CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211723Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	New Molecular Entity/ Original New Drug Application
Application Number(s)	NDA 211723
Priority or Standard	Priority
Submit Date(s)	May 23, 2019
Received Date(s)	May 23, 2019
PDUFA Goal Date	January 23, 2020
Division/Office	Office of Oncologic Diseases / Division of Oncology 3
Established/Proper Name	tazemetostat
(Proposed) Trade Name	TAZVERIK
Code Name	EPZ-6438, E7438
Pharmacologic Class	methyltransferase inhibitor
Applicant	Epizyme, Inc.
Doseage form	Tablets, 200mg
Applicant proposed Dosing Regimen	800 mg orally twice daily (BID)
Applicant Proposed Indication(s)/Population(s)	For the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	Epithelioid sarcoma
Recommendation on Regulatory Action	Accelerated approval
Recommended Indication(s)/Population(s)	For the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.
Recommended SNOMED CT Indication Disease Term for each Indication	Epithelioid sarcoma
Recommended Dosing Regimen	800 mg orally twice daily

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AESI	adverse event of special intertest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AR	adverse reaction
AST	aspartate aminotransferase
AT/RT	atypical teratoid rhabdoid tumor
AUC	area under the curve
BIRC	blinded independent review committee
BID	twice daily
BLA	biologics license application
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CNS	central nervous system
CR	complete response
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DCR	disease control rate
DHOT	Division of Hematology Oncology Toxicology
DLT	dose-limiting toxicity
DME	drug metabolizing enzyme
DMC	data monitoring committee
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	epithelial membrane antigen
EOP2	end-of-Phase 2
ES	epithelioid sarcoma
ESRD	end stage renal disease
EZH-2	enhancer of zeste homolog 2
FDA	Food and Drug Administration
FISH	fluorescent in situ hybridization
GCP	good clinical practice
GD	gestation day
GLP	good laboratory practice

GOF	gain of function
H3	histone 3
HMT	histone methyl transferase
HR	hazard ratio
ICH	International Conference on Harmonisation
IND	Investigational New Drug
INI1	integrase interactor 1
IRB	internal review board
ITT	intent to treat
IV	intravenous
MC	methylcellulose
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mo	months
mPFS	median progression-free survival
MPN	myeloproliferative neoplasm
NAI	no action indicated
MRT	malignant rhabdoid tumor
MT	methyltransferase
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSCLC	non-small cell lung cancer
ODAC	Oncologic Drugs Advisory Committee
OPQ	Office of Pharmaceutical Quality
ORR	overall response rate
OS	overall survival
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBMC	peripheral blood mononuclear cells
PD	pharmacodynamics
PFS	progression free survival
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PND	post-natal day
PMR	postmarketing requirement
PPI	proton pump inhibitor
PR	partial response
PRC2	polycomb repressive complex 2
PRO	patient reported outcome
PT	preferred term
PS	performance status

Q3W	every three weeks
REMS	risk evaluation and mitigation strategy
RECIST	Response Evaluation Criteria in Solid Tumors
RO	reverse osmosis
RPLS	reversible posterior leukoencephalopathy
SAE	serious adverse event
SAM	S-adenosyl-L-methionine
SCS	summary of clinical safety
STS	soft tissue sarcoma
SWI/SNF	switch/sucrose non-fermentable
T-ALL	T-cell lymphoblastic leukemia
T-LBL	T-cell lymphoblastic lymphoma
TEAE	treatment emergent adverse event
ULN	upper limit of normal
US	United States
USPI	United States Prescribing Information

1 Executive Summary

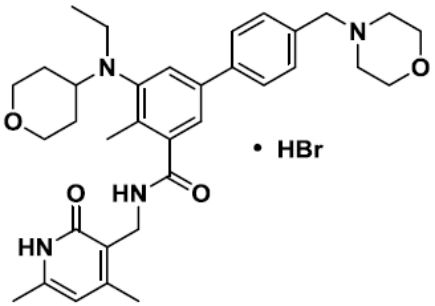
1.1. Product Introduction

On May 23, 2019, Epizyme submitted NDA 211723 under 21 CFR 314.50 and section 505 (b)(1) of the Federal Food, Drug, and Cosmetic Act, seeking accelerated approval of tazemetostat tablets (200 mg) for the following proposed indication:

> *the treatment of patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery.*

The Applicant is requesting accelerated approval under Subpart H.

Tazemetostat, a new molecular entity, is a small molecule inhibitor of the methyltransferase enhancer of zest homolog 2 (EZH2). The chemical name of the hydrobromide salt is [1,1'-Biphenyl]-3-carboxamide, N-[(1,2-dihydro-4,6-dimethyl-2-oxo-3-pyridinyl)methyl]-5-[ethyl(tetrahydro-2H-pyran-4-yl)amino]-4-methyl-4'-(4-morpholinylmethyl)-, hydrobromide (1:1). The molecular formula is $C_{34}H_{44}N_4O_4 \cdot HBr$ (HBr salt). The molecular weight is 653.66 (HBr salt). The molecular structure is:



Tazemetostat tablets (200 mg) are for oral use. Each tablet contains 228 (b) (4) mg of tazemetostat hydrobromide, equivalent to 200 mg tazemetostat free base. The tablet contains the following inactive ingredients in the tablet core: hydroxypropyl cellulose, lactose monohydrate, low-substituted hydroxypropyl cellulose, magnesium stearate and sodium starch glycolate. The tablets are film-coated; the film-coat contains hypromellose, polyethylene glycol, red iron oxide, talc, and titanium dioxide.

The proposed dosing schedule is 800 mg administered orally twice daily (BID) (b) (4) until disease progression or unacceptable toxicity.
On August 12, 2019, during the review of the New Drug Application (NDA), FDA issued a "Proprietary Name Request - Conditionally Acceptable" letter, stating that the Applicant's proposal for the proprietary name, TAZVERIK, was found to be conditionally acceptable.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The following is excerpted from the Office Director (or designated signatory authority) Comments Section of the Review:

> After consideration of the FDA Review documents, selected documents submitted to the NDA, ODAC materials, discussions with the review team, and discussion at the December 18, 2019 ODAC, I conclude that the application for tazemetostat meets the statutory standards for marketing approval under 21 CFR 314, subpart H, with consideration of the principles described in 21 CFR 312, subpart E, for the following indication:
>
> > treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

Please refer to the Division Director (Clinical) Comments and Office Director (or designated signatory authority) Comments in this Review for additional discussion of these conclusions on the substantial evidence of effectiveness as well as benefit-risk considerations.

The remainder of Section 1.2 and Section 1.3 is written by the Clinical Team Leader (and CDTL) of the Application.

The clinical reviewer for this application has concluded that the data submitted by the Applicant does not provide substantial evidence of the effectiveness of tazemetostat for the treatment of metastatic or locally advanced epithelioid sarcoma not eligible for complete resection under 21 CFR 314.5 Subpart H regulations. These regulations require that a product provide "meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy." This conclusion is based on the results of a single, open-label, single-arm cohort (Cohort 5) of a multi-center study (EZH-202) in patients INI1-negative, metastatic, relapsed or refractory epithelioid sarcoma that demonstrated an overall response rate (ORR) of 15% (95% CI: 7, 26). Supportive data from Cohort 6 and pooled efficacy data from Cohort 5 and 6 demonstrated similar results, with ORRs of 11% (95% CI: 4, 25) and 13% (95% CI: 7, 21), respectively. The lower bound of the associated confidence interval implies that the true ORR may be as low as the single digits.

Doxorubicin was approved in 1974 for the first-line treatment of soft tissue sarcoma (STS) based on a response rate of 24% (95% CI: 19, 30). Since its approval, published studies in this patient population have demonstrated response rates ranging from 8% to 19% with limited

data on the duration of response (DOR). Doxorubicin can have significant toxicity including myelosuppression, cardiac toxicity, and the risk of secondary malignancies (USPI doxorubicin). Pazopanib was approved in 2009 for the second-line treatment of patients with STS after chemotherapy. The approval was based on a progression-free survival of (PFS) 4.6 months versus 1.6 months in the placebo arm (HR: 0.35 [95% CI: 0.26, 0.48]). The ORR was 4% (95% CI: 2.3, 7.9) for pazopanib versus 0% for placebo with a median DOR of 9 months (95% CI: 3.9, 9.2). There was no statistically significant difference in overall survival (OS). Pazopanib can cause significant hepatotoxicity, prolonged QT interval, torsades de pointes and cardiac dysfunction (USPI pazopanib).

There is limited data on the effectiveness of approved therapies in the subset of patients with epithelioid sarcoma. Four small, retrospective case studies in patients with advanced epithelioid sarcoma who were administered anthracycline as a single-agent and in combination with ifosfamide, and pazopanib were identified in the literature by the clinical reviewer. Although a direct comparison is difficult due to limited data on the patient populations and eligibility criteria, the response rates reported in these studies are similar to what was previously demonstrated with doxorubicin and pazopanib in patients with STS. The ORR for single-agent anthracycline ranged from 0% to 20%; anthracycline in combination with ifosfamide ranged from 0% to 22%, and for pazopanib the ORR ranged from 0% to 27%. Durability of responses were generally not reported in these studies.

Conclusions regarding ORR
I concur with the clinical reviewer that the Applicant has not presented evidence demonstrating that tazemetostat confers a higher ORR than doxorubicin, which I consider to be an available therapy for patients with epithelioid sarcoma. My rationale for considering doxorubicin to be an available therapy for patients with epithelioid sarcoma is that it is approved for the broader population of patients with STS, and we could not find evidence in the literature or in the Applicant's natural history study to substantiate the claim that patients with ES are less likely to respond to doxorubicin or pazopanib than patients with other forms of sarcoma. Additionally, several of the sarcoma specialists present during the Oncologic Drugs Advisory Committee (ODAC) meeting held to discuss this application agreed that a doxorubicin-based regimen represents the current standard of care for previously untreated advanced or metastatic, unresectable epithelioid sarcoma.

The ORR observed with tazemetostat in patients with epithelioid sarcoma who have received prior therapies is numerically higher than the ORR observed on the pivotal trial that led to the approval of pazopanib in the 2L+ setting, although the confidence intervals overlap due to small patient numbers. An approval of tazemetostat in patients with epitheloid sarcoma who have progressed after at least one prior therapy would thus potentially meet the regulatory requirement for an improvement over available therapies on an intermediate endpoint for the purposes of accelerated approval. However, it is difficult to argue that if tazemetostat is approved, it should only be approved for patients who have received at least one prior therapy as the observed response rate to tazemetostat was similar regardless of number of prior lines

of therapy and there is no biologic rationale to limit the conclusions of efficacy regarding tazemetostat to only a portion of the studied population.

Conclusions regarding DOR
Of the 14 responding patients on Cohorts 5 and 6 of EZH-202, 9 had responses that lasted > 6 months and 4 had responses lasting > 12 months. Median DOR was not estimable and 7 patients had ongoing responses at the time of data cutoff. We were unable to establish the expected duration of response to doxorubicin in patients with epithelioid sarcoma as there is only very limited published data regarding this effect. Sarcoma experts in the ODAC discussion asserted that it is expected to be very short, perhaps a few months, though no objective data was presented to support this assertion. The median DOR of pazopanib was 9 months on the clinical trial that supported its approval, though it should be noted that this was based on responses observed in just 11 patients and thus may not be a stable estimate. The range of DOR observed on the pazopanib trial was 3.9 to 9.2 months.

I concur with the conclusions of the ODAC that the very limited available data concerning durability of response appears to favor tazemetostat over available therapies. However, whether the presented data represent substantial evidence of effectiveness, and are sufficient to *conclude* that tazemetostat provides a durability of response better than available therapy and that this may be reasonably likely to predict clinical benefit of tazemetostat, is a judgement call. With respect to this judgement call, I concur with the clinical reviewer that the Applicant has provided insufficient data in the application to enable the FDA to draw such a conclusion at this time.

Conclusions regarding other endpoints
ORR is an intermediate endpoint and generally not a measure of direct clinical benefit in patients with STS. The Applicant has not provided any data regarding Patient-Reported Outcomes or other quality of life measures that would allow the FDA to conclude that tazemetostat confers direct clinical benefit in excess of its toxicities and thus would be a candidate for regular approval. At the ODAC meeting, the Applicant asserted that the periods of stable disease observed in some non-responding patients should be considered in the evaluation of benefit. The FDA does not consider stable disease to be a reliable endpoint in a single arm trial as it is not possible to assess whether any observed period of stable disease is due to drug effect or represents the natural history of the patient's tumor. Several sarcoma experts who participated in the ODAC meeting asserted that periods of prolonged stable disease are not expected in patients with epithelioid sarcoma treated with current standard of care therapies. While this was heavily discussed by the ODAC and may have contributed to the favorable recommendation, the Applicant did not present any data supporting this conclusion. For example, the Applicant did not collect data regarding the duration of time patients were on therapies prior to tazemetostat without progression, which may have allowed an assessment of DOR in the context of each individual responding patient's prior disease and treatment history. Tazemetostat appears to be less toxic than therapies currently used for epithelioid sarcoma. However, the FDA has not historically accepted an improvement in safety as a regulatory

endpoint to support approval in oncology, particularly in the absence of data confirming that a reduction in toxicity is not associated with a reduction in efficacy/potency.

Summary
Epithelioid sarcoma represents an area of unmet medical need. Approved therapies for this disease are unsatisfactory, with low response rates and serious toxicities. New therapies with a favorable risk:benefit profile are needed. However, it is my conclusion, and that of the clinical reviewer, that the Applicant has presented insufficient evidence of the effectiveness of tazemetostat to meet the regulatory standard for accelerated or regular approval. As the ODAC voted 11-0 in favor of the opposite conclusion, I recognize that the clinical reviewer and I hold a minority view. If, after consideration of this by the Office of Oncologic Diseases, the application receives accelerated approval, we recommend that the Applicant be required to collect ORR and DOR data from additional patients to confirm and further describe the findings of Study EZH-202 in a shorter period of time than the 8-10 years expected for the randomized confirmatory trial to read out. It should be noted that if this application is not approved, the Applicant verbally committed during the ODAC to provide tazemetostat on a compassionate use basis to patients with epithelioid sarcoma who are unable to receive it on a clinical trial.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Epithelioid sarcoma is a rare malignant soft tissue sarcoma that accounts for less than 1% of all soft tissue sarcomas. The NCI estimates that there are approximately 125 new case of epithelioid sarcoma diagnosed in the United States every year. Patients are typically diagnosed between 20 and 40 years of age and there is a 2:1 male preponderance. There is a high propensity for local and regional spread of the disease, and approximately 50% of patients have metastatic disease at the time of diagnosis. Patients with metastatic disease have a reported 5-year survival of 0%. Epithelioid sarcoma is distinguished from other soft tissue sarcomas by characteristic pathology findings and distinct immunohistochemical, or IHC staining. Approximately 90% of cases of epithelioid sarcoma show nuclear loss of INI-1 by IHC.

Wide surgical excision is the mainstay of treatment for localized disease. Neoadjuvant or adjuvant radiation therapy is often administered to reduce local relapse, but systemic chemotherapy is typically reserved for advanced stage disease. Although there are no therapies approved specifically for patients with epithelioid sarcoma, doxorubicin and pazopanib are both approved for the broader population of patients with soft-tissue sarcoma and are administered to patients with epithelioid sarcoma. These therapies confer low response rates and significant toxicity; there is a need for new therapies for this disease with a favorable risk:benefit profile.

Tazemetostat is a first-in-class, orally administered, small molecule inhibitor of the methyltransferase enhancer of zeste homolog-2, otherwise known as EZH-2. The Applicant has postulated that tazemetostat acts by restoring balance to a set of proteins involved in chromatin remodeling and gene expression in tumors that have lost the tumor suppressor gene INI-1. However, the resultant impact on the biology of epithelioid sarcoma is not well understood. The observation that tazemetostat appears to have more robust activity in tumors with gain-of-function EZH2 mutations than it does in tumors with loss of INI-1 may indicate that INI-1 loss is not a reliable predictor of a response to tazemetostat, and that the target of tazemetostat may be less relevant for cancer cell survival in epithelioid sarcoma.

The data submitted by the Applicant to support the safety and efficacy of tazemetostat in patients with epithelioid sarcoma come from Study EZH-202, an ongoing, non-randomized trial of tazemetostat in patients with various tumor types. The Applicant submitted the efficacy and safety results of Cohort 5, which enrolled 62 patients with epithelioid sarcoma as the primary basis on which they are seeking approval of tazemetostat in this indication. Cohort 6 of this study had similar eligibility criteria and enrolled an additional 44 patients with epithelioid sarcoma. FDA considers that Cohort 6 is in some sense a 'repeat experiment' that adds relevant information to the assessment of the efficacy of tazemetostat.

In Cohorts 5 and 6, the overall response rate according to independent review using RECIST v1.1 criteria was similar at 15% (95% CI: 7, 26) and

11% (95% CI: 4, 25), respectively. Pooled analysis demonstrated an ORR of 13% (95% CI: 7, 21). The pooled duration of response ranged from 3.5 months to more than 24 months, also similar across cohorts.

The most common adverse events experienced by patients enrolled in Cohort 5 were pain, fatigue, and GI symptoms. 48% of patients experienced a Grade 3 or 4 adverse event, and 37% of patients had a serious adverse event. It is important to note that these adverse events are not all necessarily attributed to tazemetostat. One of the limitations of a single arm trial is that it is not possible to determine whether individual adverse events are present at a higher frequency in patients who receive tazemetostat than those who do not and thus establish a causal relationship. Although 34% of patients required a dose interruption for toxicity, dose reductions and discontinuations of tazemetostat for toxicity were uncommon.

An important risk of tazemetostat is the risk of secondary malignancies associated with its use. In the pooled safety population of 822 adults and pediatric patients with solid tumors or hematologic malignancies, 6 (0.7%) developed secondary myelodysplastic syndrome, acute myeloid leukemia, or T-cell lymphoblastic lymphoma. As T-cell lymphoblastic lymphoma occurred in juvenile and adult rats during 13-week toxicity studies and EZH2 loss-of-function mutations have been identified in patients with spontaneous hematologic malignancies, the development of secondary malignancies may be an on-target effect of tazemetostat.

Given the limited clinical experience with tazemetostat and lack of comparative data, FDA brought this application to the Oncologic Drugs Advisory Committee (ODAC) to enable public discussion of the results of EZH-202 and whether the evidence is sufficient to demonstrate the benefit of tazemetostat in patients with epithelioid sarcoma. A key uncertainty regarding the application is whether the low response rate observed on EZH-202 will translate into a positive impact on survival or other clinical benefit. Epizyme is planning a randomized confirmatory trial of tazemetostat with doxorubicin compared to doxorubicin alone in patients with epithelioid sarcoma which may address this uncertainty; however, enrollment into this trial has not yet begun. The ODAC voted 11-0 that the benefits of tazemetostat outweighed the risks in the proposed indication. Although the committee acknowledged the low response rate, the stated reasons for their favorable vote included the occurrence of prolonged responses to tazemetostat in a few patients, the number of patients who experienced some period of stable disease on tazemetostat, and the rarity of the disease and lack of satisfactory therapies. The committee members asserted that the drug appeared well-tolerated and that the risk of secondary malignancies was not a concern in this patient population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Epithelioid sarcoma is a rare subtype of STS comprising only 1% of all STS • Approximately 125 cases of epithelioid sarcoma are diagnosed in the US annually; over half are metastatic at diagnosis. • Approximately 90% of patients with epithelioid sarcoma have loss of INI1 by immunohistochemistry. • The 5-year survival of patients with metastatic disease is 0%.	Advanced or metastatic, unresectable epithelioid sarcoma is rare, incurable and represents a population with a high unmet medical need. At times in its natural history, epithelioid sarcoma can have periods of slow growth.
Current Treatment Options	• There are no therapies specifically approved for epithelioid sarcoma. • Doxorubicin was approved in 1974 for patients with STS (including epithelioid sarcoma) based on a response rate of 24% and is the accepted standard of care for advanced or metastatic unresectable epithelioid sarcoma, with or without other chemotherapeutic agents. The response rate of doxorubicin in patients with epithelioid sarcoma using modern response criteria is not known with certainty. • Pazopanib was approved in 2012 in patients with STS (including epithelioid sarcoma) after chemotherapy based on a PFS of 4.6 months versus 1.6 months for placebo. The ORR on the pazopanib arm was 4% (95% CI: 2, 8) with a mDOR of 9 months; there were no responses on the placebo arm. • The median duration of response for doxorubicin and pazopanib in patients with epithelioid sarcoma is unknown.	On the basis of very limited data, doxorubicin and pazopanib appear to have similar response rates in patients with epithelioid sarcoma as they do patients with other forms of STS. Doxorubicin and pazopanib are unsatisfactory therapies with marginal efficacy and significant toxicity. Therapies with improvement in risk:benefit profile are needed.
Benefit	• The ORR in patients with epithelioid sarcoma enrolled on Study EZH-202 Cohort 5 was 15% (95% CI: 7, 26). The ORR in a similar patient population enrolled in Cohort 6 was 11% (95% CI: 4, 25). • Median duration of response is not estimable due to the small number of responding patients. Nine of the 14 responders on	The response rate of tazemetostat does not appear better than that of doxorubicin. Durability of response to tazemetostat is insufficiently characterized to determine whether

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the study had responses that lasted > 6 months and 4 had responses lasting > 12 months; 7 patients had ongoing responses at the time of data cutoff. • The relevance of INI1 loss characteristic of epithelioid sarcoma to the mechanism of action of tazemetostat is uncertain. • A randomized study of tazemetostat in combination with doxorubicin versus doxorubicin alone in patients with epithelioid sarcoma is planned, with a primary endpoint of PFS. The study is projected to complete in approximately 8-10 years.	it is better than that of available therapies. There is insufficient evidence to conclude that an ORR of 11-15% (lower bound of the 95% CI in the single digits) is likely to predict clinical benefit in patients with epithelioid sarcoma. The planned confirmatory study assumes that tazemetostat will confer a 7-month improvement in PFS which may be unrealistic. Additionally, the study may be difficult to enroll once tazemetostat is commercially available. If this drug is approved, while the Applicant should make every effort to conduct this trial with due diligence, [redacted] (b) (4)
Risk and Risk Management	• Toxicity profile includes pain, fatigue, and gastrointestinal toxicities. Toxicities were generally manageable with dose interruption; dose modifications and discontinuations due to toxicity were rare. • Treatment with tazemetostat appears to confer a risk of secondary hematologic malignancies.	The overall safety profile of tazemetostat is acceptable for treatment of a serious and life-threatening condition. If this drug is approved, the risk of secondary malignancies should be fully characterized in long-term follow-up. The safe use of tazemetostat can be managed through the product labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable [e.g., Section 6.1 Study endpoints]
	☐	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):		
X	**Patient experience data was not submitted as part of this application.**			

X

Cross Discipline Team Leader (Ashley Ward, M.D., this section was finalized Dec 22, 2019)

2 Therapeutic Context

2.1. Analysis of Condition

Epithelioid sarcoma is a rare, slow-growing, malignant soft tissue sarcoma (STS) that accounts for less than 1% of all STS (Asano 2015). The SEER database estimates that there are 12,000 new cases of STS diagnosed annually in the US, or approximately 125 epithelioid sarcoma cases diagnosed per year (SEER 2019). Epithelioid sarcoma predominately affects the subcutaneous tissue, fascia, or tendon sheaths most commonly in the distal upper extremities (Asano 2015) and presents as a painful and tender enlarging soft tissue mass (Chase 1985) that can go undiagnosed or misdiagnosed for years. Patients are typically diagnosed between the ages of 20 to 40 years and there is a 2:1 male to female ratio (Jones 2012). It is commonly misdiagnosed as one of the more common benign or malignant tumors with similar morphology (Spillane 2000). There is a high propensity for locoregional spread and approximately 50% of patients are diagnosed with metastatic disease at diagnosis (Thway 2016). Patients with metastatic disease have a 5-year survival of 0% (Pink 2014).

There are two distinct types of epithelioid sarcoma. Classic (distal-type) epithelioid sarcoma commonly affects the distal upper extremity of adolescents and young adults. The proximal variant of epithelioid sarcoma is diagnosed less frequently, affects young to middle-aged adults and has been associated with a more aggressive clinical course. These tend to be deep, infiltrating soft-tissue masses, commonly with hemorrhage and necrosis, affecting axial proximal regions (Thway 2019).

Epithelioid sarcoma is diagnosed based on histological and immunohistochemical (IHC) staining for both mesenchymal and epithelial markers. Epithelioid sarcoma has a distinct immunoprofile with characteristic expression of cytokeratins and epithelial membrane antigen (EMA), and about 50% are positive for CD34. Approximately 90% of epithelioid sarcoma tumors of both classic and proximal types show IHC nuclear loss of INI1 (Thway 2016).

2.2. Analysis of Current Treatment Options

Wide surgical excision remains the mainstay of treatment for localized disease. Neoadjuvant or adjuvant radiation therapy is often administered to reduce local relapse, but the role of adjuvant chemotherapy in this setting is unclear. Systemic chemotherapy is typically reserved for advanced stage disease. Although there have been no prospective studies evaluating the use of systemic therapies for epithelioid sarcoma, doxorubicin with or without another chemotherapy agent is considered standard of care (Pink 2014). Other agents that are used include ifosfamide, gemcitabine, docetaxel, and pazopanib.

Although there are no therapies approved specifically for patients with epithelioid sarcoma, doxorubicin and pazopanib are both approved for the broader population of patients with STS

for which epithelioid sarcoma is a part and are considered available therapy for epithelioid sarcoma patients. Doxorubicin was approved for STS in 1974 based on a response rate of 24% (95% CI: 19, 30) in 234 patients. Pazopanib was approved in 2012 for the treatment of patients with STS after prior chemotherapy based on the results of a randomized, placebo-controlled trial that showed that pazopanib resulted in an improvement in PFS when compared to placebo with an estimated hazard ratio of 0.35 (95% CI: 0.26, 0.48). Median PFS was 4.6 months in the treatment arm versus 1.6 months in the placebo arm.

Table 1. FDA Approved Therapies for the Treatment of Epithelioid Sarcoma

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Doxorubicin	STS	1974	60 to 75 mg/m^2 as a single IV injection once q3w	Single-arm ORR: 26% (95% CI: 20, 33)	Tissue necrosis, cardiac toxicity, secondary leukemias and myelodysplastic syndrome, myelosuppression, hepatotoxicity
Pazopanib	Advanced STS who have received prior therapy	2012	800 mg orally once daily	Pazopanib vs. placebo mPFS 4.6 mo vs. 1.6 mo HR: 0.35 (95% CI: 0.26, 0.48) ORR: 4% (95% CI: 2.3, 7.9) DOR: 9.0 (95% CI: 3.9, 9.2)	Hepatotoxicity, prolonged QT interval and torsades de pointes, cardiac dysfunction, fatal hemorrhage, arterial and venous thrombotic events, GI perforation or fistula, RPLS, hypertensive crisis

Source: Doxorubicin USPI, Blum et al 1974, Pazopanib USPI
Abbreviations: STS: soft tissue sarcoma; IV: intravenous; q3w: every three weeks; ORR: overall response rate; mPFS: median progression-free survival; mo: month; HR: hazard ration; CI: confidence interval; DOR: duration of response; GI: gastrointestinal RPLS: reversible posterior leukoencephalopathy

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Tazemetostat has not been previously approved for any indication.

3.2. Summary of Presubmission/Submission Regulatory Activity

The following summarizes the presubmission regulatory activity for tazemetostat as a single-agent for the treatment of patients with metastatic or locally advanced epithelioid sarcoma.

- On June 12, 2015, a pre-IND meeting was held to gain alignment on the nonclinical and clinical data to support the initiation of clinical studies in adult patients with tumors characterized by INI1-deficiency.
- On July 23, 2015, IND 124608 was submitted.
- On March 24, 2015, the sponsorship for IND 124608 was transferred to Epizyme.
- On May 12, 2017, an End-of-Phase 2 (EOP2) meeting was held to obtain feedback on the acceptability of Trial EZH-301 to support an NDA submission and discuss the preliminary results of study EZH-202. Key FDA comments included:
    - FDA did not agree with the proposed primary endpoint of disease control rate. FDA agreed that ORR may be an acceptable primary endpoint for accelerated approval if supported by an adequate characterization of durability of response.
    - FDA stated that ORR should be determined by blinded independent review and that an application based on this endpoint should have a minimum follow up time of 6 months from the onset of response for responding patients.
    - FDA agreed that a randomized, active-controlled trial to evaluate the efficacy and safety of tazemetostat for the first-line treatment of patients with epithelioid sarcoma is an appropriate design for a confirmatory study. If claims will be sought in a treatment-refractory population, a randomized, placebo-controlled trial or a trial employing physician's choice of best alternative therapy also could be acceptable. In either scenario, the trial should be designed to demonstrate an improvement in overall survival or a treatment effect on PFS that is large in magnitude such that it can be considered direct evidence of clinical benefit.
    - FDA agreed that evaluation of databases among cooperative groups and centers of excellence may provide greater insight on the natural history and response to therapy of epithelioid sarcoma. However, FDA cautioned that comparisons of time-to-event endpoints against an historical population are challenging because of difficulties in ensuring matching for known and unknown prognostic factors, which may confound the assessment of observed differences.
- On June 15, 2017, Orphan Drug Designation was granted for STS.
- On November 21, 2017, Fast Track Designation was granted for the treatment of patients with metastatic or locally advanced epithelioid sarcoma who have progressed

on or following an anthracycline-based regimen.

- On February 9, 2018, a meeting was held to seek concurrence from FDA that a companion diagnostic would not be required for the safe and effective use of tazemetostat for epithelioid sarcoma. FDA stated that to support an all-comer indication, regardless of INI1 status, Epizyme should enroll all patients. If, on the other hand, Epizyme believed INI1 loss was required for the mechanism of action of tazemetostat, a companion diagnostic would likely be required.
- On February 27, 2019, a telephone-conference to clarify the FDAs position on the need for a companion diagnostic was held. FDA agreed that an NDA application could be reviewed prior to submission of a premarket approval application for a companion diagnostic but that the final determination on the need for a companion diagnostic would be a review issue.
- On April 19, 2018, a partial clinical hold was imposed for new patient enrollment based on the report of a patient developing T-cell lymphoblastic lymphoma (T-LBL).
- On September 21, 2019, the partial clinical hold was removed after Epizyme modified the informed consent document to describe the risk of secondary malignancies and modified the clinical trial protocols to incorporate additional risk mitigation processes.
- On January 14, 2019, a Type C pre-NDA meeting was held to gain alignment on the format and content to be included in an NDA submission. FDA stated that the ORR of 13% (95% CI: 6%, 24%) observed to date may be insufficient to serve as evidence of a treatment effect that is reasonably likely to predict clinical benefit in patients with locally advanced or metastatic epithelioid sarcoma. FDA recommend that Epizyme include top-line data, information of natural history of epithelioid sarcoma patients, and an analysis of the effectiveness of available therapies in a comparable patient population.
- On April 29, 2019, a Type B pre-NDA meeting was held to align on the proposed confirmatory evidence required to verify clinical benefit for full approval of tazemetostat in epithelioid sarcoma. FDA did not agree with Epizyme's proposal to use their natural history study in patients with epithelioid sarcoma as a comparator arm to support regular approval. In addition, FDA stated that doxorubicin and pazopanib were considered available therapy for patients with epithelioid sarcoma. FDA reiterated that the ORR of 15% (95% CI: [7, 26]) does not appear to be better than available therapy.
- On May 23, 2019, Epizyme submitted an NDA requesting accelerated approval under 21 CFR 314, subpart H for tazemetostat 800 mg BID based on the results of EZH-202 Cohort 5 showing an ORR of 15% (95% CI: [7, 26]) in patients with epithelioid sarcoma.
- On July 18, 2019, priority review designation was granted.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI review team determined that the data submitted in support of this application appear reliable based on the available information from the inspections of four clinical trial sites and the contract research organization (CRO) that performed independent central review of tumor response data.

Four clinical sites, Dr. Mrinal Gounder (Site #8002), Dr. Victor Villalobos (Site #8008), Dr. Thierry Jahan (Site #8004), and Dr. Silvia Stacchiotti (Site #5001) were selected for audit. There were no significant inspection findings and the final compliance classification for all investigators is No Action Indicated (NAI). The inspection of the CRO, (b) (4) focused on the process for conducting independent review and examined the qualification and training of participating radiologists as well as the related quality control in the CRO's electronic systems. The reported best overall responses submitted by the Applicant were examined against the CRO's records and found to be consistent. No GCP compliance deficiencies were identified.

4.2. Product Quality

Tazemetostat is a new molecular entity that has low solubility, but high permeability. The drug product is manufactured by (b) (4) The manufacturing process has remained consistent through development and into the proposed commercial process, changing only sites and batch size. Bridging to early formulations and dosage strengths was not necessary.

The primary issue cutting across the CMC review disciplines was that the applicant proposed a single tier control for the particle size distribution, controlling the d_{90} of the drug substance at (b) (4) µm. Particle size for the drug substance is typically controlled with three tiers of acceptance criteria at d_{10}, d_{50}, and d_{90}. The risks to inappropriate drug substance particle size control are manufacturability challenges (b) (4) , impacts on in vitro release, content uniformity of dosage units and assay. The drug product formulation has a (b) (4) % drug load, which the OPQ process reviewer confirmed helps to mitigate manufacturability issues. No impact has been seen for batches manufactured with drug substance in this particle size distribution. Similarly, the content uniformity and assay data suggests (b) (4) with this size distribution. The OPQ biopharmaceutics reviewer confirmed that the sponsor evaluated three lots with d_{90} values of (b) (4) µm, (b) (4) µm, and (b) (4) µm. These batches are different from each other in terms of their dissolution, with f2 value being lower than 50. However, all three batches show nearly complete dissolution by 30 minutes, and the proposed product has T_{max} of

in the range of 1-2 hour. Therefore, the difference in dissolution trend during first 30 minutes does not have clinical implications. Finally, the drug substance manufacturing process (b) (4) consistently generates drug substance batches with d_{90} values in the (b) (4) µm range. The applicant's proposed particle size distribution controls were accepted. **The drug product is recommended for approval from OPQ.**

4.3. Clinical Microbiology

Not Applicable.

4.4. Devices and Companion Diagnostic Issues

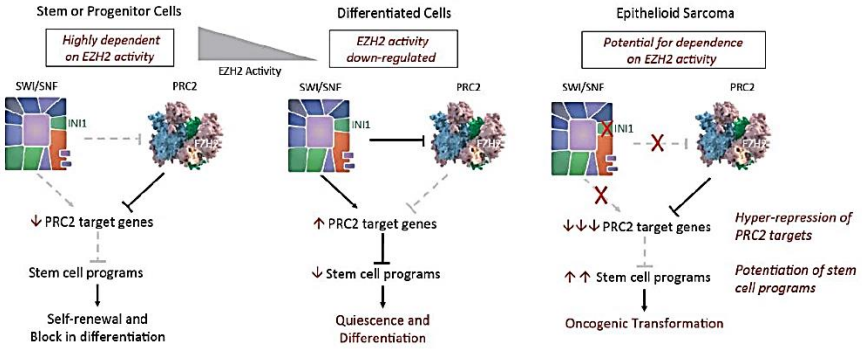
The Applicant did not develop a companion diagnostic for the use of tazemetostat. In response to the concerns expressed by the FDA during development that study eligibility required a diagnostic test (i.e., demonstration of INI1 loss by immunohistochemistry) but that the requested indication was in all patients with epithelioid sarcoma, regardless of INI1 status, the Applicant added an additional cohort of unselected patients onto their clinical trial, EZH-202. Data from this cohort is reviewed in Section 8.1. Due to the very small population size, it is not possible to conclude from the data presented that patients with INI1 retention respond differently to tazemetostat than patients with INI1 loss. This, combined with some uncertainty about the relevance of IN1 loss to the mechanism of action of tazemetostat in epithelioid sarcoma (see Section 5) led the FDA to conclude that a companion diagnostic for IN1 was not necessary to identify patients with epithelioid sarcoma who may benefit from tazemetostat.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Enhancer of zeste homolog 2 (EZH2) is a methyltransferase. While EZH2 can methylate other proteins, its best-characterized activity is as the catalytic subunit of the multi-protein polycomb repressive complex 2 (PRC2) that catalyzes the mono-, di-, and tri-methylation of lysine 27 of histone H3 (H3K27), leading to repression of target genes. The full set of target genes of PRC2 is substantial and not fully elucidated but studies implicate the complex in repression of cell differentiation genes (allowing more stem cell like gene expression) and some cell cycle regulators like p16INK^{4A} (Wilson et al. 2010). Human EZH2 may contain one of several gain of function mutations in the catalytic domain such as Y646F, Y646N, Y646S, Y646H, Y646C, A677G, and A687V leading to aberrant repression of target genes and induction of stem cell like programs and oncogenic transformation. The Switch/sucrose non-fermentable (SWI/SNF) complex is a multi-protein ATP-dependent chromatin remodeling complex that uses ATP hydrolysis to disrupt DNA-nucleosome contacts, enabling DNA access for various transcription factors. The SWI/SNF and PRC2 complexes each balance and antagonize the activity of the other. Loss of the INI1 (SMARCB1/SNF5/BAF47) subunit of the SWI/SNF complex destabilizes its binding to chromatin and can lead to aberrant activity of PRC2, increased expression of EZH2, or both (Nakayama et al. 2017).

