of study initiation:	03/02/2021
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	(b) (4), EB20-229101, 97.9%

Key Study Findings

The [redacted] impurity was negative in the Ames assay at up to [redacted] µg/plate in the presence or absence of external metabolic activation systems.

Methods

Strains:	Salmonella typhimurium LT2 Strains TA1535, TA1537, TA98 and TA100, and Escherichia coli WP2 Strain uvrA/pKM101
Concentrations in definitive study:	[redacted] µg
Basis of concentration selection:	Toxicity to bacterial strains
Negative control:	Dimethyl formamide (DMF)
Positive control:	2-Aminoanthracene, sodium azide, 9-aminoacridine.HCl, 2-nitrofluorene, potassium dichromate
Formulation/Vehicle:	DMF
Incubation & sampling time:	3 days

Study Validity

Valid.

Results

The positive and negative control conditions showed that the test system was working. The [redacted] impurity did not induce the development of revertants under any conditions. The impurity was not mutagenic.

7.2 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: [redacted]: Genetic Toxicity Evaluation using a Bacterial Reverse Mutation Test in Salmonella typhimurium LT2 Strains TA1535, TA1537, TA98 and TA100, and Escherichia coli WP2 uvrA/pKM101

Study no.:	AME01126
Study report location:	4.2.3.7.6
Conducting laboratory and location:	[redacted]
Date of study initiation:	06/11/2020
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Acalabrutinib impurity [redacted], PC04588-17-C200312003-FP-CP, 95.7%

Key Study Findings

The [redacted] impurity was negative in the Ames assay at up to [redacted] µg/plate in the presence or absence of external metabolic activation systems.

Methods

Strains:	Salmonella typhimurium LT2 strains TA1535, TA1537, TA98 and TA100; Escherichia coli WP2 strain uvrA/pKM101
Concentrations in definitive study:	(b) (4) µg
Basis of concentration selection:	Toxicity to bacterial strains
Negative control:	DMF
Positive control:	2-Aminoanthracene, sodium azide, 9-aminoacridine.HCl, 2-nitrofluorene, potassium dichromate
Formulation/Vehicle:	DMF
Incubation & sampling time:	3 days

Study Validity

Valid.

Results

The positive and negative control conditions showed that the test system was working. The (b) (4) impurity did not induce the development of revertants under any conditions. The impurity was not mutagenic.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SIMON WILLIAMS
07/11/2022 10:08:59 PM

BRENDA J GEHRKE
07/11/2022 10:14:49 PM