Figure 1: Pathways associated with PRC2 and SWI/SNF



INI1 is also known as SMARCB1 and these terms are used interchangeably.
EZH2 = enhancer of zeste homolog 2; INI1 = integrase interactor 1; SMARCB1 = SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily B, member 1; SWI/SNF = SWItch/Sucrose NonFermentable; PRC2 = polycomb repressive complex 2.
Source:[4]

(Excerpted from the Pharmacology Written Summary)

Tazemetostat (E7438, EPZ-6438) is a small molecule with an established pharmacologic class of methyltransferase (MT) inhibitor. In non-cellular biochemical assays, tazemetostat inhibited the activity of wild type human EZH2 at an IC_{50} of 11 nM, which is approximately 17 times lower than the predicted free maximum concentration (Cmax) of 188 nM tazemetostat in patients, considering 88% protein binding and a Cmax of 829 ng/mL in patients treated at the twice daily (BID) oral dose of 800 mg. Tazemetostat inhibited EZH2 gain-of-function mutants with IC_{50}

values ranging from 2 to 38 nM, with 10- to 100-fold greater activity compared to EZH1 inhibition (392 nM), and greater than 12,500-fold activity compared to inhibition of other histone methyl transferase (HMTs) enzymes. Similar studies showed that the major human metabolite EPZ-6930 (M5) had IC_{50} values of 1.79 and 1.23 µM for wild type EZH2 and Y641F mutants, respectively, suggesting little potential for contribution of activity. Site specificity analysis indicated that tazemetostat affected H3K27Me1, H3K27Me2, and H3K27Me3 methylation sites in the EZH2 wild type bearing OCI-LY19 lymphoma cell line, without altering H3 lysine methylation sites K4, K9, K36, or K79. Tazemetostat showed concentration-dependent inhibition of H3K27 trimethylation in a panel of human lymphoma cancer cell lines bearing wild type EZH2 or EZH2 mutants (Y641F, Y641N, A677G), with IC_{50} values ranging from 2 to 260 nM. Evaluation of the kinetics of H3K27Me3 depletion in WSU-DLCL2 cells (Y641N bearing B cell lymphoma line) indicated that 1µM of tazemetostat significantly reduced methylation starting after one day and reached greater than 90% reduction by Days 3 to 4. Similarly, concentration-dependent tazemetostat-mediated reductions in H3K27Me3 levels occurred in a panel of malignant rhabdoid tumor (MRT) cell lines with or without the loss of INI1 without affecting other histone methyl markers; however, tazemetostat only had anti-proliferative activity in INI1-deficient cell lines, including in INI1-deficient atypical teratoid rhabdoid tumor (AT/RT) cell lines BT-12 and CHLA-266 (IC_{50} values of 0.11 and 0.16 µM), and in synovial sarcoma cell lines bearing SS18 gene fusions that result in exclusion of INI1 from the SWI/SNF complex (Kadoch and Crabtree 2013). Tazemetostat also dose-dependently inhibited proliferation of several EZH2 Y641N and Y641F mutant bearing lymphoma cell lines in the nM range, but not EZH2 wild type bearing cells. Analysis of the mechanism by which inhibition of proliferation or cell death occurs indicated early cell cycle arrest leading to apoptosis after accumulation of cells in the G1 phase.

Tazemetostat did not significantly inhibit hERG channel current at concentrations up to 10 µM in vitro. In the isolated rabbit left ventricular wedge preparation, tazemetostat did not cause any proarrhythmic events at concentrations up to 20 µM. In addition, tazemetostat had no effect on ECG parameters or body temperature in a single escalating dose study in cynomolgus monkeys, nor was there any effect on ECG parameters in the 13-week repeat-dose toxicology study in monkeys.

To assess the safety of tazemetostat, Epizyme conducted GLP-compliant toxicology studies of up to 13-weeks in Sprague Dawley rats and cynomolgus monkeys. In the 13-week rat study, animals received tazemetostat once daily by oral gavage at doses of 100, 300, or 600 mg/kg. Six rats at the 300 mg/kg dose level died or were prematurely euthanized between Days 65-91 due to lymphoma correlated with thymic masses. These six animals showed signs of emaciation, prostration, staining of the facial area, and chromaturia. They had increased WBCs due to the presence of leukemic cells, decreased RBCs, hemoglobin, platelets, and reticulocytes, prolonged APTT, and increased erythroblasts. In total, lymphoblastic lymphoma originating from the thymus occurred in 40% of the females and 15% of the males treated at 300 mg/kg and 5% of the males treated at 600 mg/kg. Hematology changes in surviving animals included dose dependent decreases in hemoglobin, MCV, MCH, and platelets, and dose dependent increases

in reticulocytes and WBCs, all of which were reversible. Gross pathology findings were limited to enlargement and masses in multiple organs that correlated with metastasis of lymphoma in the 300 and 600 mg/kg dose groups. Lymphoma cells were strongly positive for CD3, positive for CD8, and negative for CD20 and characterized by proliferation of large lymphoblastic cells with scant cytoplasm and round to irregular nuclei; metastases were widespread in multiple organs. Additional pathology findings in the rat toxicology study included trabecular formation in several bone structures, dysplasia in the incisors, and increased hematopoiesis in the bone marrow. Exposure increased in a more than dose-proportional manner with higher tazemetostat exposure in females and higher metabolite exposure in males. AUC values in rats at the 300 mg/kg dose level, the lowest dose that resulted in lymphoma in a significant portion of the animals, were equal to or greater than 14 (males) and 24 (females) times higher than the AUC in patients (3340 ng*h/mL) given the twice daily dose of 800 mg.

In the 13-week monkey study, animals received oral tazemetostat at total daily doses of 100, 300, or 600 mg/kg/day (50, 150, 300 mg/kg BID). One out of six females treated at 600 mg/kg/day was sacrificed in moribund condition on Day 83 with histopathology changes in the spleen thymus, lymph nodes, liver, kidney, stomach (hyperplasia), lung, and bone marrow. All monkeys displayed a dose-dependent increase in emesis and abnormal feces during the study. Dose-dependent increases in AST, ALT, ALP, and triglycerides occurred during the study period with changes still elevated for AST, ALT, and ALP in the 600 mg/kg/day recovery animals. At doses ≥ 300 mg/kg/day (~equal to the human AUC at the 800 mg BID dose) gross pathology and microscopic pathology included hypertrophy and hyperplasia of the liver and bile duct. In addition, lymphoid hyperplasia occurred in the mesenteric lymph node of a single male dosed at 600 mg/kg/day.

Epizyme also conducted a GLP-compliant toxicology study of up to 13-weeks in juvenile Sprague Dawley rats starting from post-natal day (PND) 7 to 98. Animals received tazemetostat once daily by oral gavage at doses of 50, 100, 150/300, or 150/600 mg/kg. Based on intolerability of the higher doses before Day 21, animals in the top two dose levels received 150 mg/kg tazemetostat from PND 7 to 21 of the 98-day dosing period. Sixteen animals were found dead or euthanized in extremis throughout the study and recovery period and deaths occurred even at the low dose of 50 mg/kg (approximately equal to the adult human exposure at the 800 mg BID dose). The majority of deaths (10/16; 63%) in main group animals regardless of dose were due to malignant lymphoma. Clinical signs in surviving animals included red or yellow material around nose/eyes, mouth urogenital/anogenital areas and the ventral trunk, scabs on tails and limbs, swollen face and digits (edema), and masses on trunks and limbs. Most of these signs along with the finding of increased body weight gain compared to control animals at all tazemetostat dose levels were potentially secondary to metastatic lymphoma. Evaluation of sexual maturation land marks indicated a delay in the mean age at attainment of balanopreputial separation in males dosed at 150/600 mg/kg (approximately 100 times the adult human exposure at the 800 mg BID dose) compared to controls. All males also demonstrated distended testicles starting at PND 48, but without any histological correlates. Tazemetostat did not affect attainment of vaginal patency. Tazemetostat led to decreased

neuromuscular coordination as observed by changes in rotarod performance in the 150/300 and 150/600 mg/kg groups and decreased air righting reflex and hind foot splay in the 150/600 mg/kg group by the end of the dosing period. Bone was an additional target organ with increased trabecular bone at doses ≥100 mg/kg (approximately 10 times the adult human exposure at the 800 mg twice daily dose). Exposure increased in a dose dependent manner from the 50 to 150/300 mg/kg groups; however, exposures in the 150/300 and 150/600 mg/kg groups were comparable on Day 98.

Dedicated carcinogenicity studies were not conducted with tazemetostat and are not required to support the use of a drug intended to treat patients with advanced cancer; however, findings in the rodent studies demonstrate that the drug has clear carcinogenic potential and similar secondary malignancies have occurred in clinical trials. While gain-of-function mutations in EZH2 or increases in EZH2 expression following decreased SWI/SNF activity have clear associations with tumorigenesis, there are also reports of EZH2 loss-of-function mutations or deletions of EZH2 or other PRC2 proteins in humans that are associated with the development of cancer including T-ALL specifically (Kim and Roberts 2016; Kadoch et al. 2016; Antichrists et. al. 2012). Epizyme made an initial effort to determine whether the lymphomas observed in animal studies were specific to rodents; however, lymphomas have occurred in clinical trials with tazemetostat and despite the apparently much higher frequency of lymphoma associated with tazemetostat exposure in rodents compared to humans, the animal studies appear to be predicting a mechanistically driven and clinically relevant risk of secondary malignancies associated with the drug.

Epizyme did not conduct dedicated studies to assess fertility and these studies are not warranted to support the development of a drug intended to treat patients with advanced cancer. There were no histopathological findings in the chronic toxicology studies in the rat or monkey suggesting a direct effect of tazemetostat on fertility.

To assess the potential developmental and reproductive toxicity of tazemetostat, Epizyme conducted embryo-fetal development studies of oral tazemetostat in Sprague-Dawley rats (Gestation Day 7-17) and New Zealand White rabbits (GD 7-19); both studies included toxicokinetic data in pregnant animals for exposure comparisons. At 200 mg/kg (approximately 14 times the clinical tazemetostat exposure of 3340 ng*hr/mL at the 800 mg BID dose) in rats there was decreased maternal body weight gain (23% compared to controls) that correlated with decreased fetal weight (25% males, 32% females) compared to vehicle controls as well as increased post-implantation loss and malformations including missing digits, fused vertebrae, and domed heads along with fused bones of the skull. Dose-dependent increases in skeletal malformations and variations occurred starting at the lowest dose of 50 mg/kg (approximately twice the clinical tazemetostat exposure at the 800 mg BID dose). In rabbits, there was post-implantation loss and malformations including cleft palate at 400 mg/kg (approximately 7 times the clinical exposure at the 800 mg BID dose). Skeletal variations were present at doses ≥100 mg/kg/day (approximately 1.5 times the human exposure at the 800 mg BID dose) with skeletal malformations at ≥200 mg/kg/day (approximately 5.6 times the human exposure at the 800 mg

BID dose). Based on data from the embryo-fetal development studies and the drug's mechanism of action, a warning for embryo-fetal toxicity is included in the labeling for TAZVERIK. While tazemetostat showed no genotoxic potential in the standard genetic toxicology battery, based on its activity as an epigenetic modulator, the labeling also includes recommendations for female and male contraception of 6 and 3 months, respectively, consistent with recommendations for products that are positive in traditional genotoxic assays.

No studies were conducted or required to investigate the presence of tazemetostat in milk. Because many drugs are secreted in milk, the labeling includes a warning not to breastfeed during treatment with tazemetostat and for 1 week after the final dose based on a half-life of 3 hours.

Epizyme has completed all expected nonclinical studies to support the development and approval of a drug intended for the treatment of patients with advanced cancer. The toxicology studies appear adequately designed to demonstrate the toxicity of the drug. There are no outstanding issues from a pharmacology/toxicology perspective that would prevent approval of tazemetostat for the treatment of the proposed patient population.

5.2. Referenced NDAs, BLAs, DMFs

None.

5.3. Pharmacology

Primary pharmacology

A. In Vitro Studies

In Study #e7438-pd006 using a panel of wild type EZH1 and EZH2, or EZH2 enzymes bearing gain-of-function mutations in the catalytic domain (Y641F, Y641N, Y641S, Y641H, Y641C, A677G, and A687V), and additional histone methyl transferase enzymes (HMTs), EPZ-6438 inhibited the activity of wild-type and mutated human EZH2 enzymes with IC_{50} values ranging from 2 to 38 nM (Table 2), with the IC_{50} for human EZH2 (2.5 nM) being 156-fold lower compared to human EZH1 (392 nM), and at concentrations that were ≥12,500 times lower than those of other HMTs tested. To elucidate the mechanism of inhibition of wild type EZH2 by EPZ-6438 in competition assays, the Applicant investigated inhibition in the presence of increasing *S*-adenosyl-L-methionine (SAM), a universal methyl donor for catalytic reactions of histone methyltransferases, or an oligonucleosome substrate. Increasing levels of SAM resulted in higher EPZH2 IC_{50} values but increasing oligonucleosome levels had little effect, suggesting that EPZ-6438 is a SAM-competitive, nucleosome non-competitive inhibitor of EZH2 (Figure 2). Ki as measured at the y-intercept of the linear regression in the SAM plot was 2.5 nM. In a biochemical assay studying the activity of the major human metabolite EPZ-6930 (M5) against wild type EZH2 or EZH2 bearing the Y641F mutation and additional HMTs (Study #EPZ-6438-

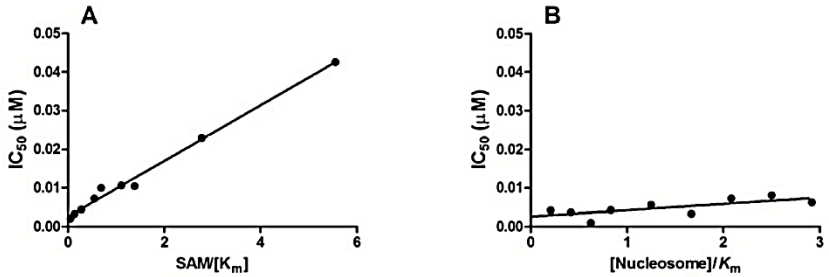
pd013), M5 inhibited EZH2 and Y641F mutations of EZH2 with IC_{50} values of 1.79 µM and 1.23 µM, respectively; IC_{50} values for other HMTs could not be determined suggesting that M5 contributes little to the activity of EPZ-6438.

Table 2: IC_{50} values for EPZ-6438 inhibition of human wild type EZH1, EZH2, and EZH2 gain-of-function mutants

Target	IC_{50} (nM)	Target	IC_{50} (nM)	Target	IC_{50} (nM)
EZH1	392	A687V EZH2	2	Y641H EZH2	6
EZH2	11	Y641C EZH2	16	Y641N EZH2	38
A677G EZH2	2	Y641F EZH2	14	Y641S EZH2	6

IC_{50} values for EPZ-6438 inhibition of additional HMT such as CARM2, DOT1L, EHMT1 and 2, PRMT1,3,5,6, and 8, SMYD 2 and 3, WHSC1 and ILI, and SETD7 were either greater than 50,000 nM or could not be determined.

Figure 2: EPZ-6438 IC_{50} plots for inhibition of wild type EZH2 with increasing SAM (A) or oligonucleosome (B) concentrations



(Excerpted from Study #e7438-pd006)

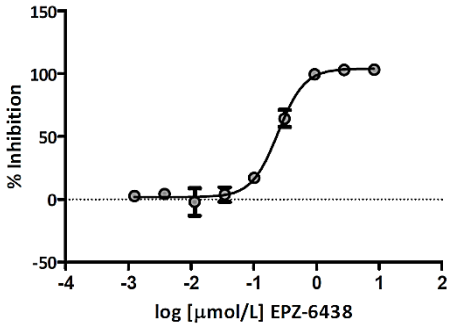
The Applicant assessed the ability of EPZ-6438 to inhibit histone trimethylation (H3K27Me3) levels using lymphoma cell lines derived from either EZH2 wild type or EZH2 gain-of-function mutation-positive (Y641F, Y641N, and A677G) tumors. Four-day incubation of both wild type and EZH2 mutation-positive lymphoma cell lines with EPZ-6438 inhibited levels of trimethylated H3K27 (H3K27Me3) in a concentration-dependent manner as measured by Western blot, with IC_{50} values ranging from 2 to 90 nM (Table 3) (Study e7438-pd009). EPZ-6438 also inhibited levels of trimethylated H3K27 in the diffuse large B-cell lymphoma line WSU-DLCL2 bearing the EZH2 Y641F mutation in a concentration-dependent manner with an IC_{50} value of 260 nM after a 4-day treatment (Study e7438-pd007) as detected by ELISA (Figure 3). In Study e7438-pd009, analysis of site specificity for methylation on Histone 3 (H3) using Western blot indicated that 270 nM of EPZ-6438 affected H3K27Me1, K3K27Me2, and H3K27Me3 in the EZH2 wild type bearing OCI-LY19 cell line treated for 96 hours, without altering H3K4 and 9, H3K36, or HK79 methylation sites (data not shown in review). Evaluation of the kinetics of H3K27Me3 depletion, indicated that 1µM of EPZ-6438 caused a significant reduction in methylation starting after one day of treatment and reaching greater than 90% reduction by Days 3 to 4 in the WSU-DLCL EZH2 Y641F mutant cell line (Figure 4). In Study # e7438-pd011, using a panel of MRT cell lines with or without the loss of INI1 (also known as SMARCB1 or SNF5), a subunit of the SWI/SNF complex, EPZ-6438 led to a concentration-dependent reduction in H3K27Me3

levels in both INI1-deficient and INI1-wild type cells (Table 4), without affecting other histone methyl markers (Figure 5); however, EPZ-6438 showed anti-proliferative activity only in INI1-deficient cell lines after 14 days (Table 4).

Table 3: EPZ-6438 IC_{50} values for inhibition of H3K27Me3 in a panel of human lymphoma cell lines

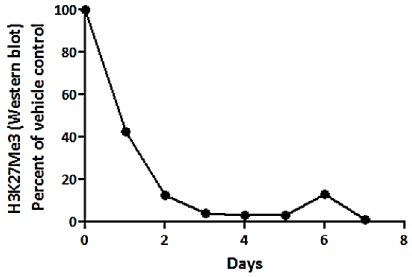
Cell Line	EZH2 status	IC_{50} (nM)
OCI-LY19	Wild type	8
Karpas422	Y641N	90
Pfeiffer	A677G	2
RL	Y641N	22
SUDHL-6	Y641N	20
WSU-DLCL2	Y641F	9

Figure 3: IC_{50} plot for inhibition of H3K27Me3 as detected by ELISA in WSU-DLCL2 cells after a 4-day treatment



(Excerpted from Study #e7438-pd007)

Figure 4: Inhibition of H3K27Me3 in WSU-DLCL2 cells by 1 µM EPZ-6438 over a 7-day period



(Excerpted from Study #e7438-pd009)

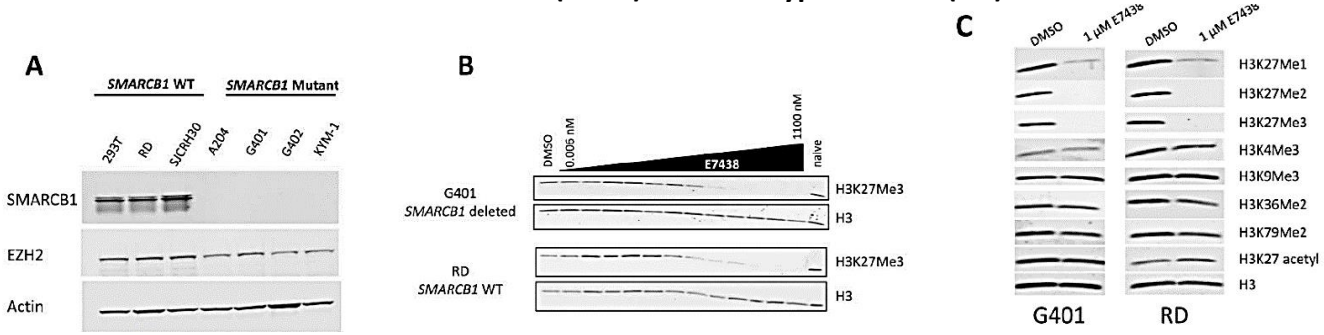
Table 4: EPZ-6438 IC_{50} values for inhibition of methylation and proliferation in MRT cell lines with or without INI1 deficiency

Cell Line	INI1 status	Methylation IC_{50} (nM)	Day 14 Proliferation IC_{50} (nM)
G401	Mutant	2.7	135
A204	Mutant	1.4	1000
G402	Mutant	1.7	144
KYM-1	Mutant	4.3	32

Cell Line	INI1 status	Methylation IC_{50} (nM)	Day 14 Proliferation IC_{50} (nM)
RD	Wild type	5.6	6100, >10000*
293	Wild type	2.4	>10000
SJCRH30	Wild type	4.9	5100, >10000*

*Mean calculations of duplicate experiments were not possible, individual values are shown.

Figure 5: EPZ-6438 effects on H3K27Me3 and other histone methylation markers in INI1-deficient cell line (G410) and wild type cell line (RD)



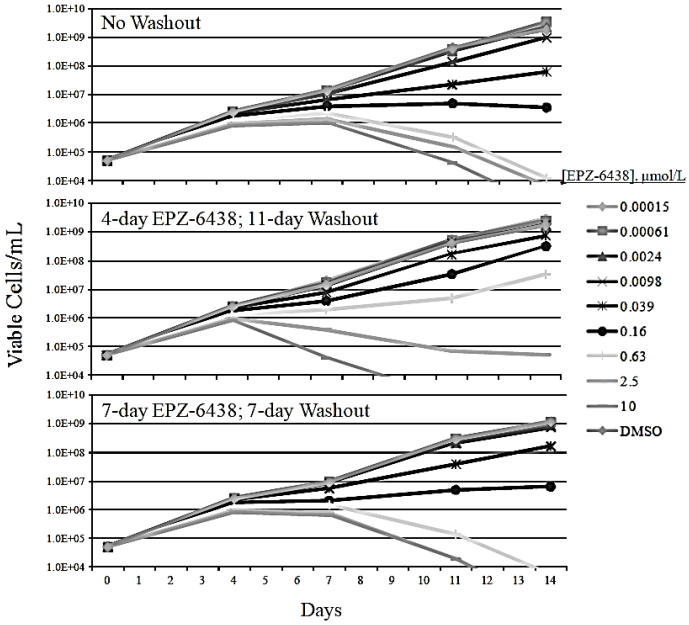
(Excerpted from Study #e7438-pd011)

Incubation of increasing concentrations of EPZ-6438 with WSU-DLCL2 (EZH2 Y641F) cells for 6 days resulted in decreased proliferation with an IC_{50} value of 280 nM (Study e7438-pd008; data not shown in review). In an 11-day proliferation assay (Study e7438-pd009), increasing concentrations of EPZ-6438 inhibited proliferation of EZH2 Y641N and Y641F mutant bearing lymphoma cell lines in the nM range with the exception of EZH2 Y641N bearing RL cells. EPZ-6438 did not have anti-proliferative effects on EZH2 wild type cells (Table 5). Evaluation of the duration of the anti-proliferative activity of EPZ-6438 on WSU-DLCL2 EZH2 Y641F cells showed that incubation for 4 out of 14 days only led to decreased numbers of viable cells only at the 2 highest EPZ-6438 concentrations (10 and 2.5 µM), while incubation for 7 out of 14 days resulted effects comparable to that of a 14-day continuous incubation (IC_{50} values of 0.01 and 0.0086 µM, respectively; Figure 6).

Table 5: EPZ-6438 inhibition of proliferation in a 11-day proliferation assay in a panel of lymphoma cell lines with various EZH2 status

Cell Line	EZH2 status	IC_{50} (nM)
DOHH-2	Wild type	1700
Farage	Wild type	99
OCI-LY19	Wild type	6200
Toledo	Wild type	7600
Karpas422	Y641N	1.8
Pfeiffer	A677G	0.5
RL	Y641N	5800
SU-DHL10	Y641F	5.8
SU-DHL6	Y641N	4.7
WSU-DLCL2	Y641F	8.6

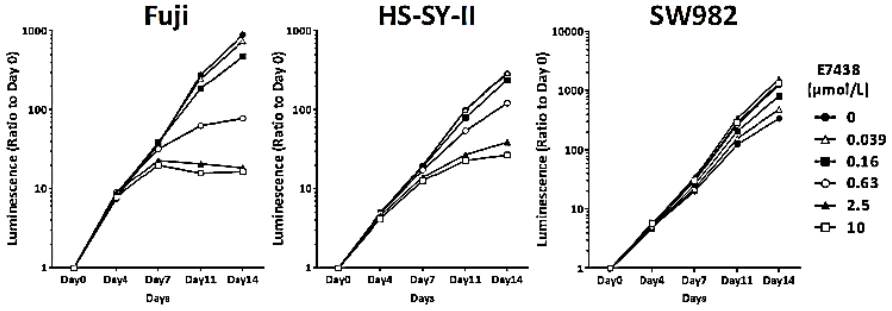
Figure 6: EPZ-6438 washout effect on viable cell counts of WSU-DLCL2 cells



(Excerpted from Study #e7438-pd009)

In Study #epz006438-ATRT-pd001, EPZ-6438 had anti-proliferative activity in atypical teratoid rhabdoid tumor (AT/RT) cell lines BT-12 and CHLA-266, both of which are INI1(SMARCB1)-deficient, with IC_{50} values of 0.11 and 0.16 µM, after a 14-day incubation. In study M14023, investigators incubated tazemetostat for 14 days with the synovial sarcoma cell lines Fuji, HS-SY-II (both with fusions between the SS18 gene and the SSX2 or SSX1 gene, respectively, that lead to an altered SWI/SNF complex that lacks INI1), or the wild type sarcoma cell line SW982. Tazemetostat had at least modest anti-proliferative activity against the 2 fusion cell lines, but not the wild type SW982 line (Figure 7).

Figure 7: Anti-proliferative effects of tazemetostat against human synovial sarcoma cell lines

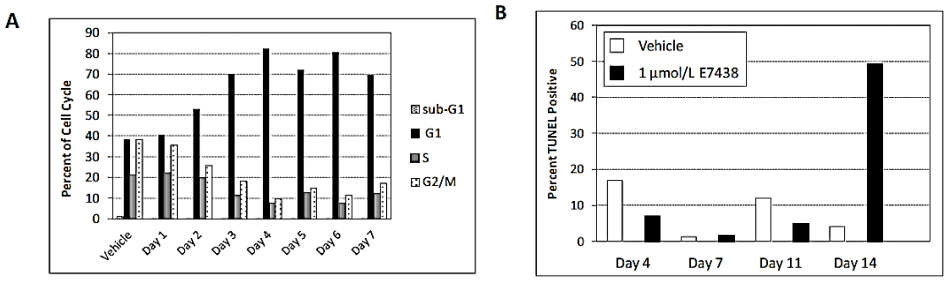


(Excerpted from Study #M14023)

Analysis of the mechanism by which cell killing occurs indicated that when WSU-DLCL2 (Y641F) cells were treated with 1 µM of EPZ-6438 for 7 days there was an increase in cells in G1 with a decrease of cells in G2/M-phase after 2 days of treatment that reached a maximum at Day 4 with no increase in the subG1 fraction, suggesting that apoptosis had not occurred within the 7 day treatment period (Figure 8A). In a second experiment using the same cell line, TUNEL-

positive cells increased only on Day 14 compared to vehicle controls, suggesting that there is cell cycle arrest early in treatment that then leads to apoptosis after accumulation of cells in the G1 phase (Figure 8B). Similar cell cycle and apoptosis data was obtained in the MRT cell lines with SMARC1(INI1)-deficiency in study e7438-pd011; data not shown in review).

Figure 8: Effects of EPZ-6438 on cell cycle progression and apoptosis in WSU-DCLC2 EZH2 Y641F cells



(Excerpted from Study #e7438-pd009)

B. In Vivo Studies

Studies 1052-001-V5, 1052-005, and 1052-007

The Sponsor investigated the in vivo anti-tumor activity of EPZ-6438 in a series of studies (1052-001-v5 and 1052-007) using several patient-derived synovial sarcoma xenograft lines bearing SS18 fusions that lead to INI impairment. After tumors reached 100-300 mm^3 immunocompromised adult female nude mice bearing human synovial sarcoma (CTG-0331, CTG-0771, or CTG-1169) xenografts in one flank received one of the following treatment regimens: oral EPZ-6438 twice daily (BID), intravenous doxorubicin (once every 7 days) either alone or in combination with 250 mg/kg EPZ-6438, or vehicle. In CTG-0331 tumor bearing mice, EPZ-6438 led to dose-dependent tumor growth inhibition (TGI) by Day 35, with the 400 mg/kg dose showing greater TGI compared to doxorubicin (69% vs. 37%, respectively; Table 6). In CTG-0771 tumor bearing mice, 2 animals treated with EPZ-6438 (400 mg/kg) were euthanized on Day 2 due to significant weight loss, and one animal treated with doxorubicin (27 mg/kg) was euthanized due to drug-related toxicities. Similarly to the TGI in the CTG-0331 model, EPZ-6438 led to dose-dependent TGI by Day 35, with greater TGI at the 400 mg/kg dose compared to doxorubicin (79% vs. 49%, respectively; Table 6). In CTG-1169 tumor bearing mice, 2 animals treated with EPZ-6438 at 125 mg/kg and one at 500 mg/kg were found dead with no known cause or clinical signs; EPZ-6438 at 250 and 400 mg/kg showed an increase TGI compared to doxorubicin alone or in combination with 250 mg/kg of EPZ-6438 by Day 34.

In Study 1052-005, the Sponsor evaluated the in vivo anti-tumor activity of oral EPZ-6438 twice daily (BID), vincristine/Doxil/cyclophosphamide, or vehicle in immunocompromised adult female nude mice bearing subcutaneous xenografts of the rhabdomyosarcoma cell line CTG-0800 after tumors reached 100-300 mm^3. EPZ-6438 had modest effects on TGI at 125 and 250 mg/kg but no effect at 500 mg/kg, while vincristine/Doxil/cyclophosphamide led to CTG-0800 TGI of greater than 100% (Table 6).

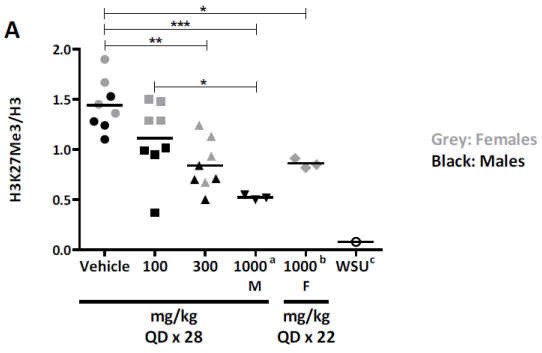
Table 6: Tumor growth inhibition summary in synovial sarcoma and rhabdomyosarcoma xenograft models

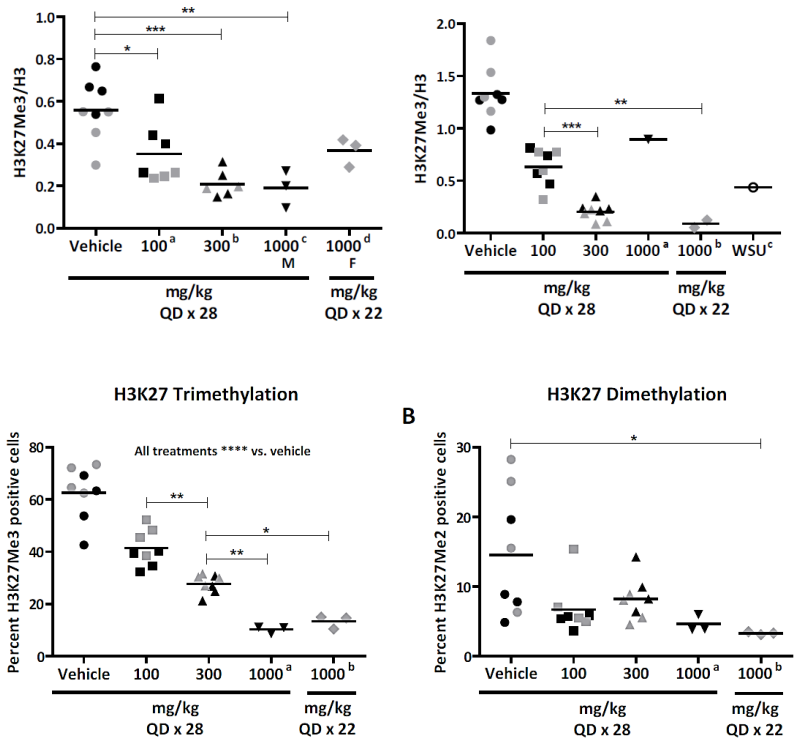
			TGI					
Tumor model	Tissue type	TGI Day	EPZ-6438			Doxo.	Doxo + EPZ-6438	Vin/doxil/ Cyclo.
			125 mg/kg	250 mg/kg	400/500* mg/kg			
0331	Synovial sarcoma	35	28%	51%	69%	37%	-	-
0771	Synovial sarcoma	35	60%	69%	79%	49%	-	-
1169	Synovial Sarcoma	34	27%	46%	39%	18%	32%	-
0800	Rhabdo myosarcoma	13	26%	24%	-2%	-	-	103%

TGI=tumor growth inhibition. *CTG-0331 was dosed at 400 mg/kg BIDx35 days; CTG-0771 was dose at 500 mg/kg BIDx18 days, followed by a 24-hour dosing holiday, then BIDx17 days at 400 mg/kg; CTG-0800 and CTG-1169 were dosed at 500 mg BIDx13 days and x35 days, respectively. Vincristine/Doxil/cyclophosphamide were dosed at 1, 3, and 100 mg/kg respectively. Intravenous doxorubicin was dosed at 27 mg/kg in model 0331 and 0771 and 3 mg/kg alone and in combination with 250 mg/kg EPZ-6438 in model 1169.

In Study E7438-PD004, the Applicant collected tissue samples from male and female Sprague Dawley rats dosed daily at 100, 300, and 1000 mg/kg in the 28-day repeat-dose toxicology study for analysis of the methylation status of histone H3 lysine 27 (H3K27). Samples showed a dose dependent down regulation of trimethylation of H3K27 in bone marrow, peripheral blood mononuclear cells (PBMCs), spleen, and skin with the highest degree of inhibition occurring in the bone marrow. Females in the 1000 mg/kg group were euthanized early and are represented in the Day 22 data in Figure 9. As expected for inhibition of wild type EZH2, tazemetostat also showed inhibition of dimethylation of H3K27, at all concentrations. Tissues from the 28-day monkey toxicology (daily dosing of E7438 at 50, 150, or 500/300 mg/kg BID) showed similar results (E7438-PD005).

Figure 9: Target inhibition in spleen (top), PBMCs (middle left), bone marrow (middle right), and skin (bottom) in rats treated with E7438 for 22 or 28 days





(Excerpted from study E7438-PD004)
Spleen, PBMC, and bone marrow data collected via ELISA and skin data via immunohistochemistry. WSU = histones from the WSU-DLCL2 cell line treated with 25 µM E7438 for 4 days as a comparator.

Secondary Pharmacology

The Applicant screened for off-target activity of tazemetostat using a panel of targets (receptors, ion channels, and transporters) in Study EPZ006438. Incubation with tazemetostat at 10 µM resulted in greater than 50% inhibition or activation only for the muscarinic receptor M_4. Upon further analysis, the IC_{50} for inhibition of M_4 by tazemetostat was 4.6 µM.

Analysis of the biochemical inhibitory activity of metabolites of EPZ-6438 against EZH2 in Study e7438-pd018, showed that the major human metabolites EPZ-034163 (M1), EPZ-6931 (M3), and EPZ-6930 (M5) inhibited EZH2 with IC_{50} values of 5.9, 1.5, and 0.12 µM, respectively. In a cellular assay, EPZ-034163 and EPZ-6931 inhibited H3K27Me3 in WSU-DLCL2 cells with an IC_{50} >50 µM, while EPZ-6930 inhibited K3K27Me3 with an IC_{50} of 15.5 µM, a concentration 300-fold higher than EPZ-6438.

Table 7: Biochemical and cellular IC_{50} values for major human metabolites of EPZ-6438

Metabolite	IC_{50} for EZH2 inhibition	IC_{50} for H3K27Me3 inhibition
EPZ-034163 (M1)	5.9 µM	>50 µM
EPZ-6931 (M3)	1.5 µM	>50 µM
EPZ-6930 (M5)	0.12 µM	15.5 µM

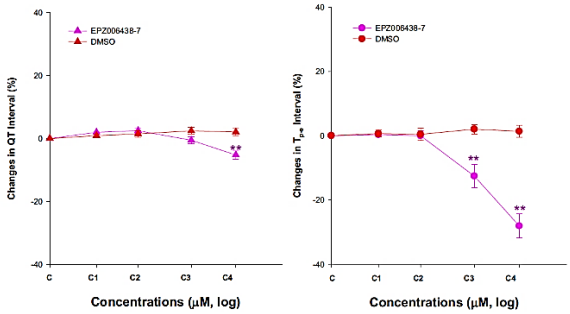
Safety Pharmacology

In non-GLP Study #110517.FQJ, HEK293 cells stably expressing the human hERG potassium channel were incubated with tazemetostat at 10 µM or 0.3% DMSO (negative control) followed by measurement of potassium current using the patch-clamp technique. The negative control behaved as expected. Tazemetostat inhibited the hERG potassium current with values ranging from 11.4 to 18.1% at 10 µM, making the IC_{50} greater than 10 µM suggesting a low potential for interference of cardiac repolarization and low risk of QT prolongation in humans given tazemetostat.

The non-GLP Study #LIMR-20110801, examined the effects of tazemetostat (0.75, 2, 7, 20 µM) or DMSO on QRS duration, QT interval, and T_{p-e} interval in the isolated rabbit (New Zealand) left ventricular wedge preparation using a HP ECG amplifier with extracellular silver/silver chloride electrodes. Tazemetostat did not affect QRS duration compared to controls at any concentration tested. Concentrations of 0.75 to 7 µM did not affect the QT interval compared to controls; however, a small but significant decrease did occur at 20 µM. Concentrations of 0.75 and 2 µM did not affect T_{p-e} interval; however, concentrations ≥ 7 µM significantly decreased the interval (Figure 10).

In GLP-compliant Study #20026297, radiotelemetry-instrumented female (n=4) cynomolgus monkeys received escalating doses of tazemetostat at 100, 300, and 1000 mg/kg with a 1-week washout between doses to assess the effects of tazemetostat on cardiovascular parameters. Clinical signs, body weights, food consumption, hemodynamic parameters (heart rate and blood pressure), ECG, activity, and body temperature were recorded from two hours before to 24 hours post dose. No changes in body weight or food consumption occurred at any dose. Emesis occurred at 300 and 1000 mg/kg. No changes from control animals occurred in QA interval, body temperature, PR, QRS, and QT intervals in tazemetostat treated animals.

Figure 10: Changes in QT and T_{p-e} interval in the rabbit left ventricular wedge prep in response to increasing concentrations of tazemetostat



C1 = 0.75, C2 = 2, C3 = 7, C4 = 20 µM.
(Excerpted from Study #LIMR-20110801)

5.4. ADME/PK

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Protein Binding</td></tr>
<tr><td>Study #161025: In vitro plasma binding of EPZ-6438 in mouse, rat, rabbit, monkey, and human plasma</td><td>Concentration-dependent protein binding only occurred in rat and mouse. EPZ-6438 was most highly bound in the mouse. Protein binding in human plasma ranged from 88.4 to 91.1%.
<table>
<tr><th>Species</th><th>Conc. (µM)</th><th>% unbound</th><th>% bound</th></tr>
<tr><td>Mouse</td><td>1</td><td>1.9</td><td>98.1</td></tr>
<tr><td></td><td>3</td><td>2.73</td><td>97.3</td></tr>
<tr><td></td><td>10</td><td>5.4</td><td>94.6</td></tr>
<tr><td></td><td>30</td><td>8.2</td><td>91.8</td></tr>
<tr><td>Rat</td><td>1</td><td>5.3</td><td>94.7</td></tr>
<tr><td></td><td>3</td><td>7</td><td>93</td></tr>
<tr><td></td><td>10</td><td>9</td><td>91</td></tr>
<tr><td></td><td>30</td><td>11.2</td><td>88.8</td></tr>
<tr><td>Rabbit</td><td>1</td><td>8.1</td><td>91.9</td></tr>
<tr><td></td><td>3</td><td>8.2</td><td>91.8</td></tr>
<tr><td></td><td>10</td><td>8.6</td><td>91.4</td></tr>
<tr><td></td><td>30</td><td>8.9</td><td>91.1</td></tr>
<tr><td>Monkey</td><td>1</td><td>16.7</td><td>83.3</td></tr>
<tr><td></td><td>3</td><td>15.3</td><td>84.7</td></tr>
<tr><td></td><td>10</td><td>16.7</td><td>83.3</td></tr>
<tr><td></td><td>30</td><td>15.9</td><td>84.1</td></tr>
<tr><td>Human</td><td>1</td><td>11.6</td><td>88.4</td></tr>
<tr><td></td><td>3</td><td>12.3</td><td>87.7</td></tr>
<tr><td></td><td>10</td><td>8.9</td><td>91.1</td></tr>
<tr><td></td><td>30</td><td>12</td><td>88</td></tr>
</table></td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Study #DMPKA2012-060: Pharmacokinetics of E7438 following intravenous and oral administration to Sprague Dawley rats

and

Study #1045-022: Pharmacokinetics of E7438 following intravenous and oral administration to cynomolgus monkeys</td><td>A single-dose PK study in the rat using an intravenous (IV) doses of 5 or 10 mg/kg and oral doses of 5, 30, or 100 mg/kg showed that oral bioavailability increased significantly with increasing dose and that this increase was not dose-proportionate.

<u>Rats</u>
<table>
<tr><th>Administration Route</th><th colspan="2">IV</th><th colspan="3">Oral</th></tr>
<tr><th>Parameter</th><th>5 mg/kg</th><th>10 mg/kg</th><th>5 mg/kg</th><th>30 mg/kg</th><th>100 mg/kg</th></tr>
<tr><td>Cmax (ng/mL)</td><td>-</td><td>-</td><td>41.86</td><td>836.13</td><td>4964.99</td></tr>
<tr><td>AUC (ng*hr/mL)</td><td>1262.93</td><td>2791.88</td><td>NC</td><td>1624.04</td><td>21652.97</td></tr>
<tr><td>F% (AUC)</td><td>NA</td><td>NA</td><td>3.2</td><td>21.4</td><td>85.7</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>0.4</td><td>0.7</td><td>NC</td><td>0.9</td><td>1.1</td></tr>
</table>
NA: not applicable, NC: not calculated; "-": not available

A single-dose PK study in the monkey using single IV dose of 3.09 mg/kg and oral doses of 5, 30, or 100 mg/kg showed low bioavailability following oral administration; concurrent administration of food decreased absorption of E7438.</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td></td><td><u>Monkeys</u>
<table>
<tr><th>Administration Route</th><th>IV</th><th colspan="3">Oral</th></tr>
<tr><th>Dose</th><th>3.09 mg/kg</th><th>5 mg/kg</th><th colspan="2">30 mg/kg</th><th>100 mg/kg</th></tr>
<tr><th>Parameter</th><td>-</td><td>Fasted</td><td>Fasted</td><td>Fed</td><td>Fasted</td></tr>
<tr><td>Cmax (ng/mL)</td><td>-</td><td>29.07</td><td>1081.41</td><td>112.9</td><td>2110.24</td></tr>
<tr><td>AUC (ng*hr/mL)</td><td>2081.01</td><td>145.36</td><td>2954.59</td><td>622.65</td><td>8420.28</td></tr>
<tr><td>F% (AUC)</td><td>-</td><td>1.9</td><td>15.3</td><td>3.2</td><td>14</td></tr>
<tr><td>$T_{1/2}$ (hr)</td><td>1.6</td><td>2.8</td><td>1.9</td><td>2.3</td><td>2.7</td></tr>
</table>
'-' = not available.</td></tr>
<tr><th colspan="2">Distribution</th></tr>
<tr><td>Study #DMPKA2012-062: In vitro blood to plasma ratio determination of E7438 in multiple species</td><td>CD-1 mice, Sprague Dawley rats, cynomolgus monkeys, and human blood spiked with 50, 500, 5000, and 50,000 ng/mL of E7438 and incubated for 30 minutes at physiological temperature resulted in slightly higher E7438 concentrations in the plasma with minimal differences between species.
<table>
<tr><th>Species</th><th colspan="4">Blood/plasma ratio</th></tr>
<tr><td>ng/mL</td><td>50</td><td>500</td><td>5000</td><td>50000</td></tr>
<tr><td>Mouse</td><td>0.53</td><td>0.53</td><td>0.63</td><td>0.87</td></tr>
<tr><td>Rat</td><td>0.62</td><td>0.61</td><td>0.67</td><td>0.78</td></tr>
<tr><td>Monkey</td><td>1.06</td><td>0.82</td><td>0.76</td><td>0.89</td></tr>
<tr><td>Human</td><td>0.77</td><td>0.71</td><td>0.71</td><td>0.96</td></tr>
</table></td></tr>
<tr><td>Study #45n-1402: E7438: Excretion mass balance, pharmacokinetics and quantitative whole-body autoradiography in male Sprague Dawley and Long-Evans rats following a single oral dose of [^{14}C] E7438</td><td>Quantitative whole-body radiography to determine tissue distribution in the male Long Evans and Sprague Dawley rats following administration of a single 50 mg/kg oral dose of [^{14}C] tazemetostat (200 µCi/kg) evaluated for up to 168 hours showed comparable distribution between the two species, with the exception of distribution to melanin containing tissues in the pigmented Long Evans rats.

The highest mean Cmax values were observed in alimentary canal, bile, urine, and liver. Tissues of the CNS were below quantifiable levels.</td></tr>
<tr><th colspan="2">Metabolism</th></tr>
<tr><td>Study #45N-1404: E7438: in vitro metabolism of [^{14}C] E7438 in cryopreserved hepatocytes of Sprague Dawley rats, New Zealand white rabbits, Cynomolgus</td><td>No human specific metabolites were detected.

Thirteen metabolites occurred in all plasma samples with three major metabolites (>10%) in human and monkey plasma samples; EPZ-6930, EPZ-6931, and EPZ034163</td></tr>
</table>

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>monkeys, and humans

Study# DMPKA2012-042: Metabolite identification</td><td></td></tr>
<tr><td colspan="2">Excretion</td></tr>
<tr><td>Study 45N-1402: E7438: Excretion mass balance, pharmacokinetics and quantitative whole-body autoradiography in male Sprague Dawley and Long-Evans rats following a single oral dose of [^{14}C] E7438

Study #11661(514N-1501): Absorption, excretion/mass balance, and radiokinetics of [^{14}C] EPZ-6438 in non-naïve male and female cynomolgus monkeys following single intravenous and oral administration</td><td>[^{14}C]-tazemetostat elimination occurred primarily through fecal excretion (rat 86%; monkey 82%) after oral (rat 50 mg/kg; monkey 50 mg/kg) or IV (monkey 5 mg/kg) administration. In humans, [^{14}C]-tazemetostat was eliminated primarily through fecal excretion with minimal excretion in the urine (<6%) after oral administration.

Elimination was completed by 24 hours in rats and 48 hours in monkeys regardless of route of administration.

Percent Administered Dose Recovered
<table><tr><th>Route of administration</th><th colspan="2">Oral</th><th colspan="2">IV</th></tr><tr><th>Route of excretion</th><th>Feces</th><th>Urine</th><th>Feces</th><th>Urine</th></tr><tr><td>Rat</td><td>86.1</td><td>8</td><td>-</td><td>-</td></tr><tr><td>Monkey</td><td>81.6</td><td>4</td><td>79.2</td><td>5.2</td></tr></table>
Percent Total Recovery Radioactivity
<table><tr><th>Route of administration</th><th>Oral</th><th>IV</th></tr><tr><th>Species</th><th>Total</th><th>Total</th></tr><tr><td>Rat</td><td>94.4</td><td>-</td></tr><tr><td>Monkey</td><td>89.2</td><td>86.6</td></tr></table></td></tr>
</table>

5.5. Toxicology

5.5.1. General Toxicology

Study #K14009: E7438: A 13-Week Oral Toxicity Study with 4-Week Recovery Period in Rats

Key Study Findings

- 25% (5/20) main toxicology group rats and 12.5% (1/8) toxicokinetic group rats died or were prematurely euthanized at the 300 mg/kg dose
- Lymphoblastic lymphoma originating from the thymus occurred in rats at the 300 and 600 mg/kg dose
  - 300 mg/kg → present in 5 females euthanized or found dead, 2 surviving females, and 1 recovery female (40% total females); 1 male found dead or euthanized, 2 surviving males (15% total males)
  - 600 mg/kg → present in 1 surviving male at 600 mg/kg (5% total males)
- Lymphoma was cause of death between Days 65 and 91 in animals at the 300 mg/kg dose level
- Target organs include lymphoid organs, bone, upper gastrointestinal tract, and kidneys at the 300 and 600 mg/kg doses

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 100, 300, 600 mg/kg once daily for 13 weeks
Route of administration:	Oral
Formulation/Vehicle:	0.5 w/v % methylcellulose with 0.1 w/v% Tween 80
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	10/sex/group main toxicity study; 6/sex/group recovery animals
Age:	8 weeks
Satellite groups/ unique design:	4/sex/group for toxicokinetic analysis
Deviation from study protocol affecting interpretation of results:	None that impacted interpretation of study results

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>300 mg/kg/day: 6 rats euthanized or found dead
<table>
<tr><th>Animal</th><th>Sex</th><th>Dose</th><th>Day</th><th>Death</th><th>Clinical signs</th></tr>
<tr><td>02M12</td><td>Male</td><td>300 mg/kg</td><td>65</td><td>Sacrificed in moribund condition</td><td rowspan="7">Note all animals exhibited the same clinical signs and had same cause of death.

Clinical signs →Emaciation, prostration, staining of nose or eye region, discoloration of eye, chromaturia

Hematology findings → Increased WBCs due to leukemic cells, decreased RBCs, hemoglobin, platelets, reticulocytes, prolonged APTT, increased erythroblast in blood smears

Cause of death → lymphoma correlated with thymic mass</td></tr>
<tr><td>02F03</td><td>Female</td><td>300 mg/kg</td><td>91</td><td>Sacrificed in moribund condition</td></tr>
<tr><td>02F05</td><td>Female</td><td>300 mg/kg</td><td>88</td><td>Sacrificed in moribund condition</td></tr>
<tr><td>02F12</td><td>Female</td><td>300 mg/kg</td><td>72</td><td>Sacrificed in moribund condition</td></tr>
<tr><td>02F16</td><td>Female</td><td>300 mg/kg</td><td>84</td><td>Sacrificed in moribund condition</td></tr>
<tr><td>06F01</td><td>Female</td><td>300 mg/kg (TK satellite group)</td><td>67</td><td>Found dead</td></tr>
</table></td></tr>
<tr><td>Clinical Signs</td><td>
<table>
<tr><th rowspan="2">Clinical sign</th><th colspan="2">100 mg/kg</th><th colspan="2">300 mg/kg</th><th colspan="2">600 mg/kg</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>Labial nodules or crust of the mouth</td><td>1/16</td><td>-</td><td>5/16</td><td></td><td>5/16</td><td>4/16</td></tr>
<tr><td>Swelling of the foot</td><td>-</td><td>-</td><td>-</td><td>-</td><td>6/16</td><td>-</td></tr>
<tr><td>Induration of the tail</td><td>-</td><td>-</td><td>-</td><td>-</td><td>5/16</td><td>-</td></tr>
<tr><td>Mass on back/neck</td><td>-</td><td>-</td><td>-</td><td>1/16</td><td>1/16</td><td>-</td></tr>
<tr><td>Shortening of lower incisors</td><td>-</td><td>-</td><td>-</td><td>-</td><td>2/16</td><td>8/16</td></tr>
</table>
'-' = no findings. Clinical signs started approximately 7 weeks into the study and continued throughout the dosing period. During the recovery period, labial nodules of the mouth, swelling of the foot, and induration of the tail remained in the mid and high dose animals. Additional noted clinical signs include decreased activity, bradypnea, and decreased feces in 2-3 rats starting on Day 77, all of which recovered.</td></tr>
<tr><td>Body Weights</td><td><u>Decreases in body weight gain</u>
300 mg/kg/day: Males (↓ 6%), Females (↓ 4%) vs. controls by Day 91; correlated with decreased food consumption in the early deaths

600 mg/kg/day: Males (↓ 18%) vs. controls by Day 91; correlated with decreased food consumption

Body weight changes recovered in all groups by end of recovery period.</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
</table>

<table>
<tr><td>Hematology</td><td>
Day 92 hematology parameters
<table>
<tr><th rowspan="2">Hematology Parameters</th><th colspan="2">100 mg/kg</th><th colspan="2">300 mg/kg</th><th colspan="2">600 mg/kg</th></tr>
<tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td>Hemoglobin</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↓13%</td><td>↓15%</td></tr>
<tr><td>MCV</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↓8%</td><td>↓6%</td></tr>
<tr><td>MCH</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↓10%</td><td>↓10%</td></tr>
<tr><td>Reticulocytes</td><td>↓6%</td><td>↓18%</td><td>↑9%</td><td>↑9%</td><td>↑64%</td><td>↑71%</td></tr>
<tr><td>Neutrophils</td><td>↑38%</td><td>-</td><td>↑190%</td><td>↓7%%</td><td>↑191%</td><td>↑33%</td></tr>
<tr><td>Monocytes</td><td>↑56%</td><td>↑40%</td><td>↑289%</td><td>↑320</td><td>↑522%</td><td>↑320%</td></tr>
<tr><td>Eosinophils</td><td>↑40%</td><td>-</td><td>↑140%</td><td>↑63%</td><td>↑80%</td><td>↑100%</td></tr>
<tr><td>Platelets</td><td>↓7%</td><td>-</td><td>↓11%</td><td>-</td><td>↓26%</td><td>↓8%</td></tr>
<tr><td>Lymphocytes</td><td>-</td><td>-</td><td>↑15%</td><td>-</td><td>-</td><td>-</td></tr>
</table>
'-' = no findings. MCV – mean corpuscular volume. MCH – mean corpuscular hemoglobin. Values are percent changes from control animals.

Findings were reversible with no notable hematology changes in recovery animals.
</td></tr>
<tr><td>Clinical Chemistry</td><td>600 mg/kg rats:
Males → 3-fold increased bilirubin compared to controls
Females → 1.7-fold increased bilirubin compared to controls

Findings were reversible with no notable clinical chemistry changes in recovery animals.</td></tr>
<tr><td>Urinalysis</td><td>600 and 300 mg/kg rats:
Males and Females→ increased turbidity

All doses:
Unequally-sized globules with dose dependent increases in quantity

Findings were reversible with no notable changes observed in recovery animals.</td></tr>
<tr><td>Gross Pathology</td><td>No findings occurred in the 100 mg/kg group.</td></tr>
</table>

	<table><tr><th>Gross Pathology Findings</th><th colspan="2">300 mg/kg</th><th colspan="2">600 mg/kg</th></tr><tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td>Thymus</td><td></td><td></td><td></td><td></td></tr><tr><td>Mass</td><td>2 (1)</td><td>1 (4)</td><td>-</td><td>-</td></tr><tr><td>Small</td><td>1</td><td>-</td><td>3</td><td>3</td></tr><tr><td>Lymph node</td><td></td><td></td><td></td><td></td></tr><tr><td>Enlarged</td><td>- (2)</td><td>- (6)</td><td>1</td><td>-</td></tr><tr><td>Spleen</td><td></td><td></td><td></td><td></td></tr><tr><td>Enlarged</td><td>1 (1)</td><td>- (5)</td><td>-</td><td>-</td></tr><tr><td>Raised area</td><td>-</td><td>1</td><td>-</td><td>-</td></tr><tr><td>Ovaries</td><td></td><td></td><td></td><td></td></tr><tr><td>Enlarged</td><td>na</td><td>- (2)</td><td>na</td><td>-</td></tr><tr><td>Liver</td><td></td><td></td><td></td><td></td></tr><tr><td>Enlarged</td><td>-</td><td>-(1)</td><td>-</td><td>-</td></tr><tr><td>Incisor</td><td></td><td></td><td></td><td></td></tr><tr><td>Short</td><td>-</td><td>-</td><td>2</td><td>5</td></tr><tr><td>Gingiva</td><td></td><td></td><td></td><td></td></tr><tr><td>Swelling</td><td>-</td><td>-</td><td>2</td><td>9</td></tr><tr><td>Lips of mouth</td><td></td><td></td><td></td><td></td></tr><tr><td>Nodule</td><td>1</td><td>-</td><td>3</td><td>-</td></tr><tr><td>Foot</td><td></td><td></td><td></td><td></td></tr><tr><td>Nodule</td><td>-</td><td>-</td><td>1</td><td>-</td></tr><tr><td>Swelling</td><td>-</td><td>-</td><td>3</td><td>1</td></tr><tr><td>Subcutis</td><td></td><td></td><td></td><td></td></tr><tr><td>Mass</td><td>-</td><td>1</td><td>1</td><td>-</td></tr><tr><td>Tail</td><td></td><td></td><td></td><td></td></tr><tr><td>Induration</td><td>-</td><td>-</td><td>2</td><td>-</td></tr><tr><td>Adrenal</td><td></td><td></td><td></td><td></td></tr><tr><td>Enlarged</td><td>-</td><td>-</td><td>1</td><td>-</td></tr></table> na = not applicable. '-' = no findings. ( )= number found dead or moribund animals. Lymph node includes submaxillary, mesenteric, iliac, and inguinal.
Organ Weights	Increased organ weights correlated with metastasis of lymphoma in spleen, liver, and ovary. Additional lymphoma metastases locations are listed in **Histopathology**. <table><tr><th rowspan="2">Organ</th><th colspan="2">100 mg/kg</th><th colspan="2">300 mg/kg</th><th colspan="2">600 mg/kg</th></tr><tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td colspan="7">Terminal Necropsy*</td></tr><tr><td>Spleen</td><td>↑5%</td><td>↑8%</td><td>↑29%</td><td>↑27%</td><td>↑43%</td><td>↑27%</td></tr><tr><td>Liver</td><td>↑5%</td><td>↑6%</td><td>↑19%</td><td>↑11%</td><td>↑28%</td><td>↑26%</td></tr><tr><td>Adrenal</td><td>↑9%</td><td>-</td><td>↑9%</td><td>-</td><td>↑82%</td><td>↑13%</td></tr><tr><td>Kidney</td><td>↑2%</td><td>↓5%</td><td>↑2%</td><td>↓5%</td><td>↑16%</td><td>-</td></tr><tr><td>Ovaries</td><td>NA</td><td>↑6%</td><td>NA</td><td>↑33%</td><td>NA</td><td>↓3%</td></tr><tr><td colspan="7">Recovery Necropsy</td></tr><tr><td>Spleen</td><td>NA</td><td>NA</td><td>↑28%</td><td>↑9%</td><td>↑41%</td><td>↑18%</td></tr></table> *Data from moribund/found dead animals not included in analyses. NA – Not available. Values are organ weight relative to body weight percent changes compared to controls.
Histopathology Adequate battery: Yes	<u>*Lymphoma Findings*</u> • **300 mg/kg:** 3 males / 7 females / 1 recovery female • **600 mg/kg:** 1 male • Metastases occurred in several organs

	Sex / **Organ Finding Dose (mg/kg)** / **No. of animals examined** / Thymus / Lymphoblastic Lymphoma **Male**: 0: 14[6]; 100: 14; 300: 14(1)[5]; 600: 14[6] Lymphoblastic Lymphoma: 0[0]; 0; 2(1)[0]; 1[0] **Female**: 0: 14[6]; 100: 14; 300: 11(5)[4]; 600: 14[6] Lymphoblastic Lymphoma: 0[0]; 0; 2(5)[1]; 0[0] (): found dead/ moribund sacrificed animals. []: recovery sacrificed animals. (Excerpted from Study #K14009) **Characterized by:** • Proliferation of large lymphoblastic cells with scant cytoplasm and round to irregular nuclei • Correlated with grossly observed thymic mass • Immunohistochemistry indicated strongly positive for CD3, positive for CD8, and negative for CD20 • Metastases occurred to various tissues and organs ○ Peri-thymic adipose tissue, heart, spleen, lymph nodes, bone marrow, bone, liver, GI tract, ovary, and eyes *See* Table 8.
Toxicokinetics	**E7438** • Exposure increased in a more than dose-proportional manner in males and females • Higher exposure occurred in females compared to males due to lower metabolism in females

Dose (mg/kg/day)	100		300		600	
Sex	M	F	M	F	M	F
Day 1						
Cmax (ng/mL)	1932	9380	5136	17455	7127	34243
AUC0-24h (ng*h/mL)	6985	40363	35382	160969	74737	408016
Tmax(h)	2	2	3	3	4	4
Day 91						
Cmax (ng/mL)	4311	13488	10018	20720	19082	24423
AUC0-24h (ng*h/mL)	18033	55037	99546	166305	285998	286031
Tmax(h)	2	2	4	2	8	5

Metabolite ER-897387-00
- De-ethylated metabolite of E7438
- Higher exposure occurred in males compared to females

Dose (mg/kg/day)	100		300		600	
Sex	M	F	M	F	M	F
Day 1						
Cmax (ng/mL)	4842	1007	11778	2145	15633	3824
AUC0-24h (ng*h/mL)	15741	3752	64102	21705	235642	61002
Tmax(h)	2	2	3	3	4	8
Day 91						
Cmax (ng/mL)	5232	2398	10017	4378	9190	7721
AUC0-24h (ng*h/mL)	22236	8766	116254	39836	134816	103642
Tmax(h)	2	2	6	2	8	6

Table 8: Rat Histopathology

Sex		Males			Females		
Dose (mg/kg/day)		100	300	600	100	300	600
# main group (found dead/moribund), # recovery		14,-	14,5	14,6	14,-	14,4	14,6
Thymus							
Lymphoid depletion	Sight		2	11,1		5	14
	Moderate			1			
	Marked			1			
Lymphoma, lymphoblastic	NA		3	1		7,1	
Spleen							
Lymphoid depletion	Slight		5	11		4	11,1
	Moderate			2			
Increased extramedullary hematopoiesis	Slight		1	4			
Abscess	Slight			1			
Submaxillary lymph node							
Lymphoid depletion	Slight			1			3
	Moderate		1				
Femur							
Trabecular formation	Slight		1,1	9,4		2,4	6,4
	Moderate			2,2			1,1
Sternum							
Trabecular formation	Slight		2,1	7,3		7,3	8,2
	Moderate			3,3			4,4
Bone Marrow							
Increased hematopoiesis			1	4		1	-,2
Incisor							
Dysplasia	Slight			4			5,1
	Moderate			2,4			5,5
Alveolar bone							
Increased bone formation	Slight			4,4			10,6
Stomach							
Erosion/ulcer	Slight			1		1	
Regeneration, mucosa	Slight		4	3		5	7
	Moderate			5			1
Duodenum							
Hyperplasia, crypt	Slight		1	2			1
Kidney							

Sex		Males			Females		
Dose (mg/kg/day)		100	300	600	100	300	600
# main group (found dead/moribund), # recovery		14,-	14,5	14,6	14,-	14,4	14,6
Granular material, pelvis	Slight			1		1	3
Lips of mouth							
Abscess, subcutis	Slight	1	1				-,1
	Moderate			2			
	Marked			1			
Foot							
Abscess	Slight			1		1	
	Moderate			1		1	2
Inflammatory cell infiltration	Slight			1,1			
Tail							
Abscess/folliculitis	Slight			1			
Inflammatory cell infiltration	Slight			1			
Subcutis							
Abscess	Marked			1			
Mammary gland							
Acinar atrophy	Slight			5			
	Moderate			1			
Eyes							
Retinal dysplasia			-,1				
Lung							
Foamy cell accumulation, alveolar, focal	Slight		2	7,3		1,1	3
Inflammatory cell infiltration, focal	Slight			1			
Adrenals							
Cortical hypertrophy	Slight			2			
Ovaries							
Atrophy	Slight						1
Uterus							
Atrophy	Slight						4
Vagina							
Atrophy, epithelium	Slight					1	6

No findings occurred in control animals. NA-not available

Study title/ number: E7438: A 13-Week Oral Toxicity Study followed by a 28-day recovery period in cynomolgus monkeys

Key Study Findings

- 1/6 females at 600 mg/kg sacrificed in moribund condition on Day 83
- AST, ALT, ALP, and triglycerides increased in animals treated at 300 and 600 mg/kg
- Target organs included liver, lymphoid tissue, GI tract, and kidney
- Of concern was bile duct hyperplasia at terminal and recovery sacrifices in the mid and high dose monkeys

Conducting laboratory and location (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 100, 300, 600 mg/kg/day divided into two daily doses (BID 50, 150, 300 mg/kg)) for 13 weeks
Route of administration:	Oral via gavage
Formulation/Vehicle:	0.5 w/v % methylcellulose with 0.1 w/v% Tween 80 in deionized water
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	6/sex/control, mid, and high dose groups; 4/sex/low dose group
Age:	2.5-6.1 years
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None that impacted study outcome

Observations and Results: changes from control

<table>
<tr><th>Parameters</th><th>Major findings</th></tr>
<tr><td>Mortality</td><td>600 mg/kg female (1/6):
Sacrificed in moribund condition on Day 83
Clinical signs included decreased activity, cold to touch, hunched posture, and shivering/tremor
Histopathology changes occurred in spleen, thymus, lymph nodes, liver, kidney, stomach, lung, and bone marrow</td></tr>
<tr><td>Clinical Signs</td><td>Dose-dependent emesis and abnormal (soft/mucoid, discolored) feces</td></tr>
<tr><td>Body Weights</td><td>Unremarkable</td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
<tr><td>Hematology</td><td>Unremarkable</td></tr>
<tr><td>ECG</td><td>600 mg/kg/day
RR interval shortening occurred compared to controls</td></tr>
<tr><td>Clinical Chemistry</td><td>Dose dependent increases in AST, ALT, ALP, and triglycerides occurred
<table>
<tr><th>Dose
Parameter Sex</th><th colspan="2">100 mg/kg/day</th><th colspan="2">300 mg/kg/day</th><th colspan="2">600 mg/kg/day</th></tr>
<tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td colspan="7">Terminal animals</td></tr>
<tr><td>AST</td><td>-</td><td>1.2</td><td>2.1</td><td>3.7</td><td>2.6</td><td>3.7</td></tr>
<tr><td>ALT</td><td>-</td><td>-</td><td>10.4</td><td>2.7</td><td>15.6</td><td>17.7</td></tr>
<tr><td>ALP</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.8</td><td>1.9</td></tr>
<tr><td>Triglycerides</td><td>-</td><td>2.1</td><td>-</td><td>2.1</td><td>2.6</td><td>2.1</td></tr>
<tr><td colspan="7">Recovery animals</td></tr>
<tr><td>AST</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>2.8</td></tr>
<tr><td>ALT</td><td>-</td><td>-</td><td>-</td><td>-</td><td>10</td><td>10</td></tr>
<tr><td>ALP</td><td>-</td><td>-</td><td>-</td><td>-</td><td>1.4</td><td>1.5</td></tr>
</table></td></tr>
</table>

<table>
<tr><td></td><td>Data is fold increase compared to pre-dose levels.</td></tr>
<tr><td>Urinalysis</td><td>Unremarkable</td></tr>
<tr><td>Gross Pathology</td><td>300 mg/kg
4/8 animals had discoloration of the liver and prominent lobular architecture
Correlated with microscopic findings of hypertrophy of centrilobular hepatocytes, Kupffer cell hypertrophy/pigmentation, and bile duct hyperplasia
1/4 recovery animals had discoloration of the liver, which correlated with Kupffer cell pigmentation and bile duct hyperplasia
600 mg/kg
6/7 animals had discoloration of the liver and prominent lobular architecture
Correlated with microscopic findings of hypertrophy of centrilobular hepatocytes, Kupffer cell hypertrophy/pigmentation, and bile duct hyperplasia</td></tr>
<tr><td>Organ Weights</td><td>Kidney and liver weights increased at all dose levels compared to controls.<table><tr><th rowspan="2">Organ</th><th colspan="2">100 mg/kg</th><th colspan="2">300 mg/kg</th><th colspan="2">600 mg/kg</th></tr><tr><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr><tr><td colspan="7">Terminal Necropsy</td></tr><tr><td>Kidney</td><td>23%</td><td>-</td><td>23%</td><td>-</td><td>77%</td><td>-</td></tr><tr><td>Liver</td><td>48%</td><td>28%</td><td>57%</td><td>23%</td><td>161%</td><td>62%</td></tr></table>Values are percent change compared to controls.
Liver weights remained increased after recovery in males and females at 600 mg/kg.</td></tr>
<tr><td>Histopathology
Adequate battery: Yes</td><td><table><tr><td></td><td>Sex</td><td colspan="3">Males</td><td colspan="3">Females</td></tr><tr><td></td><td>Dose (mg/kg/day)</td><td>100</td><td>300</td><td>600</td><td>100</td><td>300</td><td>600</td></tr><tr><td></td><td># main group, # recovery,(found dead/moribund)</td><td>4,-</td><td>4,2</td><td>4,2</td><td>4,-</td><td>4,2</td><td>3,2,(1)</td></tr><tr><td>Thymus</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Lymphoid depletion</td><td>Slight</td><td></td><td></td><td>1</td><td></td><td>2,1</td><td>1</td></tr><tr><td></td><td>Moderate</td><td></td><td>3</td><td></td><td></td><td>1</td><td>2</td></tr><tr><td></td><td>Marked</td><td></td><td></td><td>2</td><td></td><td></td><td></td></tr><tr><td>Liver</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Kupffer cell hypertrophy/pigmentation</td><td>Sight</td><td></td><td>4,2</td><td>-,1</td><td></td><td>3,1</td><td>2</td></tr><tr><td></td><td>Moderate</td><td></td><td></td><td>2,1</td><td></td><td></td><td>1,2</td></tr><tr><td></td><td>Marked</td><td></td><td></td><td>2</td><td></td><td></td><td></td></tr><tr><td>Hypertrophy, hepatocytes, centrilobular</td><td>Slight</td><td></td><td>2</td><td>4</td><td></td><td>2</td><td>3</td></tr><tr><td>Hyperplasia, bile ducts</td><td>Slight</td><td></td><td>3</td><td></td><td></td><td>2</td><td>2,1</td></tr><tr><td></td><td>Moderate</td><td></td><td>1</td><td>2,1</td><td></td><td></td><td>1,1</td></tr><tr><td></td><td>Marked</td><td></td><td></td><td>2</td><td></td><td></td><td></td></tr><tr><td>Spleen</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Decreased germinal centers</td><td>Slight</td><td></td><td>4,1</td><td>4</td><td></td><td>3</td><td>3</td></tr><tr><td>Submaxillary lymph node</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Decreased germinal center</td><td>Slight</td><td></td><td>4</td><td>4,1</td><td></td><td>2</td><td>3</td></tr><tr><td>Mesenteric lymph node</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Decreased germinal center</td><td>Slight</td><td></td><td>4</td><td>4</td><td></td><td>4,1</td><td>3,1</td></tr><tr><td>Lymphoid hyperplasia</td><td>Slight</td><td></td><td></td><td>1</td><td></td><td></td><td></td></tr><tr><td>Kidneys</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Pigmentation, tubular epithelial cells</td><td>Slight</td><td></td><td></td><td>2</td><td></td><td></td><td></td></tr><tr><td>Glomerulopathy</td><td>Slight</td><td></td><td></td><td>2</td><td></td><td></td><td>1</td></tr><tr><td>Pyelonephritis</td><td>Slight</td><td></td><td></td><td></td><td></td><td></td><td>-,-,(1)</td></tr><tr><td>Adrenal</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Cortical hypertrophy, bilateral</td><td>Slight</td><td></td><td>1</td><td>3</td><td></td><td></td><td>1</td></tr><tr><td>Ectopic liver</td><td>NA</td><td></td><td></td><td>1</td><td></td><td></td><td>1</td></tr><tr><td>Hemorrhage, focal</td><td>Slight</td><td></td><td></td><td></td><td>1</td><td></td><td></td></tr><tr><td>Lung</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Inflammatory cell infiltrate</td><td>Slight</td><td></td><td></td><td>3</td><td></td><td></td><td>1</td></tr><tr><td>Thrombosis</td><td>Slight</td><td></td><td></td><td>1</td><td></td><td></td><td></td></tr><tr><td>Epididymides</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Inflammatory cell infiltrates</td><td>Slight</td><td></td><td></td><td>1</td><td></td><td></td><td></td></tr><tr><td>Stomach</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Hemorrhage, glandular stomach</td><td>Slight</td><td></td><td></td><td></td><td></td><td>1</td><td></td></tr><tr><td>Regenerative hyperplasia, glandular stomach</td><td>Slight</td><td></td><td></td><td></td><td></td><td></td><td>-,-,(1)</td></tr><tr><td>Rectum</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Ulcer</td><td>Slight</td><td></td><td></td><td></td><td></td><td></td><td>-,-,(1)</td></tr></table>No findings occurred in control animals.</td></tr>
</table>

Toxicokinetics

E7438

- Day 1 Cmax in females did not increase with an increase in dose between 300 and 600 mg/kg
- Day 91 exposure increased as dose increased

Dose (mg/kg/day)	100		300		600	
Sex	M	F	M	F	M	F
Day 1						
Cmax (ng/mL)	483	500	2481	1998	4651	1611
$AUC_{0\text{-}12h}$ (ng*h/mL)	1560	1377	9707	7118	23875	8070
Tmax(h)	2	1	3	2	4	2
Day 91						
Cmax (ng/mL)	147	165	596	725	1297	1241
$AUC_{0\text{-}12h}$ (ng*h/mL)	641	599	3136	3574	8116	6215
Tmax(h)	1.5	1.5	3	2	4	4

Metabolite ER-897387-00

- De-ethylated metabolite of E7438

Dose (mg/kg/day)	100		300		600	
Sex	M	F	M	F	M	F
Day 1						
Cmax (ng/mL)	1620	1988	5835	4839	7397	3767
$AUC_{0\text{-}12h}$ (ng*h/mL)	4815	4593	25036	18033	47766	18889
Tmax(h)	2	1	3	2	3	2
Day 91						
Cmax (ng/mL)	859	1125	3427	3668	4084	4507
$AUC_{0\text{-}12h}$ (ng*h/mL)	3154	2877	20238	18072	31036	26806
Tmax(h)	2	2	4	3	4	4

General toxicology; additional studies

In the 4-week acute oral toxicity study in adult Sprague Dawley rats (Study #K12004) treated with 100, 300, or 1000 mg/kg E7438.Target organs included stomach (erosion/ulceration and mucosal hyperplasia), jejunum (crypt hyperplasia), ileum, kidney, bone marrow, lymphoid tissues (lymphoid depletion), and bone (osteoblast hyperplasia and new trabecular bone formation). Changes in hematology and clinical chemistry parameters were similar to those observed in the 13-week chronic toxicology study in rats reviewed in detail in Section 5.5.1.

In the 4-week acute oral toxicity study in adult cynomolgus monkeys (Study #20024293) treated with 100, 300, of 1000/600 mg/kg/day. Moribund animals at 1000 mg/kg/day had decreased muscle tone and changes in the gastrointestinal tract at necropsy. At 1000/600 mg/kg/day there were test article-related changes in the liver and kidney, and at ≥300 mg/kg/day there

was dose-dependent lymphoid depletion. Target organs at all dose levels included the GI tract and liver. Findings in the 4-week study were consistent with findings in the 13-week study.

5.5.2. Genetic Toxicology

Study #9600848: E7438: Reverse mutation assay in bacteria

Key findings

- No substantial increases in revertant colony numbers occurred in any strain at any dose level, in either the presence or absence of S9.

Summary

The mutagenicity potential of E7438 was tested in an GLP-compliant study using the Ames assay with the pre-incubation method. E7438 at concentrations 0, 2.29, 6.86, 20.6, 61.7, 185, 556, 1667, and 5000 µg/plate was incubated with and without activation agent S9 mix in the following *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2 uvrA. Precipitation occurred starting at concentrations equal to or greater than 556 µg/plate, in the absence of S9, and at 5000 µg/plate in the presence of S9. DMSO served as the negative control. The study was considered valid: cytotoxicity (reduction in the number of revertants) was observed at dose level of 5000 µg/plate of E7438 for strain TA1535, in the presence of S9, and for strain TA1537 in the absence and presence of S9; positive controls demonstrated expected mutagenicity. E7438 was negative for the induction of mutagenicity in this in vitro assay.

Study #9600891: EPZ-6438 (E7438): In vitro mammalian cell micronucleus test in human peripheral blood lymphocytes

Key findings

- No substantial increases in the proportion of micronucleated binuclear cells occurred following exposure to E7438 in either the absence or presence of S9 mix.

Summary

Duplicate cultures of human peripheral blood lymphocytes were treated with E7438 for 4 hours in the absence and presence of S9 mix, and for 24 hours in the absence of S9 mix. The concentrations of E7438 used for the initial assay were 0 (vehicle), 1, 2, 4, 8, 16, 32, 64, 128, 256, and 500 µg/mL. Due to excessive cytotoxicity observed in the initial assay in the 4-hour and the 24-hour treatment regimes, in the presence and absence of S9 mix, respectively, a supplemental assay was performed using concentrations of 0 (vehicle), 125, 145, 165, 185, 205, 225, and 250 µg/mL for the 4-hour treatment regime in presence of S9 mix, and 0 (vehicle), 50, 60, 70, 80, 90, 100, and 110 µg/mL for the 24-hour treatment regime in absence of S9 mix. Mitomycin C and cyclophosphamide served as the positive controls. The study was considered

valid: the vehicle and positive controls performed as expected and a minimum of three non-toxic concentrations were used.

Study #9800206: EPZ-6438 (E7438): Micronucleus assay in rats after oral administration

Key findings

- No substantial increases in micronuclei occurred following in rat bone marrow following exposure to E7438.

Summary

The potential of E7538 to induce micronuclei in rat bone marrow was investigated by dosing rats via oral gavage 24 hours apart 2 times at doses of 500, 1000, or 2000 mg/kg. The vehicle control was 0.5% (w/v) methylcellulose and 0.1% (v/v) TWEEN® 80 in water and cyclophosphamide served as the positive control. A total of 2000 immature erythrocytes per animal were examined for the presence of micronuclei alone with total erythrocyte population. The study was considered valid; positive and negative controls performed as expected; a valid number of erythrocytes was assessed per animal. No mortalities occurred during the study and clinical signs included red skin or forepaws, red staining on fur, muzzle and periorbital fur in the 2000 mg/kg groups. Slight reductions in body weights occurred in females at 1000 mg/kg and males and females at 2000 mg/kg. No increases in micronucleated immature erythrocytes or micronucleated mature erythrocytes occurred at any dose level tested.

5.5.3. Carcinogenicity

Neither submitted nor required. Tazemetostat caused malignancies in nonclinical (rat) toxicology studies and secondary malignancies in clinical trials.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Neither submitted nor required.

Embryo-Fetal Development

Study title/ number: An Embryo-Fetal Development Study of Tazemetostat by Oral Gavage in Rats

Key Study Findings

- 200 mg/kg/day treated dams had 23% decreased body weight gain compared to controls
- Fetal weight from the 200 mg/kg dams was decreased by 25-32%
- Increased post-implantation loss at 200 mg/kg
- Dose-dependent increases in skeletal and visceral malformations occurred, including malformations in major organs and great vessels

- Exposure to tazemetostat was much higher in non-pregnant rats than pregnant rats; at 100 mg/kg/d, exposure was 55037 ng*hr/mL compared to 42700 ng*hr/mL in pregnant animals

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 50, 100, 200 mg/kg
Daily from days 7-17 of gestation

Route of administration: Oral gavage

Formulation/Vehicle: 0.5% (w/v) methylcellulose (MC) and 0.1% (w/v) Tween® 80 in reverse osmosis (RO) deionized water

Species/Strain: Sprague Dawley (Crl:CD) rats

Number/Sex/Group: 20/main study group; 6/toxicokinetic group

Satellite groups: None

Study design: Time-mated rats were treated once daily oral gavage from Days 7 to 17 post coitum; Day of mating was designated day of gestation (GD) 0

Deviation from study protocol affecting interpretation of results: None that impacted study interpretation

Observations and Results

Parameters	
Mortality	None
Clinical Signs	Unremarkable
Body Weights	**200 mg/kg** Decreased weight gain between GD 7-21 of 23% compared to controls

Necropsy findings – Cesarean Section Data

	0	**50 mg/kg**	**100 mg/kg**	**200 mg/kg**
Pregnancy index (%)	100%	100%	95%	100%
Number of females with viable fetuses for examination on GD21	20	20	19	20
Number pregnant	20	20	19	20
Number not pregnant	0	0	1	0
Mean corpora lutea	14	13.25	13.05	13.70
Mean implantation sites	12.95	12.55	12.74	13.30
Mean % preimplantation loss	8.4	4.3	2.2	2.9
Mean% postimplantation loss	4.0	2.7	2.5	19.7
Mean litter size	12.4	12.2	12.42	10.8

	Mean early resorptions	0.55	0.3	0.26	1.6
	Mean late resorptions	0	0.05	0.05	0.9
	Fetal weight changes relative to controls				
	Male	6.227 g	↓0.3%	↓0.4%	↓25%
	Female	5.968 g	↓1.4%	↓4.4%	↓32%
Necropsy findings Offspring	• Skeletal malformations occurred in fetuses from the 100 and 200 mg/kg treated dams • Skeletal variations occurred in fetuses from dams treated at ≥50 mg/kg and fell outside historical control values • Visceral (vascular) malformations were limited to one fetus in the 100 mg/kg group; relationship to tazemetostat was unclear See Table 9 for detailed findings				

Table 9: Rat Fetal Necropsy Findings

Dose	0	50mg/kg	100mg/kg	200mg/kg
Gross pathology				
Number of Fetuses/Litters Evaluated	248/20	244/20	236/19	216/20
# of fetuses affected (%)/ # of liters affected (%)				
Entire body, subcutaneous edema-generalized-**malformation**	0	0	0	1(0.5)/1(5)
Head, domed-**malformation**	0	0	0	7(3.2)/4(20)
Forepaw, small-**malformation**	0	0	0	2(0.9)/1(5)
Forepaw, absent digit-**malformation**	0	0	0	1 (0.5)/1(5)
Tail, short-**malformation**	0	0	0	4(1.9)/4(20)
Total gross malformations				
Number of fetuses (%)/number of litters (%)	-	-	-	15(6.9)/8(40)
Visceral variants/malformations				
Number of Fetuses/Litters Evaluated	118/20	117/20	114/19	104/20
Aorta, malpositioned-**malformation**	0	0	1(0.9)/1(5.3)	0
Carotid artery, malpositioned-variation	0	0	1(0.9)/1(5.3)	0
Ductus arteriosus, patent-**malformation**	0	0	1(0.9)/1(5.3)	0
Innominate artery, absent-variation	0	0	1(0.9)/1(5.3)	0
Subclavian artery origin, malpositioned-variation	0	0	1(0.9)/1(5.3)	0
Total visceral malformations				

Dose	0	50mg/kg	100mg/kg	200mg/kg
Gross pathology				
Number of fetuses (%)/number of litters (%)	0	0	1(0.9)/1(5.3)	0
Skeletal variants				
Number of Fetuses/Litters Evaluated	130/20	127/20	122/19	112/20
Forelimb				
Digits, short-malformation	0	0	0	3(2.7)/1(5)
Forepaw phalanges, absent-**malformation**	0	0	0	3(2.7)/1(5)
Metacarpal, absent-**malformation**	0	0	0	3(2.7)/1(5)
Pelvis				
Pelvic girdle, ischium, incomplete ossification-variation	0	0	0	1(0.9)/1(5)
Rib				
Absent-**malformation**	0	0	33(27)/15(78.9)	12(10.7)/6(30)
Misshapen-variation	0	0	0	21(18.8)/11/(55)
Short-variation	3(2.3)/2(10)	29(22.8)/11(55)	88(72.1)/19(100)	34(30.4)/13/(65)
Skull				
Exoccipital, fused-variation	0	0	0	89(79.5)/18(90)
Exoccipital, misshapen-variation	0	0	0	7(6.3)/3(15)
Parietal, incomplete ossification-variation	1(0.8)/1(5)	1(0.8)/1(5)	0	0
Squamosal, incomplete ossification-variation	1(0.8)/1(5)	1(0.8)/1(5)	0	0
Supraoccipital, absent-malformation	0	0	0	1(0.9)/1(5)
Supraoccipital, incomplete ossification-variation	0	0	0	36(31.3)/16(80)
Suture bone, present-variation	0	2(1.6)/1(5)	43(35.2)/13(68.4)	110(98.2)/20(100)
Skull, zygomatic arch, incomplete ossification-variation	1(0.8)/1(5)	1(0.8)/1(5)	1(0.8)/1(5.3)	0
Sternebrae				
Asymmetric-variation	0	2(1.6)/2(10)	1(0.8)/1(5.3)	4(3.6)/4(20)
Bipartite ossification-variation	0	1(0.8)/1(5)	1(0.8)/1(5.3)	14(12.5)/10(50)
Fused-variation	0	0	0	2(1.8)/2(10)
Misshapen-variation	1(0.8)/1(5)	0	1(0.8)/1(5.3)	27(24.1)/13(65)
Supernumerary rib				
Cervical, full-variation	0	0	49(40.2)/16(84.2)	15(13.4)/4(20)
Cervical, short-variation	1(0.8)/1(5)	18(14.2)/12(60)	68(55.7)/18(94.7)	7(6.3)/4/20)
Vertebra				
Cervical arch, fused-**malformation**	0	0	0	7(6.3)/3(15)
Cervical arch, incomplete ossification-variation	0	0	0	36(32.1)/15(75)
Cervical arch, misshapen-variation	1(0.8)/1(5)	12(9.4)/9(45)	59(48.4)/17(89.5)	68(60.7)/17(85)
Cervical centrum, bipartite ossification-variation	0	0	0	7(6.3)/6(30)

Dose	0	50mg/kg	100mg/kg	200mg/kg
Gross pathology				
Cervical centrum, unilateral ossification-variation	0	0	0	1(0.9)/1(5)
Lumbar arch, small-variation	0	0	1(0.8)/1(5.3)	0
Lumbar centrum, bipartite ossification-variation	0	0	0	17(15.2)/13(65)
Lumbar centrum, unilateral ossification-variation			1(0.8)/1(5.3)	
Lumbar vertebra, fused-**malformation**	0	0	0	2(1.8)/1(5)
Sacral vertebra, fused-**malformation**	0	0	0	1(0.9)/1(5)
Thoracic centrum, bipartite ossification-variation	3(2.3)/3(15)	6(4.7)/3(15)	11(9)/9(47.4)	65(58)/20(100)
Thoracic centrum, fused-**malformation**	0	0	0	1(0.9)/1(5)
Thoracic centrum, incomplete ossification-variation	0	0	0	1(0.9)/1(5)
Thoracic vertebra, absent-**malformation**	0	0	16(13.1)/10(52.6)	9(8)/4(20)
Total Skeletal malformations/variations				
Number of fetuses (%)/number of litters (%)	10(7.7)/8(40)	57(44.9)/20(100)	121(99.2)/19(100)	112(100)/20(100)

Toxicokinetics

Maternal Toxicokinetics

Dose (mg/kg/day)	50		100		200	
	tazemetostat	EPZ-6930	tazemetostat	EPZ-6930	tazemetostat	EPZ-6930
Day 7						
Cmax (ng/mL)	2770	224	4680	431	8210	1140
AUC_{0-t} (ng*h/mL)	8350	763	39600	3370	114000	15300
Tmax(h)	0.5	0.5	1	1	2	8
Day 17						
Cmax (ng/mL)	2190	287	3470	427	8850	1700
AUC_{0-t} (ng*h/mL)	14300	2400	42700	6200	96000	22600
Tmax(h)	1	1	1	8	4	4

Study #20097366: An Embryo-Fetal Development Study of Tazemetostat by Oral (Stomach Tube) Administration in Rabbits

Key Study Findings

- Maternal body weight gain decreased by 11% in the 400 mg/kg animals compared to controls
- Significantly increased post implantation loss occurred at 400 mg/kg

- Dose dependent malformations occurred at doses ≥100 mg/kg including malformations in the skeleton and major organs including heart and major vessels

Conducting laboratory and location: (b) (4)

GLP compliance:

Methods

Dose and frequency of dosing:	0, 100, 200, 400 mg/kg once daily on Days 7-19 of gestation (GD)
Route of administration:	Oral via stomach tube
Formulation/Vehicle:	0.5% (w/v) methylcellulose (MC) and 0.1% (w/v) Tween® 80 in reverse osmosis (RO) deionized water
Species/Strain:	New Zealand White female rabbits
Number/Sex/Group:	20/main study group; 3/toxicokinetic group
Satellite groups:	None
Study design:	Time-mated rabbits were treated once daily oral gavage from Days 7 to 19 post coitum; Day of mating was designated day of gestation (GD) 0
Deviation from study protocol affecting interpretation of results:	None that impacted study interpretation

Observations and Results

Parameters	Major findings
Mortality	**Control** • 2 animals, 1 found dead, 1 unscheduled euthanasia on DG10 and 16, respectively • Cause of death was intubation error due to findings of spongy lung lobes • No additional clinical signs **100 mg/kg** • 1 animal found dead on GD 11 • Cause of death was intubation error due to findings of spongy lung lobes • No additional clinical signs
Clinical Signs	No notable clinical signs in animals that carried to term. *Abortions* **Control** • One animal aborted on GD26 and subsequently euthanized

<table>
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Clinical signs included thin appearance, ungroomed coat, and abnormal fecal output
Body weight decreased 27% between GDs 18-26
No abnormalities in maternal necropsy
9 fetuses→no abnormalities detected at external or visceral examination

400 mg/kg

One animal aborted on GD 27 and was subsequently euthanized
Body weight decrease of 13% between GDs13-25
No abnormalities at maternal necropsy
8 fetuses + 1 late resorption→No abnormalities in external examination
Visceral and skeletal examinations detected findings consistent with the term fetuses in the 400 mg/kg dose group

</td></tr>
<tr><td>Body Weights</td><td>400 mg/kg

Decreased body weight gains of 11% between GD 7-20 during dosing
Weight was comparable to controls after non-dosing period

</td></tr>
<tr><td>Necropsy findings Cesarean Section Data</td><td>
<table>
<tr><th></th><th>0</th><th>100 mg/kg</th><th>200 mg/kg</th><th>400 mg/kg</th></tr>
<tr><td>Pregnancy index (%)</td><td>100%</td><td>95%</td><td>100%</td><td>95%</td></tr>
<tr><td>Number of females with viable fetuses for examination on GD29</td><td>17</td><td>18</td><td>20</td><td>18</td></tr>
<tr><td>Number pregnant</td><td>20</td><td>19</td><td>20</td><td>19</td></tr>
<tr><td>Number not pregnant</td><td>0</td><td>1</td><td>0</td><td>0</td></tr>
<tr><td>All dead or resorbed</td><td>2</td><td>1</td><td>0</td><td>1</td></tr>
<tr><td>Early euthanasia</td><td>3</td><td>1</td><td>0</td><td>1</td></tr>
<tr><td>Mean corpora lutea</td><td>10.1</td><td>10</td><td>9.8</td><td>10.2</td></tr>
<tr><td>Mean implantation sites</td><td>9.9</td><td>9.3</td><td>9.3</td><td>9.8</td></tr>
<tr><td>Mean % preimplantation loss</td><td>1.81</td><td>6.93</td><td>7.5</td><td>4.07</td></tr>
<tr><td>Mean% postimplantation loss</td><td>1.08</td><td>2.77</td><td>5.69</td><td>23.41</td></tr>
<tr><td>Mean litter size</td><td>9.8</td><td>9.1</td><td>8.7</td><td>7.5</td></tr>
<tr><td>Mean early resorptions</td><td>0.1</td><td>0.2</td><td>0.3</td><td>1.5</td></tr>
<tr><td>Mean late resorptions</td><td>0</td><td>0</td><td>0.3</td><td>0.8</td></tr>
<tr><td colspan="5">Fetal weight change relative to controls</td></tr>
<tr><td>Male</td><td>41.45 g</td><td>↑3.9%</td><td>↓1.2%</td><td>↓0.2%</td></tr>
<tr><td>Female</td><td>39.56 g</td><td>↑5.8%</td><td>↑8.6%</td><td>↑0.9%</td></tr>
</table>
</td></tr>
<tr><td>Necropsy findings Offspring</td><td>

Fetal skeletal malformations occurred at ≥200 mg/kg/day and variations at ≥100 mg/kg/day
Visceral malformations and external abnormalities occurred at 400 mg/kg/day

See Table 10 for details
</td></tr>
</table>

Table 10: Rabbit EFD Necropsy

Dose	0	100mg/kg	200mg/kg	400mg/kg
Gross pathology				
Number of Fetuses/Litters Evaluated	166/17	164/18	174/20	135/18
# of fetuses affected (%)/ # of liters affected (%)				
Ear				
Pinna, small-**malformation**	0	0	0	2(1.5)/1(5.6)
Eye				
Eye, open-**malformation**	0	0	0	2(1.5)/1(5.6)
Face				
Palate, cleft-**malformation**	0	0	0	1(0.7)/1(5.6)
Snout, cleft-**malformation**	0	0	0	2(1.5)/1(5.6)
General				
Entire body, subcutaneous edema-generalized-**malformation**	0	0	0	1(0.7)/1(5.6)
Entire body, subcutaneous edema-localized-variation	0	0	0	2(1.5)/2(11.1)
Limb				
Forelimb, hyperextension-**malformation**	0	0	0	1(0.7)/1(5.6)
Paw				
Forepaw, hyperextension-**malformation**	0	0	1(0.6)/1(5)	1(0.7)/1(5.6)
Forepaw, malrotated-**malformation**	0	0	0	2(1.5)/2(11.1)
Paw/digit				
Forepaw, absent-**malformation**	0	0	0	4(3)/3(16.7)
Forepaw, pendulous-**malformation**	0	0	0	1(0.6)/1(5.6)
Trunk				
Trunk, distended abdomen-**malformation**	0	0	0	1(0.7)/1(5.6)
Tail				
Tail, short-**malformation**	0	0	0	2(1.5)/2(11.1)
Total gross malformations, variations, incidentals				
Number of fetuses (%)/number of litters (%)	0	0	2(1.1)/2(10)	8(5.9)/6(33.3)
Visceral variants/malformations				
Number of Fetuses/Litters Evaluated	166/17	164/18	174/20	135/18
Adrenal gland				
Adrenal gland-malpositioned-**malformation**	0	0	0	1(0.7)/1(5.6)

Dose	0	100mg/kg	200mg/kg	400mg/kg
Aorta				
Aorta, dilated-**malformation**	0	0	0	1(0.7)/1(5.6)
Aortic arch, dilated-**malformation**	0	1(0.6)/1(5.6)	0	5(3.7)/5(27.8)
Brain				
Lateral ventricle, dilated, moderate-variation	0	0	1(0.6)/1(5)	0
Diaphragm				
Diaphragm, hernia-**malformation**	0	0	0	3(2.2)/3(16.7)
Ductus arteriosus				
Ductus arteriosus, patent-**malformation**	0	0	0	7(5.2)/5(27.8)
Eye				
Eye, small-**malformation**	2(1.2)/1(5.9)	0	0	3(2.2)/2(16.7)
General				
Thorax, fluid filled-variation	0	0	0	1(0.7)/1(5.6)
Great vessels				
Great vessels, transposition-**malformation**	0	0	0	1(0.7)/1(5.6)
Truncus arteriosus, persistent-**malformation**	0	1(0.6)/1(5.6)	0	14(10.4)/7(38.9)
Heart				
Atrium, large-variation	0	0	1(0.6)/1(5)	0
Ventricular septum, defect-**malformation**	0	0	0	21(15.6)/1055.6)
Kidney				
Kidney, fused-**malformation**	0	0	1(0.6)1(5)	2(1.5)/2(11.1)
Kidney, malpositioned-**malformation**	0	0	2(1.1)/2(10)	7(5.2)/5(27.8)
Kidney-absent-**malformation**	0	0	0	6(4.4)/3(16.7)
Liver				
Liver, large-**malformation**	0	0	0	1(0.7)/1(5.6)
Lung				
Lobe, absent-variation	0	1(0.6)/1(5.6)	0	3(2.2)/2(11.1)
Lung, absent-**malformation**	0	0	0	3 (2.2)/2(11.1)
Lung, small-**malformation**	0	1(0.6)/1(5.6)	0	3(2.2)/3(16.7)
Pulmonary trunk				
Pulmonary trunk, narrow-**malformation**	0	0	0	4(3)/4(22.2)
Stomach				

Dose	0	100mg/kg	200mg/kg	400mg/kg
Stomach, malpositioned-**malformation**	0	0	0	1(0.7)/1(5.6)
Ureter				
Ureter, absent-**malformation**	0	0	0	3(2.2)/1(5.6)
Total visceral malformations				
Number of fetuses (%)/number of litters (%)	2(1.2)/1(5.8)	3(1.8)/3(16.7)	4(2.3)/4(20)	32(23.7)/13(72.2)
Skeletal variants				
Number of Fetuses/Litters Evaluated	166/17	164/18	174/20	135/18
Forelimb				
Digits, absent-**malformation**	0	1(0.6)/1(5.6)	0	5(3.7)/4(22.2)
Forepaw phalanges, absent-**malformation**	0	1(0.6)/1(5.6)	0	5(3.7)/4(22.2)
Forepaw phalanges, misshapen-variant	0	1(0.6)/1(5.6)	0	4(22.2)/1(0.7)
Forepaw phalanges, small-variation	0	2(1.2)/1(5.6)	0	3(2.2)/3(16.7)
Metacarpal, absent-**malformation**	0	1(0.6)/1(5.6)	0	5(3.7)/4(22.2)
Ulna, absent-**malformation**	0	0	0	2(1.5)/2(11.1)
General				
General, skeletal, mechanical damage-incidental	2(1.2)/2(11.8)	1(0.6)/1(5.6)	6(3.6)/5(26.3)	16(11.9)/7(38.9)
Pelvis				
Pubis, incomplete ossification-variation	0	0	0	1(0.7)/1(5.6)
Pubis, unossified-variation	0	2(1.2)/1(5.6)	0	0
Rib				
Branched-**malformation**	0	0	1(0.6)/1(5.3)	0
Fused-**malformation**	0	0	1(0.6)/1(5.3)	1(0.7)/1(5.6)
Misshapen-variation	0	0	2(1.2)/1(5.3)	0
Nodulated-variation	0	0	0	1(0.7)/1(5.6)
Short-variation	0	0	0	8(5.9)/4(22.2)
Supernumerary site-variation	0	0		1(0.7)/1(5.6)
Scapula				
Scapula ala, misshapen-variation	0	0	1(0.6)/1(5.3)	0
Skull				
Exoccipital, fused-variation	0	0	0	67(49.6)/15(83.3)
Exoccipital, misshapen-variation	0	0	1(0.6)/1(5.3)	9(6.7)/6(33.3)

Dose	0	100mg/kg	200mg/kg	400mg/kg
Frontal, isolated ossification site-variation	0	0	0	8(5.9)/5(27.8)
Frontal, misshapen-variation	0	0	0	10(7.4)/5(27.8)
Hyoid ala, absent-**malformation**	0	0	0	14(10.4)/6(33.3)
Hyoid ala, bent-variation	2(1.2)/1(5.9)	3(1.8)/3 (16.7)	5(3)/4(21.1)	6(4.4)/3(16.7)
Hyoid ala, short-variation	0	0	0	21(15.6)/9(50)
Interparietal, absent-**malformation**	0	1(0.6)/1(5.6)	5(3)/4(21.1)	69(51.1)/15(83.3)
Interparietal, small-variation	0	0	8(4.8)/4(21.1)	28(20.7)/13(72.2)
Maxilla, misshapen-variation	0	0	0	2(1.5)/1(5.6)
Nasal, misshapen-variation	0	0	0	2(1.5)/1(5.6)
Nasal, isolated ossification site-variation	0	0	4(2.4)/2(10.5)	0
Palatine, cleft-**malformation**	0	0	0	1(0.7)/1(5.6)
Parietal, hole-variation	0	0	1(0.6)/1(5.3)	0
Premaxilla, misshapen-variation	0	0	0	2(1.5)/1(5.6)
Squamosal, misshapen-variation	0	0	0	1(0.7)/1(5.6)
Supraoccipital, incomplete ossification-variation	0	0	0	3(2.2)/2(11.1)
Suture, large-variation	0	0	0	2(1.5)/2(11.1)
Suture, misshapen-variation	0	0	0	7(5.2)/4(22.2)
Suture bone, present-variation	0	0	1(0.6)/1(5.3)	7(5.2)/5(27.8)
Zygomatic arch, misshapen-variation	0	0	0	1(0.7)/1(5.6)
Sternebrae				
Asymmetric-variation	1(0.6)/1(5.9)	0	1(0.6)/1(5.3)	1(0.7)/1(5.6)
Bipartite ossification-variation	0	1(0.6)/1(5.6)	2(1.2)/2(10.5)	5(3.7)/3(16.7)
Fused-variation	1(0.6)/1(5.9)	8(4.9)/5(27.8)	13(7.9)/6(31.6)	43(31.9)/13(72.2)
Incomplete ossification-variation	0	0	4(2.4)/4(21.1)	11(8.1)/8(44.4)
Isolated ossification site-variation	8(4.8).1(5.9)	19(11.7)/9(50)	31(18.8)/13(68.4)	8(5.9)/6(33.3)
Large-variation	0	0	0	2(1.5)/1(5.6)
Misshapen-variation	0	8(4.9)/5(27.8)	34(20.6)/15(78.9)	25(18.5)/9(50)
Supernumerary rib				
Cervical, full-variation	0	12(7.4)/6(33.3)	75(45.5)/16(84.2)	15(11.1)/5(27.8)
Cervical, short-variation	0	35(21.5)/9(50)	68(41.2)18(94.7)	23(17)/9(50)
Vertebra				

Dose	0	100mg/kg	200mg/kg	400mg/kg
Atlas, ventral arch, malpositioned-variation	0	0	0	1(0.7)/1(5.6)
Atlas, ventral arch, misshapen-variation	0	0	0	1(0.7)/1(5.6)
Caudal vertebra, absent-**malformation**	0	0	0	2(1.5)/2(11.1)
Caudal vertebra, fused-**malformation**	0	0	0	7(5.2)/6(33.3)
Caudal vertebra, incomplete ossification-variation	0	0	1(0.6)/1(5.3)	4(3)/4(22.2)
Caudal vertebra, misaligned-variation	0	0	2(1.2)/2(10.5)	2(1.5)/1(5.6)
Caudal vertebra, misshapen-variation	0	0	0	1(0.7)/1(5.6)
Caudal vertebra, unossified-variation	0	0	0	1(0.7)/1(5.6)
Cervical arch-fused-**malformation**	0	0	0	3(2.2)/2(11.1)
Cervical arch, incomplete ossification-variation	1(0.6)/1(5.9)	0	11(6.7)/6(31.6)	49(36.3)/15(83.3)
Cervical arch, isolated ossification site-variation	0	0	5(3)/3(15.8)	13(9.6)/9(50)
Cervical arch, misshapen-variation	0	1(0.6)/1(5.6)	2(1.2)/1(5.3)	50(37)/16(88.9)
Cervical arch, small-variation	0	0	0	8(5.9)/3(16.7)
Cervical arch, unossified-variation	0	0	0	13(6.9)/7(38.9)
Cervical centrum, bipartite ossification-variation	0	1(0.6)/1(5.6)	0	3(2.2)/1(5.6)
Cervical centrum, fused-**malformation**	0	0	0	1(0.7)/1(5.6)
Cervical centrum, incomplete ossification-variation	0	0	0	10(7.4)/7(38.9)
Cervical centrum, misshapen-variation	0	0	0	2(1.5)/2(11.1)
Cervical centrum, unilateral ossification-variation	0	0	1(0.6)/1(5.3)	3(2.2)/2(11.1)
Cervical centrum, unossified-variation	0	0	0	81(60)/16(88.9)
Cervical vertebra, absent-**malformation**	0	0	0	10(7.4)/5(27.8)
Cervical vertebra, supernumerary-**malformation**	0	0	1(0.6)/1(5.3)	0

Dose	0	100mg/kg	200mg/kg	400mg/kg
Lumbar arch, misshapen-variation	0	0	1(0.6)/1(5.3)	0
Lumbar centrum, fused-**malformation**	0	0	1(0.6)/1(5.3)	0
Lumbar centrum, misshapen-variation	0	0	2(1.2)/2(10.5)	0
Lumbar vertebra, hemivertebra-**malformation**	0	0	1(0.6)/1(5.3)	0
Sacral arch, misshapen-variation	0	0	0	1(0.7)/1(5.6)
Sacral centrum, fused-**malformation**	0	0	0	1(0.7)/1(5.6)
Sacral vertebra, fused-**malformation**	0	0	0	1(0.7)/1(5.6)
Sacral vertebra, hemivertebra-**malformation**	0	0	1(0.6)/1(5.3)	0
Thoracic arch, supernumerary-**malformation**	0	0	1(0.6)/1(5.3)	0
Thoracic centrum, bipartite ossification-variation	0	0	3(1.8)/2(10.5)	1(0.7)/1(5.6)
Thoracic centrum, fused-**malformation**	0	0	1(0.6)/1(5.3)	2(1.5)/1(5.6)
Thoracic centrum, unilateral ossification-variation	0	0	0	1(0.7)/1(5.6)
Thoracic vertebra, hemivertebra-**malformation**	0	0	1(0.6)/1(5.3)	0
Thoracic vertebra, supernumerary-**malformation**	0	0	0	1(0.7)/1(5.6)
Total Skeletal malformations				
Number of fetuses (%)/number of litters (%)	13(7.8)/5(29.4)	61(37.4)/15(83.3)	143(86.7)/19(95)	135(100)/18(100)

Toxicokinetics

Maternal Toxicokinetics

Dose (mg/kg/day)	100		200		400	
	tazemetostat	EPZ-6930	tazemetostat	EPZ-6930	tazemetostat	EPZ-6930
Day 7						
Cmax (ng/mL)	1520	3130	5960	7150	12000	11400
AUC_{0-t} (ng*h/mL)	3730	9400	24700	35200	89100	105000
Tmax(h)	1.2	1.7	2.7	2.7	2.7	2.7
Day 19						
Cmax (ng/mL)	4390	4250	11100	7240	12200	8420
AUC_{0-t} (ng*h/mL)	10100	11300	37700	33300	48500	46300
Tmax(h)	1.3	1.3	1	1.7	1.7	1.7

Prenatal and Postnatal Development

Not conducted or required.

Study #WIL-154506: An oral (gavage) juvenile Toxicity study of EPZ-6438 in Sprague Dawley rats

Key Study Findings

- Several animals were found dead or euthanized in extremis at all dose levels
- Cause of death in the majority of animals was malignant lymphoma
- EPZ-6438 led to significantly increased body weights at all dose levels
- EPZ-6438 led to distended testicles in all males at all dose levels
  - 150/600 mg/kg EPZ-6438 led to belated attainment of balanopreputial separation in males
- 150/300 and 150/600 mg/kg led to decreased coordination and motor skills
- Target organs included lymphoid tissue, bone, and subcutis

Conducting laboratory and location (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0, 50, 100, 150/300*, 150/600* mg/kg once daily for 13 weeks starting at post-natal day (PND) 7 through PND 98
*dosed at 150 mg/kg PND 7-21 then increased to 300 and 600 mg/kg on PND22 based on deaths after one or two doses ≥300 mg/kg on PND8 in the dose-range finding study

Route of administration: Oral

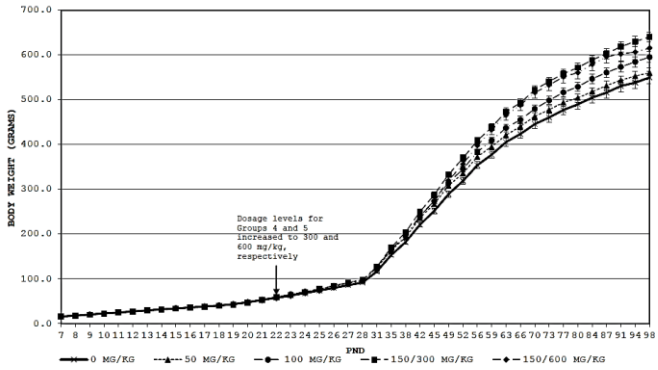
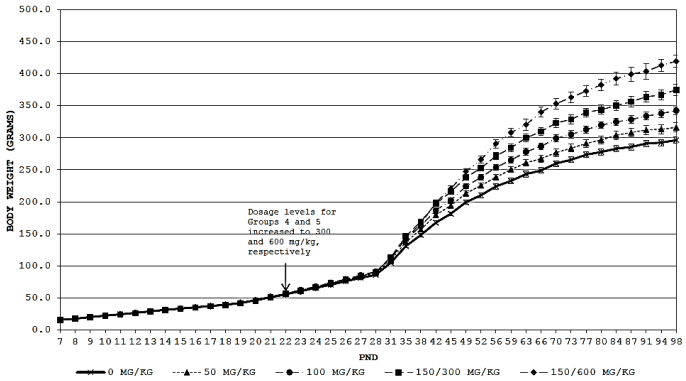
Formulation/Vehicle:	0.5 w/v % methylcellulose with 0.1 w/v% Tween 80
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	10/sex/group main toxicity study; 10/sex/group recovery animals
Age:	8 weeks
Satellite groups/ unique design:	39/sex/group for toxicokinetic analysis
Deviation from study protocol affecting interpretation of results:	None that impacted interpretation of study results

Observations and Results: changes from control

Parameters	Major findings
Mortality	**Main study animals** *Dosing phase* 50 mg/kg → 2/20 found dead Days 10 and 83 100 mg/kg → 2/20 found dead Days 9 and 7 150/600 mg/kg → 4/20 found dead or euthanized early Days 83-94 *Recovery phase* 100 mg/kg → 1/20 found dead Day 99 150/300 mg/kg → 3/20 euthanized early Days 110-119 150/600 mg/kg →4/20 found dead or euthanized early Days 101-126

Animal	Sex	Dose	Day	Death	Cause of death
Dosing Phase					
05	M	50 mg/kg	10	Found dead	Undetermined, tissues autolyzed
15	F	50 mg/kg	83	Found dead	**Malignant lymphoma**
04	M	100 mg/kg	9	Found dead	Undetermined
03	M	100 mg/kg	7	Found dead	Undetermined
06	M	150/600 mg/kg	89	Found dead	**Malignant lymphoma**
02	M	150/600 mg/kg	94	Euthanized in extremis	**Malignant lymphoma**
01	M	150/600 mg/kg	83	Euthanized in extremis	**Malignant lymphoma**
08	F	150/600 mg/kg	91	Euthanized in extremis	Drug related toxicities
Recovery phase					
08	F	100 mg/kg	99	Found dead	**Malignant lymphoma**
01	M	150/300 mg/kg	114	Euthanized in extremis	**Malignant lymphoma**
06	F	150/300 mg/kg	119	Euthanized in extremis	**Malignant lymphoma**
08	F	150/300 mg/kg	110	Euthanized in extremis	**Malignant lymphoma**
05	M	150/600 mg/kg	101	Euthanized in extremis	**Malignant lymphoma**
04	M	150/600 mg/kg	126	Found dead	**Malignant lymphoma**
07	F	150/600 mg/kg	106	Found dead	Undetermined
14	F	150/600 mg/kg	102	Euthanized in extremis	Drug related toxicities

Death in Toxicokinetic animals
50 mg/kg → 1/39 found dead Days 10
100 mg/kg → 1/39 euthanized early Day 16
150/300 mg/kg → 3/39 found dead or euthanized early Days 78-90
150/600 mg/kg → 3/39 found dead or euthanized early Days 9-91

	<table><tr><th>Animal</th><th>Sex</th><th>Dose</th><th>Day</th><th>Death</th><th>Cause of death</th></tr><tr><td>04</td><td>M</td><td>50 mg/kg</td><td>10</td><td>Found dead</td><td>Undetermined</td></tr><tr><td>13</td><td>F</td><td>100 mg/kg</td><td>16</td><td>Euthanized in extremis</td><td>Intubation error</td></tr><tr><td>04</td><td>M</td><td>150/300 mg/kg</td><td>86</td><td>Euthanized in extremis</td><td>Malignant lymphoma</td></tr><tr><td>11</td><td>F</td><td>150/300 mg/kg</td><td>90</td><td>Euthanized in extremis</td><td>Ruptured mass in buccal area</td></tr><tr><td>04</td><td>F</td><td>150/300 mg/kg</td><td>78</td><td>Found dead</td><td>Malignant lymphoma</td></tr><tr><td>03</td><td>M</td><td>150/600 mg/kg</td><td>91</td><td>Found dead</td><td>Acute pyelonephritis</td></tr><tr><td>03</td><td>M</td><td>150/600 mg/kg</td><td>88</td><td>Euthanized in extremis</td><td>Malignant lymphoma</td></tr><tr><td>04</td><td>F</td><td>150/600 mg/kg</td><td>9</td><td>Found dead</td><td>Undetermined, tissues autolyzed</td></tr></table>
Clinical Signs	**All EPZ-6438 doses** • Distended testicles starting PND48 in most all males ○ No histological correlates **All animals dosed at 150/300 and 150/600 mg/kg** • Red material around nose/eyes • Yellow material on mouth, urogenital/anogenital areas, ventral trunk • Scab on tail and limbs • Swollen face and digits • Masses on trunk and limbs
Body Weights	**All EPZ-6438 doses** • Increased body weights starting around Day 40 and continuing into the recovery period with up to a 17% increase in body weight compared to controls **Dosing phase** Males  Females 

<table>
<tr><td></td><td></td></tr>
<tr><td>Ophthalmoscopy</td><td>Unremarkable</td></tr>
<tr><td>Developmental Landmarks</td><td>Males
Delay in mean age at attainment of balanopreputial separation in males dosed with 150/600 mg/kg compared to controls
Day 45.9 vs. Day 43.3
Females
EPZ-6438 did not affect attainment of vaginal patency</td></tr>
<tr><td>FOB</td><td>Changes in sensory and neuromuscular observations indicate decreased coordination and motor skill.

<table>
<tr><th>Dose</th><th>Sex</th><th>Sensory observations</th><th>Neuromuscular observations</th></tr>
<tr><td>150/300 mg/kg</td><td>F</td><td>-</td><td>Decreased rotarod performance vs. controls (28.3 vs. 58.8 sec)</td></tr>
<tr><td rowspan="3">150/600 mg/kg</td><td>F</td><td>Uncoordinated air righting reflex (4/10 animals)</td><td>Decreased rotarod performance vs. controls (25.3 vs. 58.8 sec)</td></tr>
<tr><td rowspan="2">M</td><td>Uncoordinated air righting reflex (3/8 animals)</td><td>Decreased rotarod performance vs. controls (18.8 vs. 31.9 sec)</td></tr>
<tr><td>-</td><td>Decreased hind foot splay vs. controls (68.9 vs. 86 mm)</td></tr>
</table></td></tr>
<tr><td>Hematology</td><td>
<table>
<tr><th>Hematology Parameters</th><th colspan="2">100 mg/kg</th><th colspan="2">150/300 mg/kg</th><th colspan="2">150/600 mg/kg</th></tr>
<tr><th></th><th>M</th><th>F</th><th>M</th><th>F</th><th>M</th><th>F</th></tr>
<tr><td colspan="7">PND 99</td></tr>
<tr><td>WBCs</td><td>-</td><td>↑29%</td><td>↑34%</td><td>↑91%</td><td>↑106%</td><td>↑108%</td></tr>
<tr><td>Absolute lymphocytes</td><td>-</td><td>-</td><td>↑32%</td><td>↑57%</td><td>↑75%</td><td>-</td></tr>
<tr><td>Absolute neutrophils</td><td>-</td><td>-</td><td>-</td><td>↑144%</td><td>↑274%</td><td>↑1000%</td></tr>
<tr><td>Absolute monocytes</td><td>-</td><td>-</td><td>↑172%</td><td>↑341%</td><td>↑418%</td><td>↑395%</td></tr>
<tr><td>Absolute eosinophils</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑227%</td><td>↑255%</td></tr>
<tr><td>PTT</td><td>-</td><td>-</td><td>↑6%</td><td>↑6%</td><td>↑15%</td><td>↑16%</td></tr>
<tr><td>Platelets</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑20%</td></tr>
<tr><td>Hematocrit</td><td>-</td><td>-</td><td>-</td><td>↓9%</td><td>-</td><td>↓18%</td></tr>
<tr><td>Hemoglobin</td><td>-</td><td>-</td><td>-</td><td>↓10%</td><td>-</td><td>↓22%</td></tr>
<tr><td>MCH</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↓6%</td></tr>
<tr><td>MCV</td><td>-</td><td>-</td><td>-</td><td>↓6%</td><td>↓9%</td><td>-</td></tr>
<tr><td>RBCs</td><td>-</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↓14%</td></tr>
<tr><td>RDW</td><td>-</td><td>-</td><td>↓7%</td><td>-</td><td>-</td><td>↑41%</td></tr>
<tr><td>Reticulocytes</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑13%</td><td>↑70%</td></tr>
<tr><td colspan="7">PND 127</td></tr>
<tr><td>WBCs</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑275%</td><td>↑87%</td></tr>
<tr><td>Absolute lymphocytes</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑391%</td><td>↑88%</td></tr>
<tr><td>Absolute monocytes</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↑62%</td><td>↑257%</td></tr>
<tr><td>PTT</td><td>-</td><td>-</td><td>↑5%</td><td>↑8%</td><td>↑7%</td><td>↑11%</td></tr>
<tr><td>Reticulocytes</td><td>-</td><td>-</td><td>-</td><td>-</td><td>↓36%</td><td>-</td></tr>
</table>
Values are percent change compared to controls. Lymphoma and/or hyperplasia contributed to increased WBC values in affected animals.</td></tr>
<tr><td>Clinical Chemistry</td><td>150/300 mg/kg rats:
Males → 9% increased chloride
Females → 5% increased chloride</td></tr>
</table>

150/600 mg/kg rats:
Males → 11% increased chloride;
Females → 11% increased chloride; 8% increased calcium; 26% increased phosphorus

Findings were reversible with no notable clinical chemistry changes in recovery animals.

Urinalysis

Not conducted

Gross Pathology

No findings occurred in the control group.

Gross Pathology Findings	50 mg/kg		100 mg/kg		150/300 mg/kg		150/600 mg/kg	
	M	F	M	F	M	F	M	F
PND 99								
Thymus								
Enlarged	-	0/1	1	-	1/0	4	2/2	-
Spleen								
Enlarged	-	0/1	-	-	-	1	5/3	1
Swollen	-	-	-	-	-	1	0/1	-
Femur								
Thickened	-	-	-	-	-	-	4/1	5/1
Paws								
Nodules	-	-	-	-	-	-	-	2/1
Swollen	-	-	-	-	-	-	1/1	4
Lymph nodes (axillary)								
Enlarged	-	0/1	-	-	-	-	0/1	1
Lymph node (generalized)								
Enlarged	-	0/1	-	-	-	-	2	5
PND 127								
Thymus								
Enlarged	-	-	-	0/1	1/1	1/2	2/2	5/1
Spleen								
Enlarged	-	-	-	0/1	1/1	0/1	3/2	-
Swollen	-	-	-	-	-	-	2	1
Femur								
Thickened	-	-	-	-	-	-	4	4/1
Paws								
Nodules	-	-	-	-	-	-	0/1	-
Swollen	-	-	-	-	-	-	-	0/1
Lymph node (axillary)								
Enlarged	-	-	-	-	0/1	-	1/2	0/1
Lymph node (generalized)								
Enlarged	-	-	-	-	0/1	-	1	-

Incidence is listed as scheduled necropsy/unscheduled death.

Organ Weights

Organ	100 mg/kg		150/300 mg/kg		150/600 mg/kg	
	M	F	M	F	M	F
Terminal Necropsy PND 99						
Thymus	-	-	↑91%	↑301%	↑270%	-
Spleen	-	-	↑70%	↑119%	↑131%	↑62%
Final body weights	-	-	↑15%	↑26%	↑7%	↑39%
Recovery Necropsy PND 127						
Thymus	-	-	↑440%	-	↑794%	↑185%
Spleen	-	-	↑72%	↑83%	↑241%	↑160%
Final body weights	↑16%	↑20%	↑24%	↑27%	↑27%	↑44%

Lymphoma and hyperplasia contributed to increased organ weights in affected animals.

Histopathology Adequate battery: Yes

Sex		Males				Females			
Dose (mg/kg/day)		50	100	150/ 300	150/ 600	50	100	150/ 300	150/ 600
# main group, # recovery		11,9	12,9	10,10	11,9	10,10	10,10	10,10	11,9
Thymus									
Hyperplasia, lymphoid	Minimal	-	1,1	-	-	-	2,2	-,1	7,3
	Mild	-	1	-	-	-	1	-	1
	Moderate	-	-	-,2	-	-	1	-	1
	Marked	-	-	-	-	-	-	-	-,1
Lymphoma	NA	-	-	1,2	6,4	1	-,1	5,3	2
Femur									
Trabeculae, increased	Minimal	-	-	-,1	3,2	-	2,2	3,8	-
	Mild	-	-	-	5,1	-	-	4,2	5,5
	Moderate	-	-	-	-,3	-	-	-	6,3
	Marked	-	-	-	-	-	-	-	-,1
Sternebrae									
Trabeculae, increased	Minimal	-	-	5	5,5	-	-	5,2	5,1
	Mild	-	-	-	3	-	-	-,1	3,5
	Moderate	-	-	-	-	-	-	-	2,2
Spleen									
Increased mononuclear cells, red pulp	Minimal	-	-,3	6,2	6,4	1	4,1	3,3	1,3
	Mild	-	1,1	1,2	-,1	-	-	3	4,3
	Moderate	-	-	2	2	-	-	2	3,1
	Marked	-	-	-	-	-	-	-	-,1
Increased cellularity, white pulp	Minimal	-,1	1,4	2,1	1,1	1	4,2	4,3	1,3
Decreased cellularity, marginal zones	Minimal	-	1	4	-	-	-	2,1	-,2
	Mild	-	-	-	1,3	-	-	3,1	5,5
	Moderate	-	-	3	4	-	-	1	3,1
	Marked	-	-	-,1	4,1	-	-	1	3
Paws									
Inflammation, pyogranulomatous	Minimal	-	-	-	-	-	-	-	1
	Mild	-	-	-	-	-	-	-	5
	Moderate	-	-	3	4	-	-	1	3
	Marked	-	-	-	4	-	-	1	3
Subcutis									
Inflammation, pyogranulomatous	Moderate	-	-	-	-	-	-	1	3
	Marked	-	-	-	2	-	-	-	4
	Moderate	-	-	-	1	-	-	-	-

No findings occurred in control animals.

Toxicokinetics

Dose (mg/kg/day)	50		100		150/ 300		150/ 600	
Sex	M	F	M	F	M	F	M	F
EPZ-6438								
Day 7								
Cmax (ng/mL)	1690	1930	3840	5190	9090	9450	9690	8010
AUClast (ng*h/mL)	6850	7300	27700	22800	70100	86100	56900	55100
Day 98								
Cmax (ng/mL)	1410	3900	3800	7600	11500	17100	18200	26300
AUClast (ng*h/mL)	6340	18500	19200	67200	125000	229000	290000	425000
Metabolite EPZ-6930								
Day 7								
Cmax (ng/mL)	6060	5140	12900	12000	19900	22100	19000	19800
AUClast (ng*h/mL)	62300	59700	195000	158000	266000	321000	283000	280000
Day 98								
Cmax (ng/mL)	1430	555	3790	951	9370	3720	18600	7250
AUClast (ng*h/mL)	6700	2470	20300	5610	131000	54200	322000	134000

5.5.5. Other Toxicology Studies

Epizyme conducted several investigations of the cause or origin of lymphomas in rodents treated with tazemetostat, including investigations of retrovirus reintegration, Notch signaling, and cellular populations. The results were generally negative or inconclusive. Examination of multiple immune compartment from rats with lymphoma in the 13-week toxicology studies did, however, show that there were significant increases in the percentages of CD8+ T cells and αβ T cells with concomitant decreases in the percentage of all other cell types, indicating that the main lymphoma cell population consisted of CD8+ αβ T cells.

X
Primary Reviewer (Stephanie Aungst)

X
Team Leader (Whitney Helms)

6 Clinical Pharmacology

6.1. Executive Summary

The clinical pharmacology properties of tazemetostat were characterized throughout the clinical development program, either as part of the efficacy/safety trials, or in dedicated studies including assessment of drug-drug interactions (EZH-105 and E7438-G000-101), ADME/mass balance (EZH-103), and the effects of high-fat meals or proton-pump inhibitors on the pharmacokinetics (PK) of tazemetostat (EZH-105 and E7438-G000-101). A Population PK analysis was conducted to identify the sources of PK variability , including evaluation of the effects of hepatic and renal impairment on the PK of tazemetostat. Reports of exposure-response (E-R) analyses for efficacy and safety and assessment of the potential for QTc interval prolongation were also included in this NDA submission.

Tazemetostat is primary metabolized by CYP3A to form inactive metabolites, followed by biliary excretion. Renal excretion represents a minor (<20%) elimination pathway for tazemetostat. There was no clinically relevant effect of high fat meals or gastric acid reducing agents (ARA) on tazemetostat absorption. The Population PK analysis of tazemetostat did not identify any covariates that are of clinical significance. Based on the Population PK analysis, no dose adjustment is recommended in patients with mild hepatic impairment or any degree of renal impairment, including end stage renal disease (ESRD). The effect of moderate or severe hepatic impairment on tazemetostat exposure and safety have not been studied. Coadministration of fluconazole (a moderate CYP3A inhibitor) with tazemetostat 400 mg twice daily increased tazemetostat steady-state AUC_{last} in patients by 3.1-fold and C_{max} by 2.3-fold. A 50% reduction of tazemetostat dose is recommended when it is concomitantly used with moderate CYP3A inhibitors. It is expected that coadministration of strong CYP3A inhibitors will largely increase tazemetostat exposure, leading to increased toxicities; and coadministration of strong or moderate CYP3A inducers will largely decrease tazemetostat exposure which may result in decreased efficacy; therefore, concomitant use of them with tazemetostat should be restricted. Results from a QTc assessment did not indicate a large clinically meaningful increase (i.e., >20 ms) in QTc intervals from baseline over the therapeutic concentration range of tazemetostat.

The primary evidence of efficacy, at the proposed dosage regimen of 800 mg orally twice daily (BID), was from Study EZH-202 that includes patients with epithelioid sarcoma (Cohort 5). The primary efficacy endpoint, objective response rate (ORR) with 95% confidence interval (CI), assessed by BIRC, was 15% (7, 26). The E-R analyses suggested a trend of positive E-R relationship for efficacy; however, it is inconclusive due to the small sample size and limited exposure range as only one dose regimen was studied in the trial. Tazemetostat exposure was predictive for the occurrence of treatment-related ≥ Grade 3 adverse events (AEs) and ≥ Grade 3 hepatotoxicity. Tazemetostat at the recommended dosage regimen of 800 mg BID demonstrated an acceptable safety profile.

Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in NDA211703. This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The primary evidence of effectiveness was from study EZH-202 Cohort 5. The ORR (95% CI), as assessed by IRC, was 15% (7, 26) in patients with epithelioid sarcoma treated with tazemetostat 800 mg BID.
General dosing instructions for adults	The recommended tazemetostat dose regimen is 800 mg BID with or without food.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• No dose adjustment is recommended for patients with mild hepatic impairment. The effect of moderate or severe hepatic impairment on tazemetostat exposure is unknown. A PMR is to be issued for conducting a hepatic impairment study to determine appropriate dose(s) for this specific patient population. • No dose adjustment is recommended for patients with renal impairment, including ESRD. • A 50% dose reduction is recommended for patients with concomitant use of moderate CYP3A inhibitors. • Restriction of concomitant use with strong CYP3A inhibitors is recommended. A PMR is to be issued for conducting a PK drug interaction study with a strong CYP3A inhibitor to determine the magnitude of the effect and guide dose recommendation. • Restriction of concomitant use with strong and moderate CYP3A inducers is recommended. A PMC is to be issued for conducting a PK drug interaction study with a strong CYP3A inducer to determine the magnitude of the effect and guide dose recommendation.
Bridging between the to-be-marketed formulation and clinical trial formulations	The proposed commercial drug product (tablet at 200 mg strength) was used in the pivotal study EZH-202.
Labeling	The review team has made substantial revisions to the proposed labeling in Section 2.3 Dose Modification, Section 7 Drug Interaction, and Section 12 Clinical Pharmacology.

Post-Marketing Requirements and Commitments

PMC or PMR	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Identify tazemetostat dose in patients with moderate and severe hepatic impairment.	The primary elimination pathway of tazemetostat is hepatic metabolism followed by biliary excretion. There is no PK data available to determine appropriate dose in patients with moderate or severe hepatic impairment. The proposed study will determine appropriate tazemetostat dose(s) in this patient subpopulation.	Complete the planned clinical PK trial to determine an appropriate dosage regimen of tazemetostat for patients with moderate or severe hepatic impairment.
PMR	Determine tazemetostat dose adjustment in patients with concurrent use of strong CYP3A inhibitors	Tazemetostat metabolism is primarily mediated by CYP3A. Concomitant use of a moderate CYP3A inhibitor resulted in 3-fold increase in tazemetostat exposure at steady-state. There is no PK data to determine tazemetostat dose when used concomitantly with strong CYP3A inhibitors. The clinical trial is to determine appropriate tazemetostat dose adjustment for this drug interaction.	Complete the planned clinical PK trial to determine an appropriate dose adjustment of tazemetostat in patients who require concomitant use of strong CYP3A inhibitors.
PMC	Determine tazemetostat dose adjustment in patients with concomitant use of strong CYP3A inducers	Tazemetostat metabolism is primarily mediated by CYP3A. There is no PK data to determine tazemetostat dose when used concomitantly with CYP3A inducers. The clinical trial is to determine appropriate tazemetostat dose adjustment for this drug interaction.	Complete the planned clinical pharmacokinetic trial to determine an appropriate dose of tazemetostat in patients who require concomitant use of CYP3A inducers.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The systemic exposure of tazemetostat is approximately dose proportional over the dose range of 200 mg to 1600 mg twice daily (BID). Following tazemetostat 800 mg orally BID, the steady-state of tazemetostat exposure was reached by Day 15. The mean (%CV) C_{max} at steady-state was 829 (56%) ng/mL and the corresponding AUC_{0-12h} was 3340 (49%) ng•h/mL. Tazemetostat exhibited time-dependent PK with clearance increasing over time, which is likely due to auto-induction of CYP3A. The mean accumulation ratio (measured by AUC_{last} Day 15 /Day 1) was 0.58.

Absorption

The mean absolute oral bioavailability of tazemetostat is 34%. The median t_{max} is 1 to 2 hours.

Effect of Food

A high fat, high calorie (approximately 800 to 1000 calories) meal does not have a significant effect on tazemetostat exposure.

Distribution

The mean (CV%) apparent volume of distribution at steady-state (V_{ss}/F) in patients is 1230 L (46%). Tazemetostat is 88% bound to human plasma proteins *in vitro*. The blood-to-plasma ratio is 0.73.

Elimination

At steady-state, the estimated mean (CV%) terminal elimination half-life ($t_{1/2}$) of tazemetostat is 3.1 hours (14%) and the apparent total clearance (CL_{ss}/F) is 274 L/h (49%).

Metabolism

In vitro, tazemetostat is metabolized by CYP3A (f_m ~99%). The predominant metabolic pathway of tazemetostat is N-dealkylation of the aniline nitrogen that leads to the formation of M5 (EPZ-6930) and M3 (EPZ006931). M5 is further metabolized by CYP3A to form M1 (EPZ034163). The metabolite to parent ratios at steady-state for M5, M3 and M1 based on geometric mean AUC were 2.0, 0.67 and 0.26, respectively. None of the major circulating metabolites are active (100-fold less potent than the parent).

Excretion

Following a single oral dose of radiolabeled tazemetostat, 94% of the total radioactivity was recovered over 12 days, with 15% excreted into urine and 79% into feces.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dosing regimen is 800 mg orally BID with or without food.

Therapeutic Individualization

Specific Population

Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment. In the population PK analysis, there was no clinically significant effect of mild hepatic impairment (total bilirubin >1.0 to 1.5 times ULN or AST > ULN, n=166) on tazemetostat clearance compared to patients with normal hepatic function (total bilirubin and AST $\leq$ ULN, n=515). No dose recommendation can be provided for patients with moderate or severe hepatic impairment due to the lack of data.

Renal Impairment

No dose adjustment is recommended for patients with all degrees of renal impairment, including ESRD. In the population PK analysis, mild (eGFR ≥60 to 89 mL/min/1.73 m^2 calculated by MDRD, n= 77) or moderate renal impairment (eGFR≥ 30 to 60 mL/min/1.73 m^2, n=33) had no effect on tazemetostat clearance. The mean clearance at steady-state is 25% lower in patients with severe renal impairment (eGFR ≥ 15 to 29 mL/min/1.73 m^2,n=2) and ESRD (eGFR<15 mL/min/1.73 m^2, n=3) compared to patients with normal renal function (eGFR≥ 90 mL/min/1.73 m^2, n=164) which translates to approximately 30% higher exposure.

Food effect

Consumption of a high-fat, high-calorie meal has no clinically meaningful effect on the exposure of tazemetostat as C_{max} decreased by 24% and AUC_{last} decreased by 18% under fed condition compared to fasting state.

Drug-Drug Interactions

Strong and Moderate CYP3A Inhibitors

Coadministration of fluconazole (a moderate CYP3A inhibitor) with tazemetostat 400 mg twice daily in patients increased tazemetostat steady-state AUC_{last} by 3.1-fold and C_{max} by 2.3-fold (see detail in Section 6.3.1). A 50% dose reduction from the current dose is recommended for tazemetostat when it is concomitantly used with moderate CYP3A inhibitors.

Concomitant use of tazemetostat with strong CYP3A inhibitors has not been studied and it is expected to significantly increase tazemetostat steady-state exposure which may lead to increased toxicities. Therefore, concomitant use of tazemetostat with strong CYP3A inhibitors should be restricted.

Strong and Moderate CYP3A Inducers

The effect of strong or moderate CYP3A inducers on tazemetostat exposure has not been studied; however, it is expected to decrease exposure of tazemetostat and may be associated with reduced efficacy. Therefore, concomitant use of tazemetostat with strong or moderate CYP3A inducers should be restricted.

Gastric Acid Reducing Agents

Coadministration of omeprazole (a proton pump inhibitor) with tazemetostat 800 mg BID in patients increased tazemetostat steady-state $AUC_{0\text{-}8h}$ by 26% and C_{max} by 25%. This magnitude of effect is not expected to be clinically relevant.

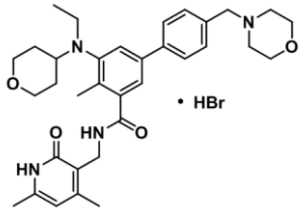
Outstanding Issues

The outstanding issues from Clinical Pharmacology perspective will be addressed by the following proposed postmarketing studies.

- PMRs to assess:
  - The effect of moderate and severe hepatic impairment on tazemetostat exposure
  - The effect of strong CYP3A inhibitors on tazemetostat exposure
- PMC to assess
  - The effect of strong CYP3A inducers on tazemetostat exposure

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Physical and Chemical Properties	
Chemical Structure and Formula	Tazemetostat (EPZ-6438, E7438)
	 Molecular formula: C34H44N4O4 (free base), C34H45BrN4O4 (HBr salt) Molecular weight: 572.75 (free base); 653.65 (HBr salt)

<table>
<tr><td>In vitro solubility</td><td>The in vitro solubility of tazemetostat is pH-dependent and is lower than the value of the proposed dose (800 mg) /250 mL (3.2 mg/mL) at intestinal pH range (pH 5 to 7). The in vitro CaCO2 membrane permeability is moderate (12.9 × 10^{-6} cm/s, apical to basal) at 2 mg/mL concentration.

<u>Solubility in aqueous buffer</u>
Buffer Solution | Buffer pH | Solubility (mg/mL)
HCl/KCl (134 mM HCl) | 1.0 | 7.27
HCl/KCl (13.4 mM HCl) | 2.0 | 7.03
Acid phthalate 50 mM | 3.0 | 6.87
Acid phthalate 50 mM | 4.0 | 6.99
Neutralized phthalate 50 mM | 5.5 | 0.508
Phosphate 50 mM | 6.8 | 0.033

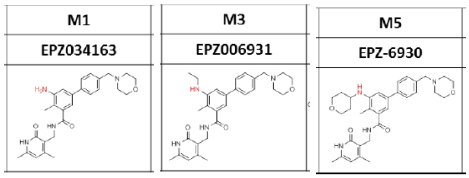
<u>Solubility in simulated physiological fluid</u>
Buffer Solution | Buffer pH | Solubility (mg/mL)
SGF | 1.2 | 7.50
FeSSIF | 5.0 | 3.83
FaSSIF | 6.5 | 0.053
SGF = Simulated Gastric Fluid, FeSSIF = Fed State Simulated Intestinal Fluid, FaSSIF = Fasted State Simulated Intestinal Fluid.</td></tr>
<tr><td colspan="2">Pharmacology</td></tr>
<tr><td>Mechanism of Action</td><td>Tazemetostat is a selective inhibitor of enhancer of zeste homologue 2 (EZH2). EZH2 catalyzes mono-, di-, and tri-methylation of lysine 27 of histone H3 (H3K27) which represses certain tumor suppressors. The IC_{50} value for tazemetostat against EZH2 was 4 nM (biochemical assay). IC_{50} for in vitro anti-proliferative activity was 110-160 nM in INI1-deficient cell lines. As reference, the mean steady-state tazemetostat C_{trough} ~111 ng/mL (200 nM) at 800 mg BID dose.</td></tr>
<tr><td>Active Moiety</td><td>Tazemetostat is the pharmacological active moiety. The most abundant metabolite (M5, EPZ-6930) exhibits low potency (IC_{50} ~1.23 μM; biochemical assay) and is unlikely to contribute to the pharmacological activity in humans.</td></tr>
<tr><td>QT Prolongation</td><td>The effect of orally administered tazemetostat, at doses ranging from 100 mg to 1600 mg twice daily for 15 days, on the QTc interval was evaluated in a dose finding study in 38 patients with advanced malignancies (E7438-G000-101). Tazemetostat and its metabolite EPZ-6930 did not cause large mean increase (i.e. >20 ms) on the QTc interval at the 800 mg BID dose. The largest mean increase (upper bound of 90% confidence interval) in QTc was 6.1 ms (8.5 ms) at the 800 mg BID and 9.3 ms (12.5 ms) at the 1600 mg BID dose.</td></tr>
<tr><td colspan="2">General Information</td></tr>
<tr><td>Bioanalysis</td><td>Tazemetostat (plasma and urine) and its metabolite (EPZ-6930, EPZ006931 and EPZ034163 in plasma) were quantified using validated LC/MS/MS methods. A summary of the bioanalytical methods is included in the appendices of this multidisciplinary review.</td></tr>
<tr><td>Healthy Volunteers vs. Patients</td><td>Tazemetostat PK were characterized in patients with cancer. Tazemetostat has not been studied in healthy subjects.</td></tr>
<tr><td>Drug exposure following the therapeutic dosing regimen</td><td>The geometric means (CV%) of C_{max} and $AUC_{0\text{-}12h}$ on Cycle 1 Day 1 and Cycle 1 Day 15 following tazemetostat 800 mg BID (Study E7438-G000-101):

<table>
<tr><th>Time</th><th>PK Parameters</th><th>Geometric Mean (CV%)</th></tr>
<tr><td rowspan="2">Cycle 1 Day 1 (n=14)</td><td>C_{max} (ng/mL)</td><td>1460 (38.7%)</td></tr>
<tr><td>$AUC_{0\text{-}12h}$ (ng•h/mL)</td><td>5750 (50.4%)</td></tr>
<tr><td rowspan="2">Cycle 1 Day 15 (n=13)</td><td>C_{max} (ng/mL)</td><td>829 (56.3%)</td></tr>
<tr><td>$AUC_{0\text{-}12h}$ (ng•h/mL)</td><td>3340 (49.3%)</td></tr>
</table></td></tr>
</table>

<table>
<tr><td>Minimal effective dose or exposure</td><td>The proposed dose is 800 mg BID, which was the only dose regimen evaluated in the pivotal ES cohort (Study EZH-202 Cohort 5). In the first-in-human study (E7438-G000-101), tazemetostat demonstrated dose/concentration-dependent inhibition of H3K27me3 in skin (biomarker for target inhibition). The estimated EC_{50} (Day 15 $AUC_{0\text{-}12h}$) of the inhibition was 734 ng•h/mL.</td></tr>
<tr><td>Maximal tolerated dose or exposure</td><td>Based on the dose-escalation data from the first-in-human Study E7438-G000-101, MTD was not reached over the evaluated dose range of 100 to 1600 mg BID. There was one DLT case (grade 4 thrombocytopenia) at 1600 mg BID.</td></tr>
<tr><td>Dose Proportionality</td><td>Greater than dose-proportional increase of steady-state exposure over 100 to 1600 mg BID (approximately 50-fold increase on Cycle 1, Day 1 and 32-fold increase on Cycle 1, Day 15 in the mean tazemetostat AUC_{12h} for a 16-fold dose increase (tablet formulation). However, the increase of tazemetostat exposure was close to dose-proportional between 200 mg and 1600 mg with the respective geometric mean values of steady-state exposure of 353 ng/mL and 2650 ng/mL for C_{max}, and 890 ng•h/mL and 7680 ng•h/mL for AUC_{12h}.
<table>
<tr><th>Dose Range</th><th>PK Parameters</th><th>Slope Estimate (90% CI)</th></tr>
<tr><td rowspan="2">100-1600 mg</td><td>C_{max}</td><td>1.164 (0.983, 1.344)</td></tr>
<tr><td>$AUC_{0\text{-}12h}$</td><td>1.213 (1.061, 1.365)</td></tr>
</table></td></tr>
<tr><td>Accumulation</td><td>There was no accumulation of tazemetostat following 800 mg BID administration, likely due to the short elimination half-life and auto-induction of CYP3A. The geometric mean tazemetostat accumulation ratios (Cycle 1, Day 15/Day 1) was 0.582 for $AUC_{0\text{-}12h}$ and 0.572 for C_{max}.</td></tr>
<tr><td>Variability</td><td>Inter-subject variabilities (CV%) at steady-state were 56% for C_{max} and 49 % for $AUC_{0\text{-}12h}$ after repeat dosing of tazemetostat 800 mg BID (n=14) in study E7438-G000-101. Larger PK variability (CV:160%) for C_{trough} was reported from study EZH-202 (n=184).</td></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>Oral Bioavailability</td><td>The absolute oral bioavailability of tazemetostat was determined in the human mass balance study (EZH-103) following IV administration of approximately 12 µg of [^{14}C]-tazemetostat and oral administration of 800 mg tazemetostat BID. The estimated F (n=3) ranged from 20.2% to 49.8% with a mean value of 34%.</td></tr>
<tr><td>Bioavailability/Bioequivalence</td><td>In the first-in human study, E7438-G000-101, the relative bioavailability of tazemetostat was assessed between an oral suspension formulation and the tablet formulation at 100 mg dose under fasting state. The geometric mean ratios (GMR) on Cycle 1 Day 1 are shown below.
<table>
<tr><th>Tablet/Suspension</th><th>C_{max}</th><th>$AUC_{0\text{-}12h}$</th></tr>
<tr><td>GMR (90% CI)</td><td>0.64 (0.16 – 2.61)</td><td>0.85 (0.16 – 4.45)</td></tr>
</table></td></tr>
<tr><td>Oral t_{max}</td><td>Following administration of a single oral dose of 800 mg tazemetostat (200 mg tablet), the median t_{max} ranged from 1.05 hours to 2.17 hours in Study E7438-G000-101.</td></tr>
<tr><td>Food effect

fed/fasted GMR (90% CI)</td><td>In Study E7438-G000-101, a high-fat meal had no clinically meaningful effect on tazemetostat exposures after a single oral dose of 200 mg tazemetostat in patients with cancer (n=12) as shown below.
<table>
<tr><th>C_{max}</th><th>AUC_{last}</th><th>AUC_{INF}</th></tr>
<tr><td>0.76 (0.46 – 1.25)</td><td>0.82 (0.56 – 1.21)</td><td>0.82 (0.56 – 1.21)</td></tr>
</table></td></tr>
<tr><td>Effect of Gastric acid reducing agents

with PPI/without PPI GMR (90% CI)</td><td>In Study EZH-105, coadministration of proton-pump inhibitor omeprazole (20 mg QD) resulted in ~ 1.3-fold increase in C_{max} and AUC_{last} for tazemetostat (800 mg BID) and the median t_{max} increased from 1.05 hours to 2.08 hours in patients with B-cell lymphoma (n=11 to 13).
Note that the first dose of omeprazole was administered one hour after tazemetostat administration on the reference day, hence the effect of PPI may be underestimated.
<table>
<tr><th>C_{max}</th><th>AUC_{last}</th></tr>
<tr><td>1.25 (0.76 – 2.03)</td><td>1.26 (0.87 – 1.82)</td></tr>
</table></td></tr>
</table>

Substrate transporter systems [in vitro]	Tazemetostat is a substrate of P-gp. Tazemetostat is not a substrate for BCRP, or renal transporters OCT2, OAT3 and MATE1 or hepatic transporters OATP1B1 and OATP1B3.
Distribution	
Volume of Distribution	The geometric mean (CV%) of apparent volume of distribution at steady-state (V_{ss}/F) was 1230 (45.8%) L based on noncompartmental analysis (NCA). The geometric mean V_z following 12 µg IV bolus of [^{14}C]-tazemetostat was 269 L.
Plasma Protein Binding	*In vitro,* tazemetostat is 87.7 to 91.1% bound to human plasma proteins over the concentration range of 1 to 30 µM.
Blood to Plasma Ratio	The mean blood-to-plasma ratio is 0.71 for tazemetostat over 50 to 5000 ng/mL.
Elimination	
Half-life	The terminal $t_{1/2}$ estimated using NCA method is 3.1 hours (13.9%).
Clearance	Tazemetostat shows time-dependent PK. The apparent CL/F after first dose is 126 L/h and CL_{ss}/F at steady-state is 274 L/h estimated by the NCA.
Metabolism	
Primary metabolic pathway(s)	Tazemetostat is metabolized primarily by CYP3A4 *in vitro* to form the inactive major metabolites M5 (EPZ-6930, product of N-demethylation) and M3 (EPZ006931), which undergo sequential metabolism to form M1 (EPZ034163), and M5 also undergoes CYP3A4 mediated metabolism *in vitro*. 

Inhibitor/Inducer	Clinical DDIs *Effect of CYP3A inhibitors on tazemetostat* Coadministration of fluconazole (a moderate CYP3A inhibitor) with tazemetostat 400 mg BID in patients with cancer increased tazemetostat steady-state C_{max} by 2.3-fold and AUC_{last} by 3.1-fold. *Effect of tazemetostat on CYP3A substrate* Coadministration of tazemetostat 800 mg BID with oral midazolam (a sensitive CYP3A substrate) in patients decreased midazolam C_{max} by 21% and AUC_{last} by 40%. *Effect of tazemetostat on CYP2C8 and 2C19 substrates* Coadministration of tazemetostat 800 mg BID with an oral cocktail of repaglinide (a sensitive CYP2C8 substrate) and omeprazole (a sensitive CYP2C19 substrate) in patients increased repaglinide C_{max} by 51% and AUC_{last} by 80%; and decreased omeprazole C_{max} by 18% and AUC_{last} by 20%. *In vitro* DDIs Tazemetostat is an in vitro inhibitor of CYP2C8, 2C9, 2C19, CYP3A4 and CYP2D6 with estimated K_i or IC_{50} values at 1.27 μM for CYP2C8, 15 μM for CYP2C9, 6.65 μM for CYP2C19, 9.16 μM for CYP2D6 and 3.06 μM for CYP3A (testosterone). The IC_{50} value are >20 μM for CYP1A2 and CYP2B6. The mean steady-state C_{max} is 933 ng/mL (1.6 μM, MW=573 free base) at the 800 mg BID dose regimen. The corresponding unbound C_{max} is approximately 0.2 μM. Tazemetostat is a time-dependent inhibitor of CYP3A, but not for CYP2C8, CYP2C9, CYP2C19, and CYP2D6. The major tazemetostat metabolites (EPZ-6930, EPZ006931 and EPZ034163) do not inhibit CYP enzymes at clinically relevant concentrations (IC_{50} values of ≥45.9 μM). Tazemetostat is an inducer of CYP3A. It also exhibits *in vitro* potential to induce CYP1A2, CYP2B6, CYP2C8 and CYP2C9 and 2C19; however, the effects are expected to be weak at the clinically relevant concentrations. Tazemetostat and EPZ-6930 are inhibitors of MATE1 and MATE2-K with IC_{50} values at 2.65 and 4.79 μM for MATE1, and at 1.89 and 12.1 μM for MATE2-K, respectively. The IC_{50} values of tazemetostat and its major metabolites are ≥ 10 μM for P-gp, BCRP, OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, and BSEP.
Excretion	
Primary excretion pathways (% dose)	In the human mass balance study EZH-103, after a single oral dose of 800 mg [^{14}C]-tazemetostat, 94% of the total radioactivity was recovered over 12 days, with a mean 79% excreted in feces and 15% in the urine.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

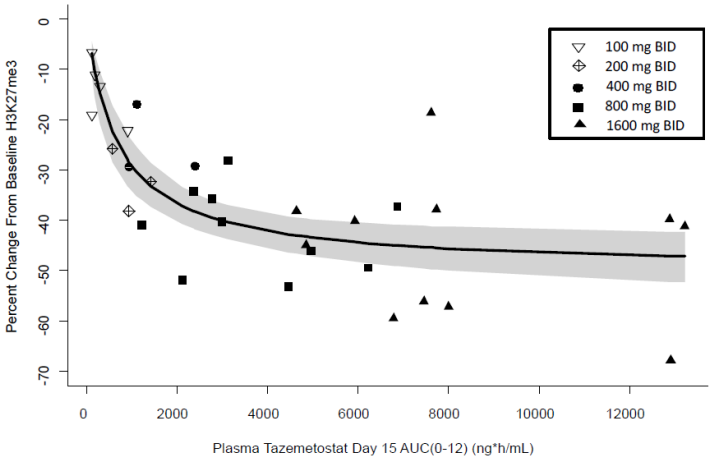
The clinical pharmacology data are supportive of the efficacy results.

The primary evidence of effectiveness at the proposed 800 mg BID regimen was from study EZH-202 Cohort 5 (pivotal efficacy cohort). As of the data cutoff, Cohort 5 enrolled a total of 62 patients with epithelioid sarcoma with confirmed loss of INI1 (59 adults ≥ 18 years of age and 3 pediatrics). The primary efficacy endpoint ORR, defined as the percentage of patients with a confirmed response of CR or PR, were reported in 9 of the 62 patients (15% [95% CI: 7%, 26%]; n=1 [2%] CR and n=8 [13%] PR) as assessed by BIRC. The median DOR was 69.7 (95% CI: 16.1, NE) weeks.

The RP2D of 800 mg BID was selected based on the totality of data obtained from the first-in-human study E7438-G000-101. Over the dose range of 100 mg to 1600 mg BID, tazemetostat demonstrated dose-dependent inhibition of trimethylated lysine 27 of histone (H3K27me3) in

skin, a biomarker for target (EZH2) engagement. The PD effect appeared to reach the plateau over the exposure range at 800 mg to 1600 mg BID (**Figure 11**). The EC_{50} and E_{max} estimates were 733 ng•h/mL and 49.8% in the inhibitory E_{max} model. The geometric mean steady-state $AUC_{0\text{-}12h}$ were 3340 ng•h/mL at 800 mg and 7710 ng•h/mL at 1600 mg, respectively, which are approximately 5 to 10 fold of the EC_{50} value.

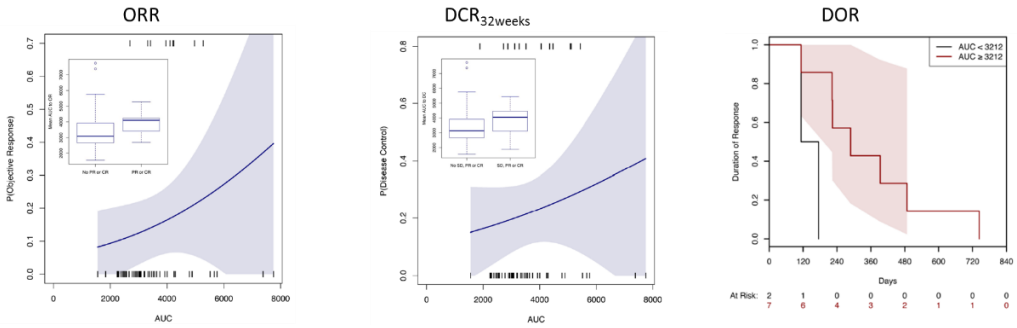
Figure 11. Inhibitory E_{max} model fit for the percentage change from baseline of H3K27me3 in the stratum spinosum layer versus $AUC_{0\text{-}12h}$ (study E7438-G000-101)



Source: summary of clinical pharmacology studies, Figure 36.

Based on Study EZH-202 Cohort 5 primary efficacy data at 800 mg BID, the Applicant's exploratory exposure-efficacy analyses indicated a trend of positive exposure-response relationship for ORR and $DCR_{32weeks}$ with shallow slopes (**Figure 12**). There was also a visual trend towards longer DOR in patients with higher exposure in the Kaplan-Meier plot. Additional univariate regression analyses did not identify exposure (time averaged AUC) as a significant predictor for efficacy. Therefore, caution should be taken when interpreting this relationship due to the small sample size (n=59) and limited range of exposure with one 800 mg BID regimen.

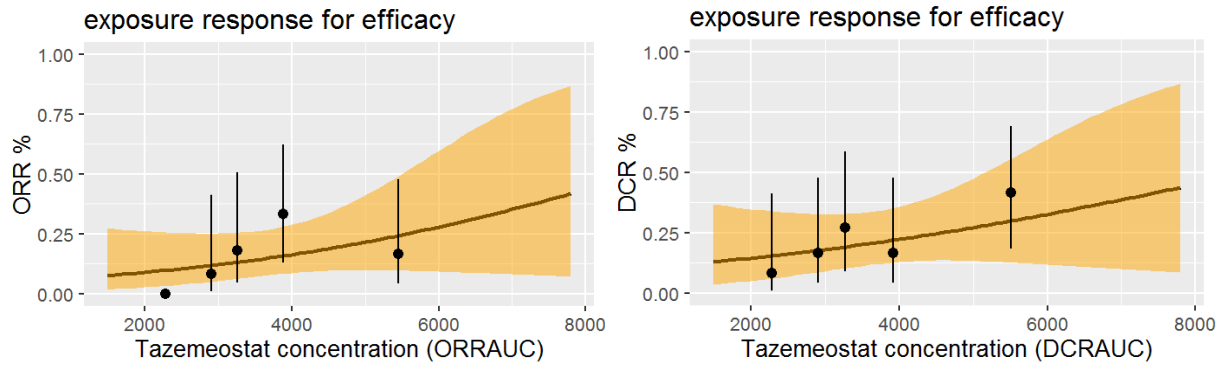
Figure 12. Applicant's exposure-efficacy analyses for ORR, $DCR_{32weeks}$ and DOR



Source: EZH-p102 study report. $DCR_{32weeks}$: disease control rate; DOR: duration of response

Consistent with Applicant's analyses, FDA-conducted analyses of study EZH-202 Cohort 5 data indicated a similar finding of a positive trend in the exposure-efficacy relationship (Section 19.4.4), where patients with a higher tazemetostat exposure (>median AUC of 3314 µg•day/mL) were associated with a numerical trend of higher ORR and DCR response rates and longer DOR compared to those with lower than median exposure (**Figure 13**). However, multivariate logistic regression modeling, including baseline ECOG score, body weight and prior lines of systemic therapy as potential risk factors, did not identify a significant relationship between tazemetostat exposure and efficacy (ORR and DCR). Furthermore, exploratory analysis of data from Study EZH-202 cohort 6 (patients with epithelioid sarcoma) did not reveal any notable E-R trend for efficacy.

Figure 13 Exposure response for efficacy by logistic regression



Source: FDA reviewer's analysis. Solid line is the logistic regression of the predicted ORR and DCR. The yellow area is the 95% CI. For each exposure quartile, the observed response rate and its 95% CI is plotted as solid circle and error bar vs the mean concentration.

Taken together, the available data suggest a positive trend in the exposure-efficacy relationship, albeit the E-R evidences are inconclusive supporting the additional clinical benefit at higher dosage than the proposed 800 mg BID.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of 800 mg BID is appropriate for the epithelioid sarcoma population. The benefit consideration is summarized as above. The safety aspect is outlined below.

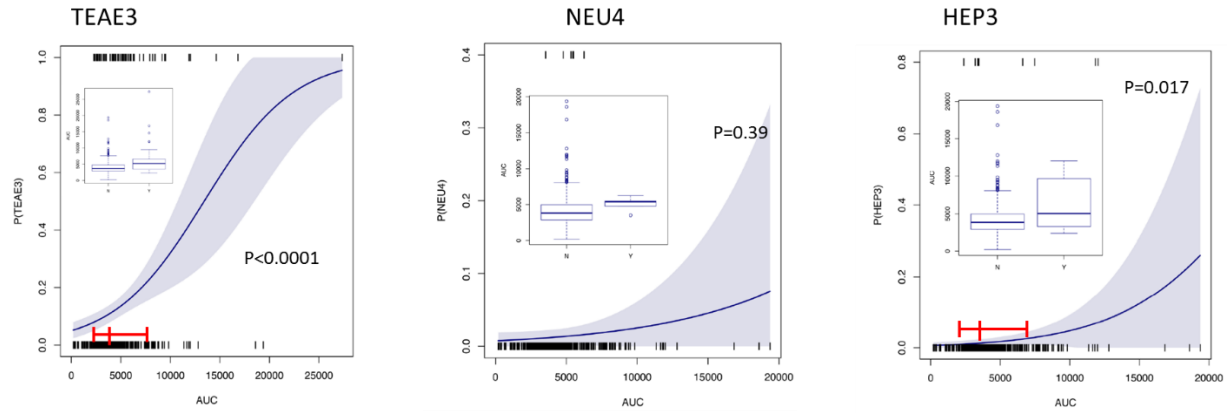
T-cell lymphoblastic lymphoma (T-LBL) was identified as a potential risk with tazemetostat. In adolescent and juvenile rats, tazemetostat exposure was a risk factor contributing to the occurrence of T-LBL. In male juvenile rats, a low incidence of T-LBL (2/60) was seen at $AUC_{0\text{-}24h}$ of 18,500 to 67,200 ng•h/mL and greater, with higher incidence at $AUC_{0\text{-}24h}$ of 125,000 to 290,000 ng•h/mL. In adolescent rats, T-LBL was seen at $AUC_{0\text{-}24h}$ of 99,600 ng•h/mL and greater. Both exposure and age were considered risk factors for the occurrence of T-LBL.

In the dose-escalation part of the first-in-human study, E7438-G000-101, maximum tolerated dose (MTD) was not reached within the evaluated dose range of 100 mg to 1600 mg BID in patients with cancer. Six out of 64 patients (9%) experienced a treatment-related TEAE assessed as Grade ≥ 3 in severity. Among these 6 patients, 1 patient (2%) experienced a TEAE resulting in dose reduction and 1 patient experienced a DLT (Grade 4 thrombocytopenia) at 1600 mg BID. Overall, 800 mg BID dosage regimen exhibited acceptable tolerability and the corresponding geometric mean steady-state $AUC_{0\text{-}12h}$ of 3340 ng•h/mL was approximately 3-fold lower than the nonclinical exposure margin associated with T-LBL risk.

The safety profiles of tazemetostat at the RP2D dose of 800 mg BID were further evaluated across the development program which demonstrated acceptable tolerability at the proposed dose. The incidence rate of dose reduction or treatment withdrawal due to AEs was 0 (0%) or 1 (1.7%) in Study EZH202 ES Cohort 5 (n=59); and 24 (4%) or 59 (9%) in target dose (800 mg) adult population (n=668). There was no AESIs reported in the Cohort 5; and in the target dose population, 2 cases of myelodysplastic syndrome (MDS) were reported by the data cutoff, in whom tazemetostat exposure were within the range of exposure in the overall population (Section 19.4.6).

Using pooled safety data from Studies E7438-G000-101 Part 1, EZH-105 and EZH-202, the applicant conducted exposure-safety analyses for safety endpoints including grade 3^+ treatment related AEs (TEAE3), grade 4^+ neutropenia (NEU4), and grade 3^+ hepatotoxicity (HEP3). Both descriptive and the univariate logistic regression analyses showed that tazemetostat exposure (AUC/Time) was a significant predictor of TEAE3 or HEP3 event (**Figure 14**). However, the risk to these toxicities is expected to be low over the exposure range with 800 mg BID dosage regimen.

Figure 14. Applicant's E-R analyses for safety endpoints



Source: EZH-p102 study report. NEU4: grade 4 or higher neutropenia; TEAE3: grade 3 or higher treatment related adverse events; HEP3: grade 3 or higher hepatotoxicity. Red lines mark the 5 to 95 percentile of steady-state exposure at 800 mg BID.

In the pediatric study EZH-102, one pediatric patient receiving tazemetostat 900 mg/m^2 BID developed T-LBL with observed $AUC_{0\text{-}24h}$ at 18,800 ng•h/mL. Relative to the pediatric exposure, adult patients at dosage of 800 mg BID had an exposure margin of approximately 2-fold for T-LBL based on mean $AUC_{0\text{-}24h}$.

In summary, the available safety data and exposure-safety analysis demonstrated acceptable safety and tolerability profile at 800 mg BID dosage, Given the potential of increased safety risk and the uncertainty of additional clinical benefit at higher dosage (e.g. 1600 mg BID), the overall benefit/risk profile supported the proposed dosage of 800 mg (b) (4) for the general patient population.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

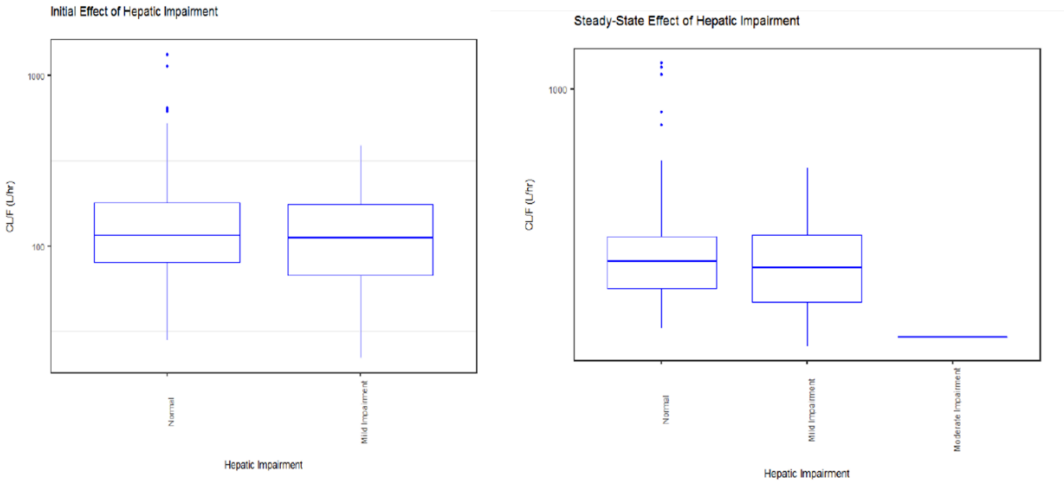
Based on the Population PK analysis, the following patient intrinsic factors including age (16 to 91 years), sex, race (White, Black, Asian), body weight (37.3 to 173 kg), drug metabolizing enzyme (DME) phenotype, and organ dysfunction (mild hepatic impairment [total bilirubin > 1 to 1.5 x ULN or AST > ULN] or renal impairment) have no clinically meaningful effects on the systemic exposure of tazemetostat; therefore, no dose adjustment is recommended with respect to these factors. Responses were limited to those patients with INI1 loss.

Hepatic impairment

Based on the Population PK analysis, no dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin > 1 to 1.5 x ULN or AST > ULN).

The results of the population PK analysis, including patients with normal liver function (n=515) and patients with mild hepatic impairment (n=166) at baseline, suggested that the status of mild hepatic impairment had no significant effect (< 10% lower median CL/F) on tazemetostat clearance (Figure 15); therefore, no dose adjustment is recommended for patients with mild hepatic impairment.

Figure 15: Comparison of post-hoc CL/F in patients with mild hepatic impairment vs. patients with normal hepatic function (left: initially and right: steady-state)



Source: EZH-p101 Population PK and simulation of tazemetostat in patients with cancer

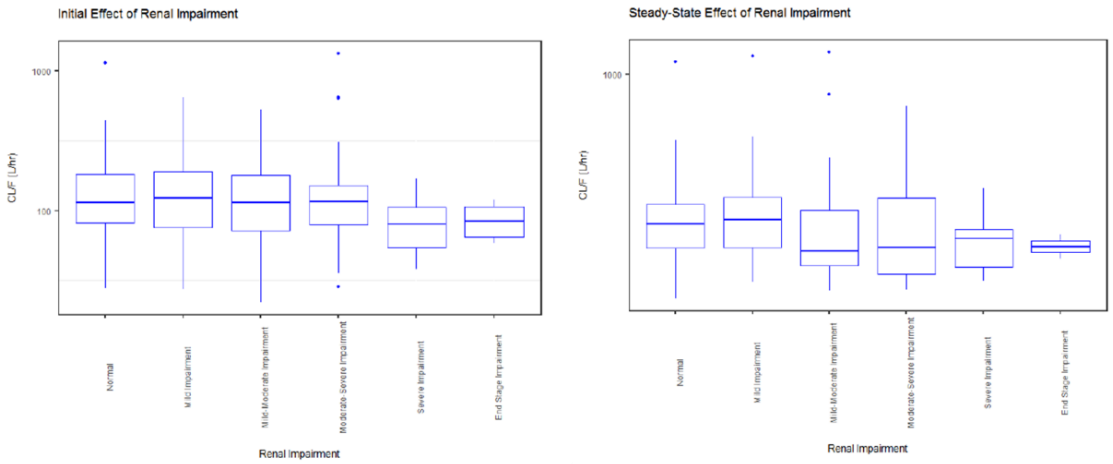
As the effects of moderate (total bilirubin > 1.5 to 3x ULN) and severe (total bilirubin > 3 x ULN) hepatic impairment on the exposure of tazemetostat and safety have not been studied, and hepatic metabolism is the major elimination pathway for tazemetostat, a dedicated hepatic impairment study will be required as a PMR.

Renal impairment

Results from the first-in-human study (E7438-G000-101) showed that the fraction excreted unchanged (f_e) was less than 6% of the doses following oral administration of tazemetostat. Across all dose cohorts evaluated, mean renal clearance (CL_r) ranged from 5.34 L/h at 200 mg to 1.81 L/h at 1600 mg on Cycle 1, Day 1; and ranged from 5.08 L/h at 200 mg to 1.8 L/h at 1600 mg at Cycle 1, Day 15. In the ADME/mass balance study, EZH-103, an average of 78% of the total radioactivity was excreted in the feces, with 15% recovered in urine over 12 days. Taken together, renal excretion is a minor pathway for tazemetostat elimination. Hence, significant effect of renal impairment (RI) on PK of tazemetostat is not expected.

The pooled population PK analysis included 337 patients with normal renal function (eGFR≥ 90 mL/min/1.73 m^2 calculated by MDRD), 209 patients with mild RI (eGFR ≥ 60 to 89 mL/min/1.73 m^2), 73 patients with mild-moderate RI (eGFR ≥ 45 to 59 mL/min/1.73 m^2), 40 patients with moderate-severe RI (eGFR≥ 30 to 44 mL/min/1.73 m^2), 17 patients with severe RI (eGFR≥ 15 to 29 mL/min/1.73 m^2) and 5 patients with end stage disease (eGFR<15 mL/min/1.73 m^2) at baseline. Creatinine clearance (CLcr) was identified as a PK covariate for CL/F. The analysis identified less than 10% reduction in CL/F for mild to moderate renal impairment. For severe and end stage renal impairment, a reduction in CL/F was 32 to 42% initially and 25% at steady state, but is not considered clinically important to warrant dose reduction (**Figure 16**).

Figure 16. Comparison of post-hoc CL/F in patients with renal impairment vs. patients with normal renal function (left: initially and right: steady-state)



Source: EZH-p101 Population PK and simulation of tazemetostat in patients with cancer

In the safety subgroup analysis, no appreciable difference in TEAEs was noted between patients with normal renal function and those with mild to moderate renal impairment (Module 2.7.3. Summary of Clinical Safety). No meaningful comparison of TEAEs could be made for patients with severe renal impairment or ERSD due to limited sample size.

DME genotype-inferred phenotype

Germline DNA samples from 681 patients in studies E7438-G000-101, EZH-105, EZH-202, and EZH203 were genotyped for CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 using DMET Plus (Affymetrix Inc.). Phenotypes were inferred based on genotypes and were analyzed against Day 1 apparent tazemetostat clearance (CL/F). CYP2B6 poor-intermediate (PM-IM, N=2) and CYP2C9 PM-IM (N=1) metabolizers showed approximately 50% and 75% lower clearance compared to all other phenotype groups, respectively, although the small number of patients with these phenotypes limit the interpretation of the results. A trend towards lower clearance was also observed for CYP2A6 PM-IMs (N=5, ~50% lower CL/F) and for CYP2D6 PMs (N=34, 14% lower CL/F). However, given that tazemetostat is predominantly metabolized by CYP3A4 and consistent with the lack of drug-drug interaction recommendations in labeling for inhibitors or substrates of these DMEs, dose adjustment is not recommended for patients based on DME genotype-inferred phenotype.

INI1 status

Prior to enrollment in study EZH-202 pivotal Cohort 5, fresh or archival tumor samples from ES patients were assessed by local laboratories and required to have either loss of INI1 protein expression by immunohistochemistry (IHC; N = 60) or bi-allelic SMARCB1 gene loss by fluorescent in situ hybridization (FISH; N=1) or next generation sequencing (NGS; N=1) for eligibility. As described above and in section 8.1, the ORR in these patients (with INI1 loss) was 15%. Study EZH-202 Cohort 6 enrolled ES patients (N=44) regardless of INI1 status. Of the 44 patients, INI1 status was available for 39 patients, and 4 of these patients (10%) had INI1 expression (i.e., INI1 retention). This frequency is consistent with literature reports suggesting that about 90% of ES tumors show loss of INI1 [Hornick, 2009; Hornick, 2014]. None of the 4 patients with retained INI1 expression had an objective response following treatment with tazemetostat.

The proposed indication is not molecularly selected. Although mechanistically plausible, enrichment of Cohort 5 for ES with INI1 loss did not appear to aid in the identification of patients more likely to respond to tazemetostat. It is possible that the SWI/SNF complex function is perturbed by alterations beyond INI1, which may confer sensitivity to EZH2 inhibition and may be more relevant to the population studied. The lack of data on other potential driver alterations and the limited number of patients with INI1 retention in Cohort 6 makes it difficult to draw conclusions. Whether and to what extent alterations other than or in combination with INI1 loss affect the response to tazemetostat remains to be determined.

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

Food-Drug Interaction

Tazemetostat can be administered with or without food.

The effect of a high-fat, high-calorie meal on systemic exposure of tazemetostat was assessed in patients with cancer receiving a single dose of 200 mg tazemetostat (tablet at 200 mg strength) under either fed or fasted conditions in a randomized, cross-over study design.

As shown in **Table 11**, consumption of a high fat meal resulted in a 24% decrease in tazemetostat C_{max} and a 18% decrease in tazemetostat AUC with a the median t_{max} delayed from 1 hour at fasting state to 2 hours at fed state . This small food effect is not clinically relevant, thereby supporting tazemetostat administration irrespective of food intake.

Table 11. Effect of food on the exposure of tazemetostat (E7438) with tablet formulation (200 mg strength)

Analyte	Parameter[a]	FASTED 200 mg QD Tazemetostat (Reference)	FED 200 mg QD Tazemetostat (Test)	Least Square Geometric Mean Ratio (90% CI) (Test / Reference)
	N	13	13	13
E7438	T_{max} (h)	1.05 (0.583, 6.08)	2.08 (1, 6)	NA
E7438	C_{max} (ng/mL)	233 (180)	174 (212)	0.76 (0.46 – 1.25)
E7438	AUC_{last} (h*ng/mL)	909 (153)	731 (188)	0.82 (0.56 – 1.21)
E7438	AUC_{0-inf}(h*ng/mL)	1260 (141)	1000 (82.1)	0.82 (0.57 – 1.18)

Source: E7438-G000-101 noncompartmental PK analysis report, Table 15

Drug-Drug Interactions (DDI)

Effects of other drugs on tazemetostat

Strong and Moderate CYP3A Inhibitors

Strong CYP3A inhibitors: Coadministration of tazemetostat with strong CYP3A inhibitors is not recommended. The effect of strong CYP3A inhibitors on the exposure and safety of tazemetostat has not been studied. As tazemetostat is exclusively metabolized by CYP3A *in vitro***,** coadministration of strong CYP3A inhibitors is expected to increase tazemetostat plasma concentration and may lead to increased tazemetostat toxicities. Therefore, concomitant use of strong CYP3A inhibitors with tazemetostat should be restricted. A PMR study is required to assess the effect of a strong CYP3A inhibitor on the exposure of tazemetostat.

Moderate CYP3A inhibitors: Coadministration of tazemetostat with moderate CYP3A inhibitors is not recommended. If coadministration with a moderate CYP3A inhibitor cannot be avoided, reduce the tazemetostat dose by 50% from the current dose.

Coadministration of fluconazole, moderate CYP3A inhibitor, with tazemetostat 400 mg BID increased tazemetostat C_{max} by 2.3-fold and AUC_{last} by 3.1-fold at steady-state (**Table 12**). The corresponding mean plasma concentration-time profiles of tazemetostat and metabolites are shown in **Figure 17**. Taking into consideration the E-R relationship for tazemetostat efficacy and safety (a positive E-R trend for efficacy and a ~ 2-fold exposure margin relative to the highest 1600 mg BID dose administered in humans), as well as the available dosage strength, a 50%

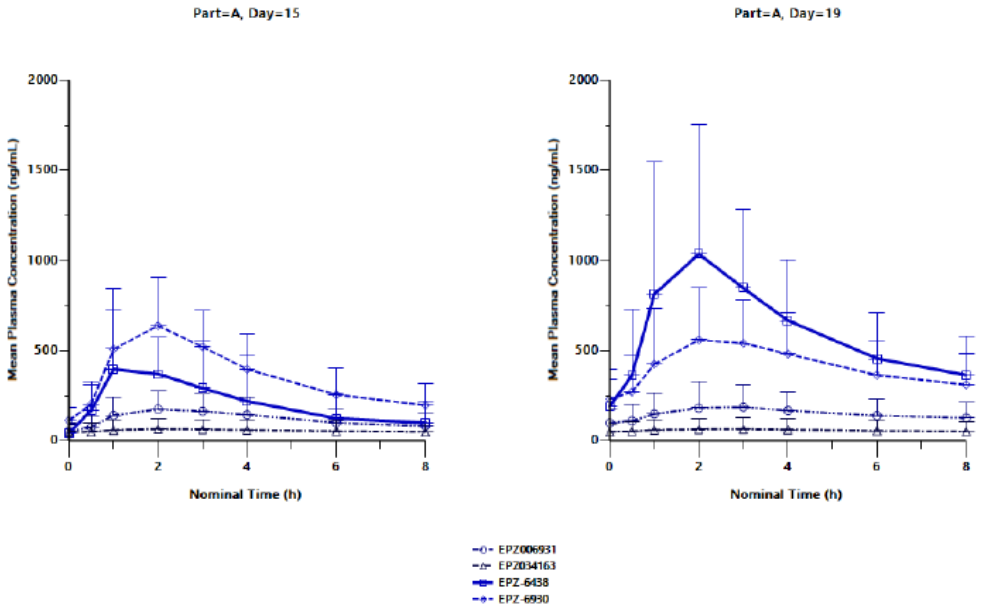
dose reduction from the current dosage is recommended when tazemetostat is coadministered with moderate CYP3A inhibitors.

Table 12. Tazemetostat (EPZ-6438) exposure at steady state following oral 400 mg BID administration with or without coadministration of fluconazole

Analyte	PK Parameters	Geometric Mean (CV%)		Geometric Mean Ratio (90% CI)
		Without fluconazole (reference, n=14)	With fluconazole (test, n=14)	
Tazemetostat (EPZ-6438)	C_{max} (ng/mL)	426 (62%)	968 (67%)	2.27 (1.75, 2.95)
	$AUC_{0\text{-last,SS}}$ (ng•h/mL)	1340 (72%)	4100 (56%)	3.06 (2.57, 3.66)

Source: EZH-105 noncompartmental PK analysis report, Table 5

Figure 17. Mean (+SD) plasma concentration-time profile of tazemetostat (EPZ-6438) and metabolites at steady-state with or without coadministration of fluconazole (Day 15: Tazemetostat alone; Day 19: Tazemetostat + Fluconazole)



Source: EZH-105 noncompartmental PK analysis report, Figure 2

Strong and Moderate CYP3A4 Inducers

Concomitant use of strong or moderate CYP3A inducers with tazemetostat is not recommended.

The effect of strong and moderate CYP3A inducers on the exposure of tazemetostat has not been studied. As tazemetostat is exclusively metabolized by CYP3A *in vitro*, coadministration of

CYP3A inducers is expected to decrease tazemetostat plasma concentration and may reduce tazemetostat efficacy. A PMC study is required to assess the effect of a strong CYP3A inducer on the exposure of tazemetostat.

Gastric Acid-reducing Agents

Dose adjustment is not recommended for tazemetostat when coadministered with proton pump inhibitors (PPI).

In vitro, tazemetostat exhibits pH-dependent solubility as shown in **Table 13**. The *in vitro* solubility over the intestinal pH range of 5 to 7 was lower than the expected drug concentration at the proposed 800 mg dose (800 mg/250 mL ~ 3.2 mg/mL).

Table 13. *In vitro* solubility of tazemetostat in aqueous media

Buffer Solution	Buffer pH	Solubility (mg/mL)
HCl/KCl (134 mM HCl)	1.0	7.27
HCl/KCl (13.4 mM HCl)	2.0	7.03
Acid phthalate 50 mM	3.0	6.87
Acid phthalate 50 mM	4.0	6.99
Neutralized phthalate 50 mM	5.5	0.508
Phosphate 50 mM	6.8	0.033

Source: RPT-00001 Tazemetostat Tablets Dissolution Method Development Report

Coadministration of a proton pump inhibitor omeprazole (20 mg QD) with tazemetostat 800 mg BID increased steady-state tazemetostat C_{max} and $AUC_{0\text{-}8h}$ by approximately 25% (**Table 14**). The median t_{max} of tazemetostat was 1.97 hours when coadministered with omeprazole (Day 19) compared to 1.07 hours when administered alone (Day 15). As omeprazole was administered approximately one hour after tazemetostat dosing on the reference day (Day 15) and gastric acid reduction was likely achieved while the absorption of tazemetostat was still ongoing, the effect of PPI could be underestimated from the study. In the population PK analysis, coadministration of proton pump inhibitors was shown to reduce tazemetostat absorption rate (K_a), however the effect of PPI on tazemetostat CL/F is not clinically relevant (<10% increase). Caution needs to be taken in interpretation of population PK results as the PPI dosing records were not well documented.

Table 14. Effect of omeprazole on exposure of tazemetostat (EPZ-6438)

Analyte	PK Parameters	Geometric Mean (CV%)		Geometric Mean Ratio (90% CI)
		Without omeprazole (reference, n=13)	With omeprazole (test, n=11)	
EPZ-6438	$C_{max.ss}$ (ng/mL)	521 (84.4%)	641 (55%)	1.25 (0.764, 2.03)

	$AUC_{0\text{-last,ss}}$ (ng•h/mL)	1780 (87.1%)	2150 (43.3%)	1.26 (0.872, 1.82)

Source: EZH-105 noncompartmental PK analysis report, Table 5

Overall, the available data suggested that concurrent use of gastric acid reducing agents has no large clinically relevant effect on tazemetostat exposure.

P-gp Inhibitors

Tazemetostat is a P-gp substrate *in vitro*. As shown in **Table 15**, P-gp-mediated tazemetostat efflux appeared to be saturated at 100 µmol/L (~ 0.057 mg/mL), which is lower than the *in vitro* solubility over the intestinal pH range (**Table 13**) and the value of dose/250 mL (3.2 mg/mL). Therefore, P-gp is expected to play a minor role in regulating tazemetostat absorption and the P-gp-mediated DDI risk at intestinal absorption is low for tazemetostat as a victim drug.

Table 15. Efflux ratios of Tazemetostat across cells expressing P-gp transporter

Transporters	Cell Lines	Efflux Ratio			
		P-gp or BCRP Control Substrate	Tazemetostat Concentration (µmol/L)[1]		
			10	30	100
P-gp[2]	LLC-PK1	3.7	1.3	0.7	0.9
	LLC-MDR1	35.5	174	41.3	4.6

Source: Module 2.6.4 Pharmacokinetics written summary, Table 22

Effects of Tazemetostat on Other Drugs

Effect of Tazemetostat on CYP3A Substrate

Tazemetostat showed multiple mechanisms of CYP3A regulation *in vitro*, including competitive- and time-dependent inhibition as well as induction. Coadministration of tazemetostat oral 800 mg BID with a single 2 mg oral dose of midazolam, a sensitive CYP3A substrate, decreased midazolam C_{max} by 21% and AUC_{last} by 40% (**Table 16** and **Figure 18**). The geometric mean ratio based on AUC_{inf} was less reliable as AUC_{inf} values were not reportable in individuals with % $AUC_{extrapolation}$ > 20%. Consistently, 4β-Hydroxycholesterol, an endogenous marker for CYP3A , also exhibited an 1.7-fold increase in exposure following tazemetostat treatment.

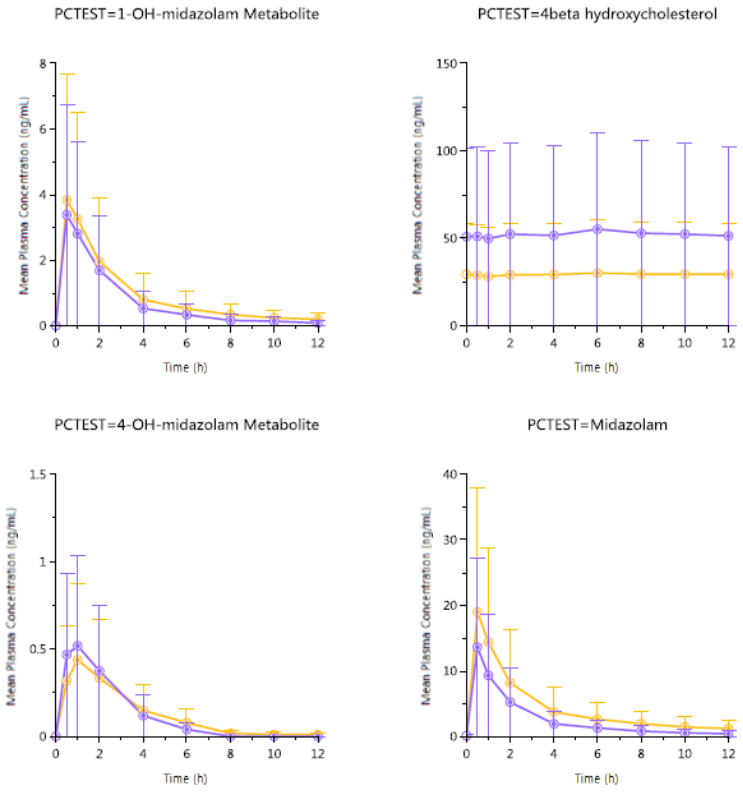
Table 16. Midazolam exposure following a single oral dose of midazolam (2 mg) with or without coadministration of tazemetostat 800 mg BID

Analyte	PK Parameters	Geometric Mean (CV%)		Geometric Mean Ratio (90% CI)
		Without tazemetostat (reference, n=14)	With tazemetostat (test, n=14)	
Midazolam	C_{max} (ng/mL)	15.5 (94.1%)	12.4 (55.6%)	0.79 (0.59 – 1.06)

	$AUC_{0\text{-last}}$ (ng•h/mL)	46.7 (84.7%)	29.6 (54.4%)	0.60 (0.48 – 0.76)
	AUC_{inf} (ng•h/mL)	46.8 (64.5%)	41.1 (62.5%)	0.86 (0.47 – 1.57)

Source: E7438-G000-101 noncompartmental PK analysis report, Table 17 and amendment

Figure 18. Mean (±SD) plasma concentration-time profiles of midazolam and metabolites following a single oral dose of midazolam (2 mg) administered with (purple line) or without tazemetostat 800 mg BID (yellow line)



Source: E7438-G000-101 noncompartmental PK analysis report, Figure 44

Effects of Tazemetostat on CYP2C8 and CYP2C19 Substrates

Tazemetostat exhibited *in vitro* potential for CYP2C8 and 2C19 inhibition, while the in vitro evaluation of CYP2C induction effect was inconclusive. In patients with cancer, coadministration of tazemetostat 800 mg BID with single oral doses of repaglinide (0.25 mg, a sensitive CYP2C8 substrate) and omeprazole (20 mg, a sensitive CYP2C19 substrate) increased repaglinide C_{max} by 50% and AUC_{inf} by 80%, while had no effect on the exposure of omeprazole (**Table 17** and **Figure 19**).

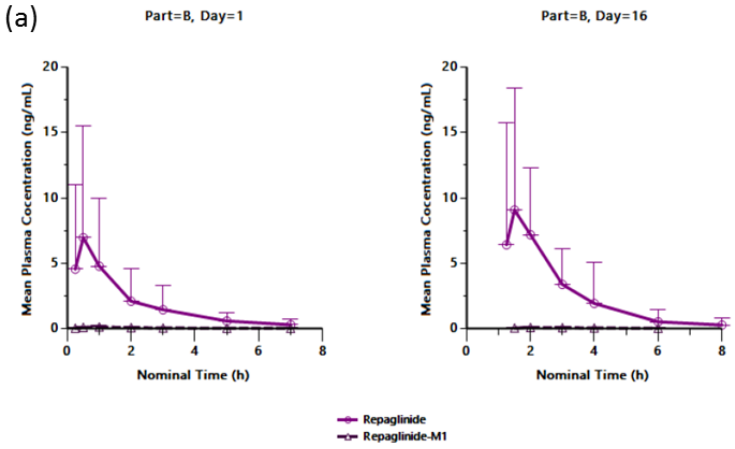
Table 17. Repaglinide and omeprazole exposure following a single oral dose of repaglinide and omeprazole with or without coadministration of tazemetostat 800 mg BID

Analyte	PK Parameters	Geometric Mean (CV%)		Geometric Mean Ratio (90% CI)
		Without tazemetostat (reference, n=13)	With tazemetostat (test, n=13)	
Repaglinide	C_{max} (ng/mL)	5.14 (110%)	7.75 (79.7%)	1.51 (0.821 - 2.78)
	$AUC_{0\text{-}8\ h}$ (ng•h/mL)	8.16 (111%)	14.7 (76.7%)	1.80 (1.12 – 2.87)
Omeprazole	C_{max} (ng/mL)	253 (97.1%)	207 (78.6%)	0.82 (0.50 – 1.35)
	$AUC_{0\text{-}8\ h}$ (ng•h/mL)	600 (117%)	480 (100%)	0.80 (0.525- 1.22)

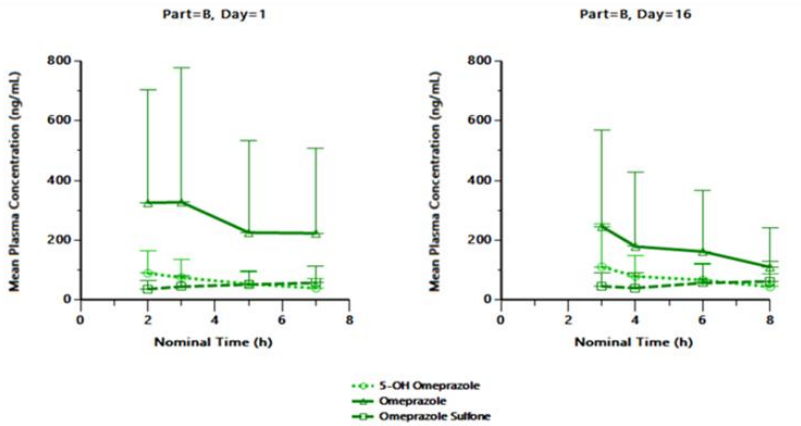
Source: EZH-105 noncompartmental PK analysis report, Table 5 and 6.

Note: plasma samples collected to 7 h post dose on Day 1 repaglinide+ omeprazole alone.

Figure 19. Mean (+SD) plasma concentration-time profiles of (a) repaglinide and metabolite and (b) omeprazole and metabolites following single oral doses of the probe cocktail administered with or without coadministration of tazemetostat 800 mg BID (Day 1: repaglinide+omeprazole alone; Day 16: repaglinide+omeprazole+tazemetostat)



(b)



Source: EZH-105 noncompartmental PK analysis report, Figure 6.

In summary, tazemetostat is a CYP3A substrate and therefore subject to DDI risk with CYP3A modulators. Dose adjustment is recommended for concomitant administration of tazemetostat with moderate CYP3A inhibitors. Concomitant administration of tazemetostat with strong CYP3A inhibitors and strong or moderate CYP3A inducers should be restricted based on expected clinical impact and lack of data. As a perpetrator, tazemetostat is classified as a weak inducer of CYP3A and 2C19; and a weak inhibitor of CYP2C8 based on the clinical DDI evaluation.

X

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 18: Table of Clinical Trials

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
EZH-202 Cohort 5	02601950	Open-label, single-arm, multicenter, multi-cohort	800 mg orally BID	Primary: ORR Secondary: DOR, DCR, and PFS and OS at 24, 32, and 56 weeks and overall	Up to 2 years	62	ES with loss of INI1	32 France, United Kingdom, Germany, Australia, Taiwan, Italy, Canada, Belgium, US
EZH-202 Cohort 6	02601950	Open-label, single-arm, multicenter, multicohort	800 mg orally BID	Primary: assess tumor immune priming Secondary: ORR, DCR, DOR, PFS and OS at 24, 32, and 56 weeks and overall	Up to 2 years	44	ES undergoing mandatory tumor biopsy	32 France, United Kingdom, Germany, Australia, Taiwan, Italy, Canada, Belgium, US

Source: CSR
Abbreviations: BID: twice daily; ORR: overall response rate; DOR: duration of response; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; ES: epithelioid sarcoma; US: United States

7.2. Review Strategy

The FDA clinical review of the NDA was conducted by one primary Clinical Reviewer and one primary Statistical Reviewer. The primary efficacy claims for the proposed indication are supported by a single trial, EZH-202. The Applicant submitted the application on the basis of efficacy data from Cohort 5 which enrolled a total of 62 patients with epithelioid sarcoma (ES) with INI loss. The review and analysis data included the Interim Clinical Study Report (CSR) for trial EZH-202, Summary of Clinical Efficacy, case report forms (CRFs), and datasets. The following efficacy endpoints were analyzed: primary efficacy endpoint: ORR; secondary endpoint: DOR.

During the review, FDA noted that Cohort 6 of trial EZH-202 enrolled a similar population to Cohort 5, and consequently the primary efficacy analyses in this review are based on data from Cohort 5 and 6, and the pooled analysis of both cohorts (See Section 8.1.1 and Table 18 for further details). Cohort 6 of trial EZH-202 enrolled a total of 44 patients with ES who underwent a mandatory biopsy and were not required to have INI1 loss. FDA requested Cohort 6 data from Study EZH-202 as supportive efficacy data for the NDA review. The review analysis included materials submitted by the Applicant on October 24, 2019: Cohort 6, EZH-202 Clinical Overview, and datasets.

The Applicant also submitted a natural history study to support the efficacy findings in study EZH-202. This study and its results are briefly summarized in Section 19.1. The Applicant designed and performed this study without FDA input on the protocol and approach. FDA does not consider the design of the study adequate to provide direct or relevant evidence of any aspect of efficacy reviewed in this application. As a result, the results of the natural history study are not considered in FDA's assessment of the efficacy of tazemetostat.

The primary clinical review of safety focused on the safety population of 62 patients from Cohort 5. The review and analysis of data included the Interim CSR, Summary of Clinical Safety (SCS), narrative reports for deaths, serious adverse events (SAEs), and AEs leading to discontinuation. Additional analysis focused on the adverse event of special interest (AESI) for secondary malignancies.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

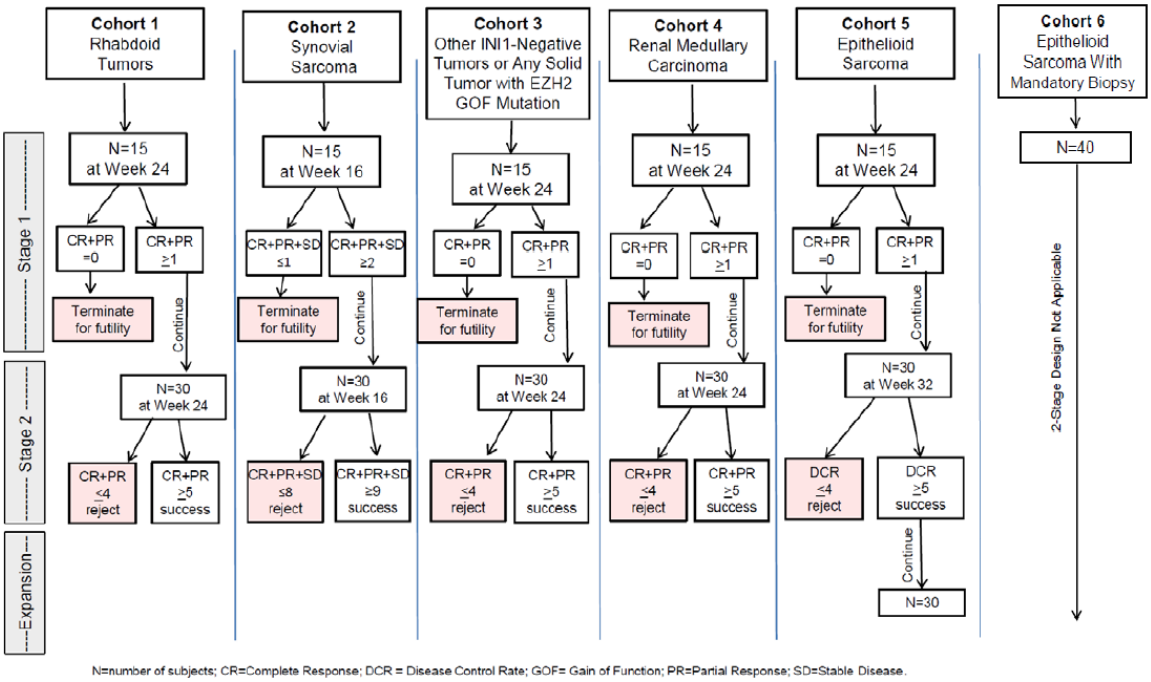
8.1.1. Study EZH-202

Trial Design

Study EZH-202 is an ongoing, open-label, single-arm, multicenter, multi-cohort study in patients with INI1-negative tumors or relapsed/refractory synovial sarcoma. The study was initially designed as a two-stage study with three cohorts. The study was later expanded to include separate cohorts for patients with metastatic or unresectable, locally advanced ES. Cohort 5 was added with amendment 3 dated March 2, 2016, based on the high enrollment rates of patients with ES into cohort 3. Cohort 5 enrolled a total of 62 patients with ES who had documented INI1 loss. Cohort 6 was added with amendment 5 dated August 7, 2017. Cohort 6 enrolled 44 ES patients regardless of INI1 status but required mandatory tumor biopsy.

Patients in Cohorts 5 and 6 received tazemetostat 800 mg BID in continuous 28-day cycles for up to 2 years or until disease progression, development of an unacceptable toxicity, withdrawal of consent, or termination of the study. The study schema for Study EZH-202 is shown in Figure 20.

Figure 20: Study Schema of EZH-202



N=number of subjects; CR=Complete Response; DCR = Disease Control Rate; GOF= Gain of Function; PR=Partial Response; SD=Stable Disease.

Source: Adapted from Figure 2 of Protocol EZH-202 version 4, pg. 38 and Figure 2 of Protocol EZH-202 version 5, pg. 41.

Key inclusion criteria for Cohorts 5 and 6 included patients ≥18 years of age (this was amended from age ≥16 years with amendment 6) with metastatic or unresectable, locally advanced epithelioid sarcoma; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤2; life expectancy of >3 months; ejection fraction of ≥50%; and QT interval corrected ≤480 msec. Key exclusion criteria included thrombocytopenia, neutropenia, or anemia of Grade ≥3. Cohort 5 was designed to evaluate the efficacy of tazemetostat in patients with epithelioid sarcoma, while Cohort 6 was designed to assess the effects of tazemetostat on tumor immune priming in patients with epithelioid sarcoma. Consequently, certain eligibility criteria were different for these two cohorts. Table 19 compares key eligibility criteria for these cohorts.

Table 19: Comparison of Eligibility Criteria in Cohorts 5 and 6 of EZH-202

Cohort 5	Cohort 6
Morphology and immunophenotypic panel consistent with INI1-negative tumors and • Loss of INI1 confirmed by IHC, or • Molecular confirmation of tumor bi-allelic INI1 loss or mutation when INI1 IHC is • Equivocal or unavailable, or • Molecular evidence of EZH2 GOF mutation	Morphology and immunophenotypic panel consistent with ES (e.g., CD34, EMA, Keratin, and INI1)
Mandatory biopsy not required	Willingness to provide informed consent to undergo pre- and post-dose biopsy
Progressed within 6 months prior to study enrollment (Cohort 5 Expansion only)	Progressed within 6 months prior to study enrollment

Source: Adapted from pg. 43 of Protocol EZH-202, amendment 6.

Reviewer's comment: In general, patients required to undergo mandatory biopsy may differ from those not required to undergo mandatory biopsy in that the location of the tumor must be easily accessible for biopsy. FDA does not consider this likely to affect the efficacy of tazemetostat. The requirement for progression within 6 months prior to study therapy may select for a population with more aggressive tumors; however, as the median time between progression on last therapy and study enrollment was < 2.5 months, FDA does not consider this likely to affect the efficacy of tazemetostat. The Applicant postulates that tazemetostat's mechanism of action may be influenced by INI1 loss, which could impact response rate. However, a sensitivity analysis (see Section 8.1.2) demonstrated that the inclusion of patients with INI1 retention does not appear to have substantially affected the reported response rate in this cohort.

Efficacy and safety data were initially submitted to the NDA for Cohorts 5 and 6 on May 23, 2019, with a data cut-off date of September 17, 2018. Upon receipt of the data from Cohort 6, FDA noted that the ORR for Cohort 6 was 5% (95% CI: [0, 16]). FDA acknowledged that the duration of follow-up for patients in Cohort 6 was shorter than that of Cohort 5, and thus requested that the Applicant submit updated efficacy data from Cohort 6 with the 120-day safety update. The new data cut-off date for Cohort 6 was July 31, 2019, which provided an additional 10 months of follow-up.

FDA noted that there were only minor differences in eligibility criteria between Cohorts 5 and 6. In addition, baseline characteristics, demographics, follow-up time, and efficacy results were similar between the two cohorts. FDA believes that Cohort 5 and 6 represent similar patient populations and may be reasonably pooled and that the minor differences between the two cohorts would not have a large impact on efficacy.

Study Endpoints

The primary endpoint of Cohort 5 was confirmed ORR by independent review committee (IRC) as assessed by RECIST v1.1. The secondary endpoints were DOR, DCR, PFS and OS at Weeks 24, 32, and 56, and overall. The primary endpoint of Cohort 6 was to assess the effects of tumor immune priming. The secondary endpoints were ORR, DOR, and DCR.

ORR was defined as confirmed complete response (CR) or partial response (PR) from the start of treatment until disease progression or the start of subsequent anti-cancer therapy as per RECIST 1.1 criteria. CR or PR was confirmed by subsequent scan at ≥4 weeks after initial documentation of CR or PR. DOR for the subset of patients with confirmed CR or PR response, was defined as the interval of time from the first documented evidence of CR or PR until the first documented disease progression or death due to any cause, using disease-appropriate standardized response.

Endpoints Included in Review

FDA considers ORR to be the primary efficacy measure for both Cohorts 5 and 6.

Statistical Analysis Plan

Cohort 5 used a Green-Dahlberg two-stage design, to allow early termination of the cohort due to lack of efficacy. A clinically meaningful ORR was specified as 20%. Table 20 shows the sample size rationale for Cohort 5.

Table 20: Sample Size Rationale for EZH-202, Including Amended Design for Cohort 5

	Each Cohort Separately: **Cohort 1[a]** (Rhabdoid tumors) **Cohort 3[a]** (Other INI1-negative tumors or any solid tumor with EZH2 GOF mutation) **Cohort 4[a]** (Renal medullary carcinoma) **Cohort 7[a]** (Chordoma)	**Cohort 2[a]** (Relapsed/refractory synovial sarcoma)	**Initial Design: Cohort 5[a]** (Epithelioid sarcoma)	**Amended Design: Cohort 5[b]** (Epithelioid sarcoma)
Stage 1: Null hypothesis	CR + PR ≤5%	CR + PR + SD at Week 16 ≤15%	CR + PR ≤5%	DCR ≤5%
Stage 1: Alternative hypothesis	CR + PR ≥20%	CR + PR + SD at Week 16 ≥35%	CR + PR ≥20%	DCR ≥20%
Stage 1 sample size (n1)[c]	15	15	15	
Stage 1 rejection of study treatment (r1)[c]	0	1	0	
Stage 2 sample size (n2)	15	15	15	15
Stage 2 rejection of study treatment (r)	4	8	4	4
Total sample size (n)	30	30	30	30

a. All subjects will have completed at least the Week 24 (Week 16 for synovial sarcoma) assessment, completed the final study visit, or terminated early from the study, whichever is sooner.
b. All subjects will have completed at least the Week 32 assessment, completed the final study visit, or terminated early from the study, whichever is sooner- based on Amendment 4.
c. Within each cohort, the interim analysis planned at the end of Stage 1 may occur sooner if the Stage 1 rejection criterion is surpassed before all 15 subjects are treated and followed for the specified time. In this scenario, the total sample size (Stage 1 + Stage 2) for a cohort would still remain unchanged at 30 subjects.
d. An additional 30 subjects may be enrolled for expanded evaluation of efficacy and safety. Enrollment in the expansion stage may be opened once the Stage 2 rejection criterion has been surpassed. If this occurs prior to the full enrollment of Stage 2, the total cohort sample size (Stage 1 + Stage 2 + expansion) will remain unchanged at 60 subjects.

Source: Protocol EZH-202, pg. 85.

In addition to the 30 patients planned for the Green-Dahlberg design, Cohort 5 allowed for an additional 30 patients to be enrolled for "expanded evaluation of efficacy and safety." Cohort 6 was not designed to power for efficacy considerations.

Protocol Amendments

Table 21 shows a timeline for EZH-202, including important protocol amendments and Independent Data Monitoring Committee (IDMC) interactions.

Table 21: Major Protocol Amendments for EZH-202

Event (Date)	Date	Amendment
Amendment 3	March 2, 2016	Patients with epithelioid sarcoma that had originally been enrolled in Cohort 3 (n=6) were moved to Cohort 5. The original planned enrollment for Cohort 5 was 30 patients (original phase). Primary endpoint ORR.
IDMC	October 4, 2016	Futility boundary passed for Cohort 5.
IDMC	October 21, 2016	The sponsor requested the IDMC re-convene to discuss amending Cohort 5 to assess DCR. The IDMC endorsed a change in primary endpoint for Cohort 5 from ORR to DCR.
Amendment 4	October 25, 2016	Expansion of Cohort 5 to N=60 patients specified. DCR added as primary endpoint. Futility bound for Stage 2 based on DCR rather than ORR Futility for Stage 2 moved from Week 30 to Week 24 Criteria for Cohort 5 expansion added that patients must have progressed 6 months prior to enrollment.
Amendment 5	August 7, 2017	Primary endpoint specified to be ORR only, DCR downgraded to secondary endpoint Cohort 6 added.
Amendment 6	September 28, 2018	Final amendment. T-LBL/T-ALL and MDS added as adverse events of special interest

Source: Reviewer's analysis.
Abbreviations: ORR: overall response rate; IDMC: Independent Data Monitoring Committee; DCR: disease control rate; T-LBL: T-cell lymphoblastic lymphoma; T-ALL: T-cell acute lymphoblastic leukemia; MDS: myelodysplastic syndrome

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in accordance with Good Clinical Practices (GCP), as defined by the International Conference on Harmonization (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and the United States (U.S.) Code of Federal Regulations (CFR), Title 21, Part 50 (21CFR50). The Applicant also stated that the study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The protocol, amendments, and subject informed consent received appropriate approval by the IRB/IEC prior to initiation of the study at the site.

Financial Disclosure

In accordance with 21 CFR 54.2, the Applicant submitted a list of the EZH-202 study investigators attached to FDA form 3454 certifying that the Principal Investigators and Sub-investigators had no financial information to disclose as defined in 21 CFR 54.2(e) that could affect the outcome of the study.

A summary of financial disclosures for Study EZH-202 is provided in the Appendix (Section 13.2). The Applicant submitted financial disclosure information from all 349 of the investigators.

Data Quality and Integrity

Data, statistical programs, and study reports of this application were submitted electronically. The overall quality of the submission is acceptable, and the reviewer was able to perform all analyses using the submitted data. Derivations for key variables were verified, as well as demographic variables. No inconsistencies were found in the reported efficacy results or patient baseline characteristics.

Data were initially submitted on June 23, 2019, with a data cut-off date of September 17, 2018. During a telephone conference on September 18, 2019, and email correspondence sent on September 26, 2019, FDA requested updated data for Cohort 6 to further characterize the efficacy of tazemetostat. FDA and the Applicant agreed to a new data cut-off date of July 31, 2019, for this cohort. This date provides a similar time of follow-up for patients in Cohort 6 as the September 17, 2018, cut-off date for patients in Cohort 5. In the analyses that follow, a cut-off date of September 17, 2018, is used for Cohort 5 and a cut-off date of July 31, 2019, is used for Cohort 6.

Efficacy Analysis Population

The primary population used in the analyses below includes patients from Cohorts 5 and 6 who received any amount of tazemetostat. This pooled efficacy population is referred to as the "Analysis Population." For tables that show results for Cohort 5, Cohort 6, and this pooled population, the population is referred to as "Pooled."

Patient Disposition

Table 22 displays the patient disposition in the analysis population of EZH-202 at the time of data cut-off for the respective cohorts.

Table 22: Patient Disposition in the Analysis Population of EZH-202

	Cohort 5 N=62 n (%)	Cohort 6 N=44 n (%)	Pooled N=106 n (%)
End of treatment status			
Ongoing	8 (13)	8 (18)	16 (15)
Discontinued	54 (87)	36 (82)	90 (85)
End of study status			
Ongoing	11 (18)	10 (23)	21 (20)
Alive	15 (24)	11 (25)	26 (25)
Discontinued	36 (58)	23 (52)	59 (56)
Reason for treatment discontinuation			
Ongoing	8 (13)	8 (18)	16 (15)
Death	4 (6)	1 (2.3)	5 (5)
Non-Compliance	0 (0)	1 (2.3)	1 (0.9)
Other	1 (1.6)	0 (0)	1 (0.9)
Physician Decision	1 (1.6)	0 (0)	1 (0.9)
Progressive Disease - Clinical	6 (10)	6 (14)	12 (11)
Progressive Disease - Radiologic	39 (63)	27 (61)	66 (62)
Subject Refused Further Treatment of Study Drug	2 (3.2)	1 (2)	3 (2.8)
Unacceptable Toxicity	1 (1.6)	0 (0)	1 (0.9)
Reason for study discontinuation			
Ongoing	26 (42)	21 (48)	47 (44)
Completion of 2 Years of Treatment or Post-Treatment Follow-Up	1 (1.6)	0 (0)	1 (0.9)
Death	31 (50)	20 (45)	51 (48)
Lost to Follow-Up	4 (6)	1 (2.3)	5 (5)
Withdrawal by Subject	0 (0)	2 (5)	2 (1.9)

Source: Reviewer's analysis.

Reviewer's comment: Because Cohort 6 was initiated after Cohort 5, a later cut-off date was

needed to yield similar follow-up between the cohorts. This later cut-off date for Cohort 6 appears to have yielded similar disposition for patients in Cohort 6 to patients in Cohort 5 whose data cut-off was September 17, 2018. We note that at the time of the respective cut-offs, 13% of patients were receiving ongoing treatment in Cohort 5 and 18% of patients were receiving ongoing treatment in Cohort 6.

Protocol Violations/Deviations

Table 23 presents a summary of protocol violations for inclusion or exclusion criteria at baseline in the analysis population of EZH-202.

Table 23: Summary of Inclusion or Exclusion Criteria Violated at Baseline in the Analysis Population of EZH-202

Patient ID	Criteria Violated	Cohort	Baseline deviation description
(b) (6)	Inclusion	Cohort 5	Insufficient tissue for mutation analysis
	Exclusion	Cohort 5	Prohibited medication
	Inclusion	Cohort 5	Inadequate hematologic, renal, or hepatic function
	Inclusion	Cohort 5	Inadequate hematologic, renal, or hepatic function
	Inclusion	Cohort 5	Inadequate hematologic, renal, or hepatic function
	Inclusion	Cohort 5	Inadequate hematologic, renal, or hepatic function
	Inclusion	Cohort 5	Insufficient tissue for mutation analysis
	Inclusion	Cohort 5	No measurable disease
	Exclusion	Cohort 5	Has CNS or leptomeningeal metastases
	Inclusion	Cohort 5	Insufficient tissue for mutation analysis
	Inclusion	Cohort 5	Prohibited medication
	Inclusion	Cohort 5	Inadequate hematologic, renal, or hepatic function
	Inclusion	Cohort 5	Insufficient tissue for mutation analysis
	Inclusion	Cohort 6	Unable to provide biopsy

Source: Reviewer's analysis.

Reviewer's comment: Patient (b) (6) *did not have measurable disease at baseline, and thus was considered a non-responder in the primary analysis of efficacy. The following inclusion/exclusion criteria are not considered likely to impact efficacy: insufficient tissue for mutation analysis and unable to provide biopsy. An assessment of the efficacy in the subpopulation of patients who did not violate inclusion or exclusion criteria likely to impact efficacy is presented in Subpopulations, below.*

Demographic and Baseline Characteristics

Overall, the demographics and baseline characteristics for Cohorts 5 and 6 were similar, as shown in Table 24 and Table 25. The majority of patients were male, White, not Hispanic, and with ECOG PS of 0. In Cohort 5, 65% of patients were from the US; 39% were from the US in Cohort 6. Most patients had stage III or IV disease at baseline; 42% of patients in the pooled population were treatment-naïve.

Table 24: Demographics of Patients in the Analysis Population

	Cohort 5 N=62 n (%)	Cohort 6 N=44 n (%)	Pooled N=106 n (%)
Gender			
Female	23 (37)	18 (41)	41 (39)
Male	39 (63)	26 (59)	65 (61)
Age			
Mean years (SD)	37 (15)	38 (13)	37 (14)
ECOG performance status			
0	36 (58)	28 (64)	64 (60)
1	21 (34)	14 (32)	35 (33)
2	5 (8)	2 (4.5)	7 (7)
Race			
Black or African American	4 (6)	1 (2.3)	5 (4.7)
Asian	7 (11)	4 (9)	11 (10)
White	47 (76)	36 (82)	83 (78)
Other/Unknown	4 (6)	3 (7)	7 (7)
Ethnicity			
Not Hispanic or Latino	53 (85)	39 (89)	92 (87)
Hispanic or Latino	7 (11)	4 (9)	11 (10)
Not reported	2 (3.2)	1 (2.3)	3 (2.8)
Country			
France	4 (6)	2 (4.5)	6 (6)
Canada	2 (3.2)	2 (4.5)	4 (3.8)
United States	40 (65)	17 (39)	57 (54)
Taiwan	3 (4.8)	3 (7)	6 (6)
Italy	6 (10)	3 (7)	9 (8)
Great Britain	2 (3.2)	9 (20)	11 (10)
Belgium	5 (8)	3 (7)	8 (8)
Australia	0	2 (4.5)	2 (1.9)
Germany	0	3 (7)	3 (2.8)

Source: Reviewer's analysis

Table 25: Baseline Characteristics of the Analysis Population of EZH-202

	Cohort 5 N=62	Cohort 6 N=44	Pooled N=106
Epithelioid sarcoma subtype (%)			
Not collected	0 (0)	44 (100)	44 (42)
Conventional	31 (50)	0 (0)	31 (29)
Missing	4 (6)	0 (0)	4 (3.8)
Proximal	27 (44)	0 (0)	27 (25)
Stage of disease at diagnosis (%)			
I/II	9 (15)	11 (25)	20 (19)
III/IV	44 (71)	31 (70)	75 (71)
Unknown	9 (15)	2 (4.5)	11 (10)
Number of lines of prior therapy (%)			
0	24 (39)	20 (45)	44 (42)
1+	38 (61)	24 (55)	62 (58)
Most common prior therapies received[1] (%)			
Doxorubicin	28 (45)	19 (43)	47 (44)
Ifosfamide	26 (42)	18 (41)	44 (42)
Gemcitabine	15 (24)	7 (16)	22 (21)
Pazopanib	12 (19)	8 (18)	20 (19)
Docetaxel	13 (21)	6 (14)	19 (18)
Time to last progressive disease (mean (sd)) (months)	2.2 (2.6)	1.7 (1.2)	2.0 (2.2)
Tumor location (%)			
Soft Tissue	21 (34)	17 (39)	38 (36)
Other	41 (66)	27 (61)	68 (64)

Source: Reviewer's analysis.
[1] Patients may have received more than one prior therapy. This list is not exhaustive.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance and accountability were described on the case report forms. The majority of patients reported taking at least one concomitant medication during the study. The most commonly administered medications were opioids, proton pump inhibitors,

glucocorticoids, benzodiazepines, antibiotics, and analgesics and antipyretics.

Efficacy Results – Primary Endpoint

The efficacy review is analyzed from data from study EZH-202. The primary population analyzed for efficacy was from Cohort 5 and consists of 62 patients with epithelioid sarcoma. Supportive efficacy data are presented from Cohort 6 which consisted of 44 patients with ES. The pooled analysis represents efficacy results for Cohorts 5 and 6. The primary endpoint was ORR as assessed by IRC according to RECIST v1.1 for Cohort 5 and will be used as the primary efficacy endpoint for Cohort 6 in this review. The pooled DOR ranged from 3.5 months to more than 24 months. There were a total of seven patients who had ongoing responses at the time of the respective data cut-offs for Cohorts 5 and 6.

In Cohorts 5 and 6, the ORR was similar at 15% and 11%, respectively. Pooled analysis demonstrated an ORR of 13% (95% CI: 7,21). Table 26 presents the analysis of confirmed ORR and DOR as assessed by IRC in the analysis population.

Table 26: Analysis of Confirmed ORR and DOR as Assessed by IRC in the Analysis Population

	EZH-202 Cohort 5 N = 62	**EZH-202 Cohort 6 N=44**	**EZH-202 Pooled N=106**
ORR	15%	11%	13%
(95% CI)	(7, 26)	(4, 25)	(7, 21)
CR (n, %)	1 (1.6)	1 (2)	2 (2)
PR (n, %)	8 (13)	4 (9)	12 (11)
DOR in months (range)	4, 24+	3.5, 18.2+	3.5, 24+
Median follow-up in months (range)	13.8 (0.2, 32)	11.8 (0.2, 21)	12.8 (0.2, 32)

Source: Reviewer's analysis.

The ORR for tazemetostat in Cohorts 5 and 6, and the pooled cohorts demonstrate similar response rates.

Reviewer's Comment: The ORR across cohorts and the pooled data are similar and may not provide sufficient evidence of an improvement over doxorubicin and other chemotherapies. From the pooled analysis, the ORR was 13% (95% CI: 7, 21). An ORR of 13% is a marginal treatment effect and does not provide sufficient evidence of clinical benefit in this patient population. Further, it is unclear if this response rate would translate into an improvement in OS or PFS.

Table 27 shows DOR by landmark time for Cohorts 5 and 6. In the pooled data, nine patients had a DOR for ≥6 months and four had a DOR ≥12 months.

Table 27: Duration of Response by Landmark Time in the Analysis Population

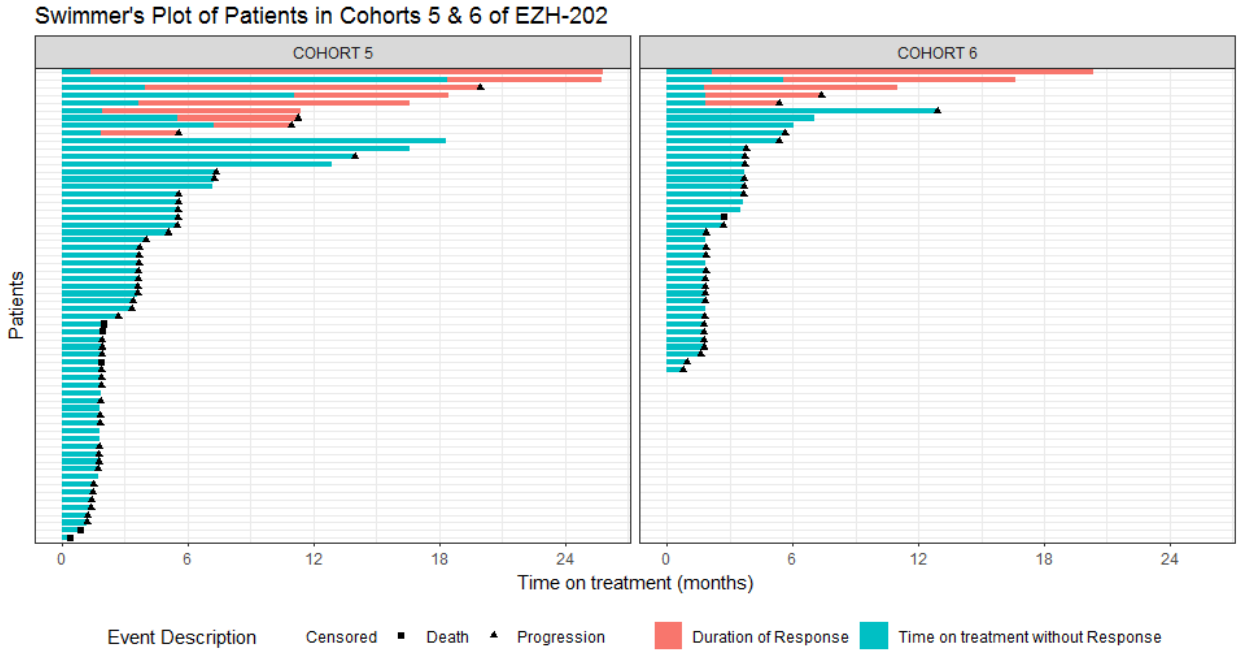
Responders	**EZH-202 Cohort 5 N = 9**	**EZH-202 Cohort 6 N = 5**	**EZH-202 Pooled N=14**
n with DOR			
≥ 3 months	9	5	14
≥ 6 months	6	3	9
≥ 9 months	4	3	7
≥ 12 months	3	1	4

Source: Reviewer's analysis.

Reviewer's comment: The DOR data are limited with only 14 responders across the pooled cohort. There are limited data on the DOR from the literature in patients who have received approved therapies for STS or epithelioid sarcoma. In most cases, the DOR associated with chemotherapeutic agents has been reported as lasting no more than a few months (Touati). For pazopanib, the median DOR was reported as 9 (95% CI: 3.9, 9.2) months in second-line treatment of patients with STS after chemotherapy. The DOR in study EZH-202 ranged from 4 to 24+ months. Although the preliminary DOR data appears promising, the small sample size makes it difficult to estimate the true effect.

Figure 21 shows a swimmer's plot of patients in the analysis population of EZH-202. In the plot below, four patients were excluded from Cohort 6 as IRC had not assessed their responses at the time of the data cut-off.

Figure 21: Swimmer's Plot of Patients in the Analysis Population of EZH-202



Source: Reviewer's analysis.

Efficacy Results – Secondary and other relevant endpoints

Study EZH-202 was a single-arm study, therefore there were no other relevant secondary endpoints to analyze.

Additional Analyses Conducted on the Individual Trial

Subpopulations

Post-hoc sensitivity analyses were performed by subgroup to look for potential differences in treatment effects. The following baseline characteristics were identified as the factors most likely to impact the efficacy of tazemetostat: number of prior lines of therapy, INI1 status at baseline, cohort, cancer stage at baseline, and protocol violations. Only protocol violations in which the inclusion or exclusion criteria were violated are considered. In addition, key demographic subgroups of age, sex, and region are included. ORR is presented for each of these subgroups in Table 28.

Table 28: Confirmed ORR by Subgroup

Baseline characteristic	Subgroup	# Responses	N	ORR (95% CI)
Prior lines of therapy				
	0	7	44	16% (7, 30)
	1+	7	62	11% (5, 22)
INI1 status at baseline				

Baseline characteristic	Subgroup	# Responses	N	ORR (95% CI)
	Missing	0	6	0% (0, 46)
	Deficient	14	96	15% (8, 23)
	Present	0	4	0% (0, 60)
Cohort				
	Cohort 5	9	62	15% (7, 26)
	Cohort 5: Original cohort	6	31	19% (7, 37)
	Cohort 5: Expansion cohort	3	31	10% (2, 26)
	Cohort 6	5	44	11% (4, 25)
Cancer stage				
	I/II	3	20	15% (3, 38)
	III/IV	9	75	12% (6, 22)
	Unknown	2	11	18% (2, 52)
Protocol Violations				
	Inclusion/Exclusion Criteria	3	13	23% (5, 54)
	No violations	11	93	12% (2, 20)
Age				
	<65	12	102	12% (6, 20)
	≥65	2	4	50% (7, 93)
Sex				
	Female	8	41	20% (9, 35)
	Male	6	65	9% (3, 19)
Region				
	United States	9	49	9% (3, 32)
	Outside United States	5	57	18% (3, 19)

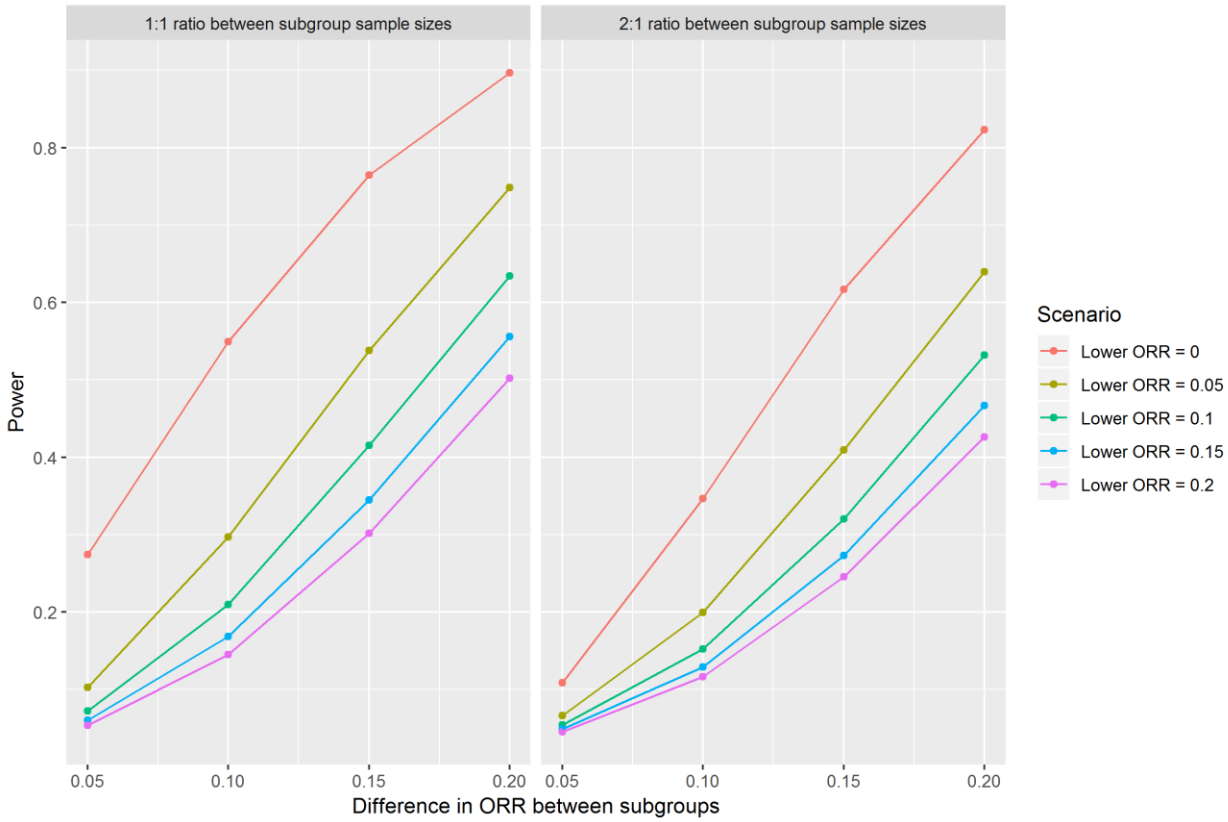
Source: Reviewer's analysis.

Reviewer's comment: The small sample size of EZH-202 makes it unlikely that small differences in ORR between subgroups will be identified, and results of subgroups should be interpreted with caution. The reviewer notes that that ORR appears to be similar across the original and expansion portions of Cohort 5 and regardless of number of prior lines of prior therapy. Cohort 6 allowed enrollment of patients with tumors that had retained INI1. There were four such patients; none of which had an objective response. When these four patients were removed from the analysis of Cohort 6, the ORR was is 12.5%. The reviewer concluded that the inclusion of patients with retained INI1 does not appear to have substantially affected the reported ORR in this cohort. However, it should be noted that the applicant has requested approval of tazemetostat in an unselected patient population - that is, patients who may or may not have INI1 loss. Therefore, FDA considers the data from Cohort 6 to be especially relevant for considering the response rate that may be expected in such an unselected patient population.

For a given sample size, the power to detect differences in ORR between subgroups depends on the true underlying difference in ORR, the ratio of sample sizes between the subgroups, and the

true ORR of one of the subgroups (as the variance of ORR depends on the magnitude of ORR). Figure 22 presents the power to detect differences in ORR ranging from 5% to 20% for scenarios in which the lower ORR of the two subgroups ranges from 0% to 20%. This range of ORRs was selected to explore power in the range of the observed ORR of tazemetostat of 13%. These calculations are based on the same sample size as EZH-202, 106 patients, and a 2-sided alpha of 0.05.

Figure 22: Power Under Various Subgroup Scenarios



Source: Reviewer's analysis.

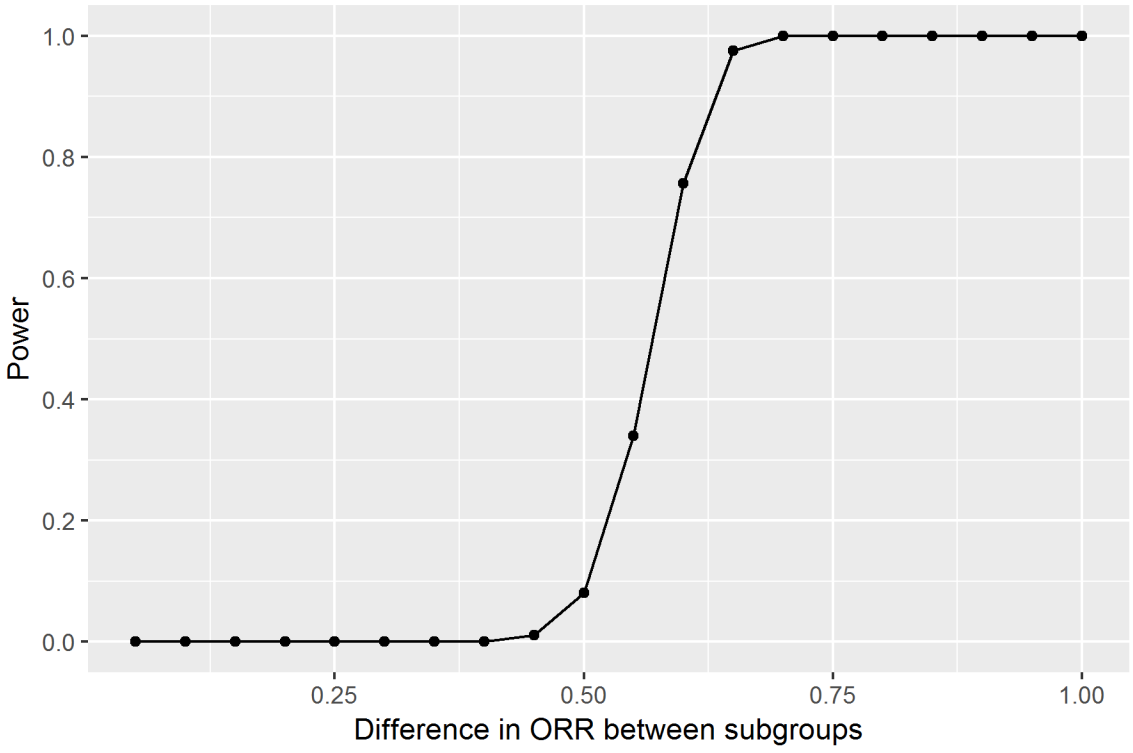
In general, power in comparing two groups is highest when the sample sizes of the respective groups are equal. Thus, each scenario considered assuming a 1:1 ratio between subgroup sample sizes has higher power than the respective scenario under a 2:1 ratio between subgroup sample sizes.

Reviewer's comment: The power to detect differences in ORR between subgroups of 10% or less is low for most scenarios. The only scenario in which the power to detect a difference of 10% is above 50% is that in which the lower ORR of the two subgroups is 0% and the subgroups have equal sample sizes. Thus, for the sample sizes of the subgroups explored in Table 28, *it is unlikely that a statistical test would detect a difference in ORR of 10% or less between the subgroups, even if it existed. In addition, the power analyses above represent a "best case" scenario, in*

which groups are randomized. The subgroup analyses presented above are based on non-randomized comparisons. Consequently, the exploratory subgroup analyses presented above are not likely to provide strong evidence of differential efficacy across subgroups and should be interpreted with caution.

Special consideration is given to the power to detect a difference in ORR between INI1 negative patients and INI1-retained patients. Due to the posited mechanism of action of tazemetostat, patients who retain INI1 are not expected to respond while on treatment with tazemetostat. However, only four patients who retained INI1 were enrolled in Cohorts 6. Figure 23 presents the power to detect various differences in ORR assuming the ORR in the 4 INI1-retained patients is 0%. The sample size for INI1 negative patients is assumed to be 96, as observed in study EZH-202.

Figure 23: Power Analysis for Detecting an ORR Difference between INI1- and INI1-retained Patients in EZH-202



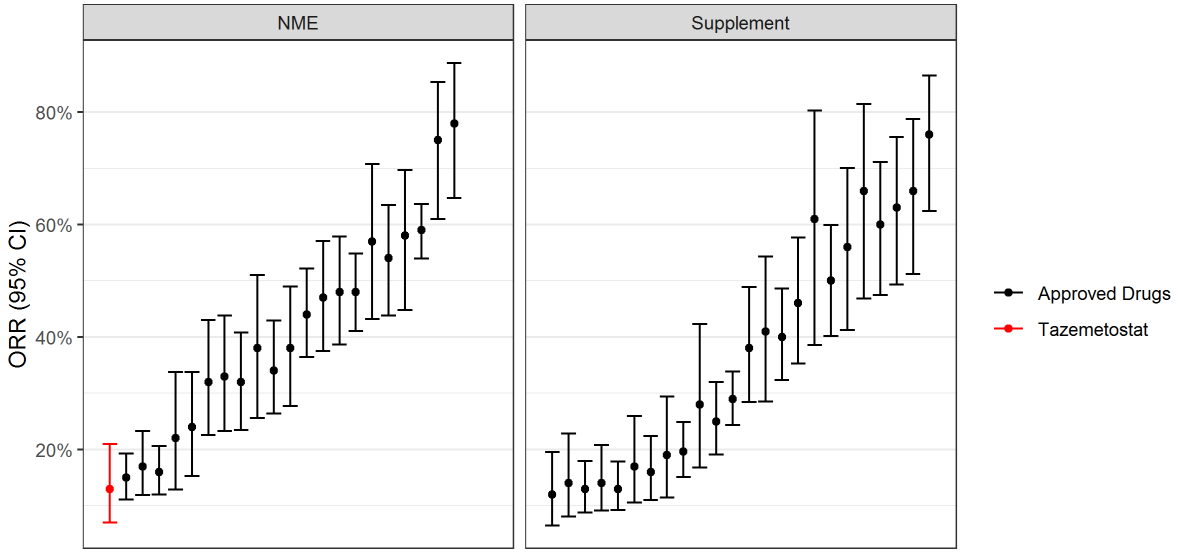
<u>Reviewer's comment</u>: The figure above demonstrates that, given a sample size of four INI1-retained patients and 96 INI1 negative patients, it is impossible to conclude a difference in ORR between these subgroups unless that difference is above 40%. While study EZH-202 was not powered to detect such a difference, we note that the claim that there is a difference in ORR between these subgroups is impossible to support via a statistical test on the efficacy data alone.

Statistical Issues Related to Approval

The observed ORR in Cohorts 5 and 6 is low compared to most therapies which FDA has approved based on a primary endpoint of ORR. This is especially true when compared to the ORRs observed in trials of other targeted therapies. FDA conducted additional analyses to 1) provide context for the magnitude of ORR reported in Cohorts 5 and 6, and 2) to explore what improvement in ORR is likely to predict improvement in PFS or OS.

Contextualizing the Magnitude of ORR in Cohorts 5 and 6
FDA conducted a review of all therapies approved since 2013 on the basis of ORR. FDA identified 45 eligible trials. The ORR point estimates and 95% confidence intervals for these approved products are plotted in Figure 24. These response rates are grouped by whether the product was an NME at time of submission or a supplement, as prior efficacy information may change the amount and level of efficacy needed to conclude a drug has a favorable risk:benefit in a new indication.

Figure 24: ORR from 2013-2019 of All Therapies Approved by FDA on the Basis of ORR



Source: Reviewer's analysis.

<u>Reviewer's comment</u>: FDA has approved other therapies with similarly low ORR. However, we note that this is more common for supplemental applications, in which efficacy information is supplemented by prior efficacy results in other disease areas, including understanding of mechanism of action. In addition, in some instances, a product was approved based on ORR when efficacy information from a randomized trial was available. Finally, the confidence interval about the estimate of ORR is wider than most other approvals with low ORR estimates.

CDTL comment: This analysis does not include agents approved prior to 2013 due to differences in the availability of information about those approvals as well as differences in how response rates were measured that reduce comparability of data. We acknowledge this limitation of the analysis, but as the science underlying advances in drug development in oncology has accelerated in recent years, we posit that a comparison of tazemetostat to other approvals in the last 7 years provides important context.

Additional Factors to Considers When Interpreting ORR

Although the magnitude and duration of response are key to interpreting overall response rate, many other factors can contribute to assessing whether an observed response rate is clinically meaningful and represents or may predict benefit to a patient. These factors can include the benefits and risks of other therapies used to treat that disease, the clinical impact of tumor burden, the mechanism of action of a drug as it relates to the biology of the tumor, the body of knowledge regarding the drug's effects in other settings, and the safety profile of the drug.

Comparing the Efficacy of Tazemetostat to Approved Therapy

There are no therapies specifically approved for patients with epithelioid sarcoma; however, epithelioid sarcoma falls within the broader patient population for STS and thus, doxorubicin and pazopanib are considered available therapies. For the approvals of doxorubicin and pazopanib, patients with epithelioid sarcoma represented a small fraction of the entire patient population.

Doxorubicin was approved for patients with STS in 1974 based on a response rate of 24% (95% CI: 19, 30) observed in 234 patients treated across 9 clinical centers. Only minimal summary data was submitted with the original approval. However, response criteria in that era generally defined a response as greater than 50% measurable decrease in tumor size, in contrast to RECIST v1.1 that define a response as at least a 30% decrease in the sum of diameters of target lesions. Other factors that limit the comparability of the data include lack of complete information regarding whether patients had received prior therapies, and exclusion of some patients who were unable to receive at least 2 doses of doxorubicin from the efficacy evaluable population, which may have inflated the response rate. Thus, the response rate used to support the approval of doxorubicin cannot be directly compared to that of tazemetostat.

Given the inability to directly compare the results of the approval of doxorubicin in patients with STS to patients from Study EZH-202, an exploratory analysis was conducted to assess the response rates in patients who received tazemetostat as first-line therapy to patients with STS who received doxorubicin as first-line therapy as reported in the literature. FDA reviewed published studies from 2010 to 2019 in which doxorubicin was the comparator arm for the treatment of patients with STS in the first line. In the 44 patients from Cohort 5 and 6 who received tazemetostat in the first-line, the ORR was 16% (95% CI: 8, 29). For patients who received doxorubicin as first-line therapy from clinical studies, the response rates ranged from

8% to 19%. There are insufficient data regarding the duration of response for both tazemetostat and doxorubicin to enable a comparison of that endpoint.

Table 29 Comparison of ORR of Tazemetostat to Doxorubicin for the First-Line Treatment

Agent	Tazemetostat EZH-202 Cohorts 5 & 6 1L N=44	Doxorubicin 1L
Tumor Type	**ES**	**STS**
ORR % (95% CI)	16 (7, 30)	8 to 19
CR n, (%)	2 (5)	NR
PR n, (%)	5 (11)	NR
DOR (months) (range)	3.5+, 24.4+	NR[1]

Source: Reviewer analysis
[1]Not present in approved label for STS. Review of the limited data in the literature suggests 6 to 8 months.
Abbreviations: 1L: one-line of prior therapy; ES, epithelioid sarcoma; STS, soft tissue sarcoma; ORR, overall response rate; CI, confidence interval; CR, complete response, PR, partial response; NR, not reported; DOR, duration of response

Reviewer's comment: Overall, the response rates for patients with STS who received doxorubicin as first-line therapy is similar to patients with epithelioid sarcoma who received tazemetostat as first-line therapy.

Pazopanib was approved in 2012 for the treatment of patients with STS after chemotherapy based on the results of a randomized, placebo-controlled study that demonstrated an improvement in median PFS when compared to placebo. The median PFS was 4.6 months in the pazopanib arm versus 1.6 months in the placebo arm. (HR: 0.35 [95% CI: 0.26, 0.48]). The response rate was 4% in the pazopanib arm. DOR ranged from 3.9 to 9.2 months.

To better compare the response rate for pazopanib to tazemetostat, a second exploratory analysis was conducted to evaluate patients with STS who received pazopanib after chemotherapy to patients with epithelioid sarcoma who received tazemetostat in the second-line or greater setting from Cohorts 5 and 6. In the 62 patients who received tazemetostat in the second-line or greater, the ORR was 11% (95% CI: 6, 22) compared to 4% (95% CI: 2, 8) for pazopanib. Although 11% is numerically higher than 4%, differences between patient populations preclude direct comparison.

Table 30 Comparison of ORR of Tazemetostat to Pazopanib for Second-Line or Greater

Agent	Tazemetostat EZH-202 Cohorts 5 & 6 2L+ N=62	Pazopanib N=246 2L+
Tumor Type	**ES**	**STS**
ORR % (95% CI)	11 (5, 22)	4 (2, 8)
CR n, (%)	0	0
PR n, (%)	7 (11)	11 (5)
DOR (months) (range)	3.7+, 18.2	NR[1]

Source: Reviewer's analysis
[1]Median reported in label as 9.0 months (95% CI: [3.9, 9.2]).
Key: 2L, second-line of therapy; ES, epithelioid sarcoma; STS, soft tissue sarcoma; ORR, overall response rate; CI, confidence interval; CR, complete response, PR, partial response; DOR, duration of response; NR, not reported

Reviewer's comments: Overall, it is difficult to make direct comparisons of the response rates of patients with epithelioid sarcoma treated with tazemetostat to that of patients with STS treated with either doxorubicin or pazopanib. Numerically the response rates appear similar but the ability to make a direct comparison is limited by differences in trial design, patient population, and response criteria. However, as shown the response rates are low across the trials and there is no evidence to suggest that treatment with tazemetostat results in a superior response rate compared to available therapies.

Literature Review of Responses to Approved Therapies in Patients with Epithelioid Sarcoma

An extensive review of the literature was conducted to identify studies that evaluated the effectiveness of approved therapies for the treatment of epithelioid sarcoma. The available data retrieved was limited and consisted of small, retrospective case studies in patients with epithelioid sarcoma. The majority of studies were in patients with advanced disease receiving systemic chemotherapy as first-line therapy. Pink, et al (2014) conducted a retrospective analysis of data from three clinical sites. A total of 13 patients with advanced epithelioid sarcoma were treated with an anthracycline with or without ifosfamide between 1989 and 2012. There were no objective responses. In another retrospective analysis conducted by Jones, et al (2012) a total of 19 patients with advanced or metastatic epithelioid sarcoma were treated between 1990 and 2009. The ORR was 20% in patients who received an anthracycline and 11% in patients who received anthracycline in combination with ifosfamide. Touati, et al (2018) reported on 24 patients with inoperable or metastatic epithelioid sarcoma. The ORR with doxorubicin alone was 0%, doxorubicin in combination with ifosfamide 13%, pazopanib 27%. Lastly, Frezza, et al (2018) conducted a retrospective case series of 85 patients with locally advanced or metastatic epithelioid sarcoma treated between 1990 and 2016 who received anthracycline-based chemotherapy, pazopanib or gemcitabine. The ORR to these agents were 22%, 0%, and 27%, respectively. Data regarding DOR was limited or not reported in any of these

analyses. Table 31 provides a summary of the treatment and response rates for patients with epithelioid sarcoma treated with approved therapies.

Table 31 Results from the Literature of Response Rate in Patients with Epithelioid Sarcoma Treated with Approved Therapies

Reference/Agent	Number of Patients With Epithelioid Sarcoma	Response Rate % (95% CI)
Tazemetostat	106	13 (7, 21)
Pink, et al (2014)[1]		
Anthracycline +/-Ifosfamide	13	0 (0, 25)
Jones, et al (2012)[2]		
Anthracycline + Ifosfamide	9	11 (0, 48)
Anthracycline	10	20 (3, 56)
Touati, et al (2018)[3]		
Doxorubicin[4]	5	0 (0, 52)
Doxorubicin[4] + Ifosfamide	8	13 (0, 53)
Pazopanib[5]	11	27 (6, 61)
Frezza, et al (2018)[3]		
Pazopanib	18	0 (0, 19)
Anthracycline-based	85	22 (14, 33)
Gemcitabine	41	27 (14, 43)

Source: FDA review of the literature

[1] Response assessed by WHO criteria and RECIST criteria

[2] Response assessed by RECIST criteria

[3] Response assessed by RECIST 1.1

[4] Received as first-line treatment

[5] Two patients received as first-line; nine as second-line

Reviewer's comment: The available data from the literature were limited. In addition to small patient numbers and the retrospective nature of these studies, different response criteria were used to assess tumor response, eligibility criteria were different, and patient populations varied across the studies. Based on this data, the reviewer can only conclude that response rates for patients with epithelioid sarcoma treated with tazemetostat or approved therapies do not appear different from those of patients with other forms of STS

Tumor Burden

In Cohorts 5 and 6 of study EZH-202, disease burden was measured at baseline and then every 8 weeks throughout treatment. Up to a maximum of 2 target lesions per organ and 5 lesions in total could be identified as a target lesion; all other lesions were recorded as non-target lesions according to RECIST v1.1. The criteria for response as specified by RECIST v1.1 (Eisenhauer 2009) require a decrease in tumor size, as measured by the percentage change from baseline of a sum of diameters (longest for non-nodal lesions, short axis for nodal lesions) of all target

lesions.

Whether a tumor response alone, in the absence of other supportive data such as patient-reported outcomes, can be considered benefit may depend, in part, on the magnitude of the disease burden prior to receiving therapy and the clinical impact of any reduction in tumor size. In some cases a reduction in tumor burden can translate into an improvement in the way a patient feels or functions leading to a direct measure of clinical benefit. The Applicant did not perform Patient Reported Outcomes (PROs) to assess if there was an improvement in the way a patient felt or functioned. FDA conducted an exploratory analysis of tumor burden at baseline and reduction in tumor burden as a potential proxy, with the idea that reduction in size of an exceptionally large tumor could provide some support for direct clinical benefit.

In Cohorts 5 and 6, most patients had two target lesions at baseline (31%), followed by one lesion (17%) or four lesions (17%); 10% of patients were deemed to not have measurable target lesions at baseline or were not assessed by the IRC at the time of the respective data cut-off. A patient's total disease burden; however, includes additional non-target lesions. Most patients had either one non-target lesion (28%) or two non-target lesions (34%). In addition, most patients had a total of 5 or fewer lesions total at baseline (74%), with the maximum being 10 lesions in total. Across the two cohorts, all nodal lesions were ≤5 cm, and 84% of non-nodal lesions had a longest diameter of ≤5 cm. Table 32 and Table 33 summarize the length of all target lesions as assessed by IRC across Cohorts 5 and 6.

Table 32 Shortest Diameter per IRC of Lymph Node Target Lesions at Baseline for Patients in Cohorts 5 and 6, Study EZH-202

	Cohort 5 N=40	**Cohort 6 N=24**	**Pooled Data N=64**
Median shortest diameter in cm (range)	2.0 (1.5, 5.0)	2.1 (1.5, 3.6)	2.0 (1.5, 5.0)

Source: Reviewer's analysis.

Table 33 Longest Diameter per IRC of Non-Lymph Node Target Lesions at Baseline for Patients in Cohorts 5 and 6, Study EZH-202

	Cohort 5 N=90	**Cohort 6 N=78**	**Pooled Data N=168**
Median longest diameter in cm (range)	2.5 (1.0, 11.6)	2.4 (1.0, 9.5)	2.4 (1.0, 11.6)
Longest diameter in cm (%)			
1-5 cm	75 (83)	66 (85)	141 (84)
5-10 cm	12 (13)	12 (15)	24 (14)
>10+ cm	3 (3.3)	0 (0.0)	3 (1.8)

Source: Reviewer's analysis.

Table 34 presents the reduction in sum of diameters as defined by RECIST v1.1 for the responders in Cohorts 5 and 6 of Study EZH-202. In the table below, "nadir" refers to the smallest sum of diameters observed at or after the initial response and prior to progression or censoring.

Table 34 Reduction in Sum of Diameters for Responders in Cohorts 5 and 6, Study EZH-202

Patient ID	Cohort	Sum of Diameters at Baseline (cm)	Sum of Diameters at Nadir (cm)	Change from Baseline (cm)	% Change from Baseline
(b) (6)	Cohort 6	1.53	0.5	-1.03	-67.3
	Cohort 6	2.11	1.18	-0.93	-44
	Cohort 6	2.25	0	-2.25	-100
	Cohort 5	2.9	2.01	-0.89	-30.7
	Cohort 5	4.42	2	-2.42	-54.6
	Cohort 5	4.56	1.66	-2.9	-63.7
	Cohort 5	4.78	3.16	-1.62	-33.9
	Cohort 5	5.2	0.5	-4.7	-90.4
	Cohort 6	6.64	1.44	-5.2	-78.4
	Cohort 5	7.62	1.89	-5.73	-75.1
	Cohort 5	10.6	3.01	-7.59	-71.6
	Cohort 5	10.64	3.26	-7.38	-69.3
	Cohort 6	17.17	10.2	-6.97	-40.6
	Cohort 5	19.45	1.73	-17.72	-91.1

Source: Reviewer's analysis.

Reviewer's comment: An important limitation of this analysis is that not all of each patient's burden of disease was measured at baseline or followed for response. Across Cohorts 5 and 6, the majority of target lesions were ≤5 cm and most patients had 2 target lesions at baseline. Most (84%) patients had individual tumors that were ≤5 cm in the longest diameter and absolute reductions in the sum of the diameters was modest. The available data are thus insufficient to conclude that tazemetostat confers direct benefit based on reduction in tumor burden alone. *Given the absence of PRO data or other clinically meaningful endpoints, it is uncertain whether the reduction in tumor burden represents clinical benefit. This reviewer recommends that quality of life data be collected during the confirmatory study.*

Response Rate Based on the Mechanism of Action of Tazemetostat

Targeted therapies are a focus of cancer drug development. Effective targeted therapies typically produce high response rates, demonstrating that the drug hits a target relevant for cancer cell survival. For example, 48% of patients with melanoma harboring a BRAFV600E mutation experienced a confirmed overall response to the BRAF inhibitor vemurafenib, a drug that conferred an overall survival benefit to this population in a randomized, controlled trial. Patients with non-small cell lung cancer (NSCLC) with ROS mutation demonstrated an ORR of

85% with entrectininb and 66% with crizotinib. Additionally, patients with EGFR mutations have likewise had response rates of 66% with afatininb.

The Applicant has described a hypothesis as to how tazemetostat may act in tumors with INI-1 loss in which EZH2 catalyzes histone H3, generally downregulating transcription. INI-1 loss leads to abnormal activity or expression of EZH2 and a subsequent oncogenic dependence on EHZ2. Tazemetostat inhibits EZH2, restoring transcriptional homeostasis. However, observed response rates to tazemetostat in patients with IN1-deficient epithelioid sarcoma are low.

The mechanism of action of tazemetostat in patients with follicular lymphoma appears to be more directly linked to the target, EZH2 based on the response rate observed to tazemetostat in these patients. The Applicant released data at the American Society of Hematology 2019 meeting showing that 69% of patients with follicular lymphoma harboring a gain-of-function EZH2 mutation respond to tazemetostat. The fact that this is twice the 35% response rate observed in patients without an EZH2 mutation confirms the relevance of the target to the biology of this particular cancer. We do not have this type of confirmation for epithelioid sarcoma as epithelioid sarcoma with retained INI-1 is exceedingly rare. However, we can say that the fact that 35% of the patients with follicular lymphoma harboring wild-type EZH2 also responded to tazemetostat suggests that tazemetostat may have a more complex mechanism of action than is currently understood.

Reviewer's comment: Given the complex proposed mechanism of action of tazemetostat in tumors with INI-1 loss, the low response rate to tazemetostat could be because the target, EZH2, is not as relevant as has been thought to the disease biology, or it could be that the target is relevant, but that inhibiting it in epithelioid sarcoma leads to effects that inhibit tumor cell growth rather than cause tumor cell death. Unfortunately, this latter effect, which might be expected to yield durable stable disease, can only be assessed in a randomized, controlled trial.

8.1.3 Integrated Review of Effectiveness

Not applicable. There was only one trial to support approval, study EZH-202.

8.1.4 Integrated Assessment of Effectiveness

Not applicable. There was only one trial to support approval, study EZH-202.

8.2 Review of Safety

8.2.1 Safety Review Approach

The primary safety review is based on data from Trial EZH-202 with a data cut-off date of September 17, 2018. The primary population analyzed for safety consisted of all patients with epithelioid sarcoma enrolled on Cohort 5 who received at least one dose of study drug (n=62, the Safety Set). The analysis of adverse events included adverse events (AEs) that occurred on study treatment or up to 30 days after discontinuation of study treatment.

The safety analyses described below were repeated using two broader safety pools: one consisting of 668 adult patients who received tazemetostat 800 mg BID and the other consisting of 709 adult patients who received any dose of tazemetostat. Patients comprising these pools enrolled on one of five phase 1 or 2 studies (E7438-G000-101, EZH-103, EZH-105, EZH-202, EZH-203) and a phase 2 rollover study (EZH-501). These analyses revealed no clinically meaningful differences in frequency, severity, or spectrum of adverse events, nor did they reveal new safety signals. Thus, only safety results from Cohort 5 of Study EZH-202 are presented in this review.

8.2.2 Review of the Safety Database

Overall Exposure

In the Safety Set, 62 patients were exposed to at least one dose of tazemetostat 800 mg BID. The majority of patients (95%) received the planned dose of tazemetostat. The median duration of treatment was 5.5 months. In the Safety Set, 44% of patients were exposed to tazemetostat for > 6 months and 24% were exposed for greater than one year. Table 35 shows the summary of exposure in the safety set.

Table 35 Exposure Data Study EZH-202

	Cohort 5 N=62 n=%
Duration of exposure (months)	
Median	5.5
Range	0.5 to 28
>3 months	46 (74)
>6 months	27 (44)
>9 months	17 (27)
>12 months	15 (24)
Total Number of Cycles (n)	
Median	6
Range	1 to 30
Average dose intensity (mg)	
Median	800
Range	450 to 800

Source: Reviewer generated from ADSL

Adequacy of the safety database:

The size of the safety database (n=62 in the Safety Set, n=709 in the broader pool) is adequate

to provide a reasonable estimate of adverse reactions that may be observed with tazemetostat and the duration of tazemetostat exposure is adequate to allow assessment of adverse reactions over time.

8.2.3 Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall data integrity and submission quality for this trial was acceptable.

Categorization of Adverse Events

AEs were graded by the investigators using NCI CTCAE version 4.03 and mapped and coded verbatim AE terms using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

FDA assessed the adequacy of the Applicant's mapping of AE verbatim terms to MedDRA preferred terms (PT) for the EZH-202 raw AE dataset. The reviewer included an audit of AE case report forms randomly in 10% of cases to assess the completeness and verify the accuracy of the raw AE datasets. The review did not raise any significant adverse event coding issues.

Routine Clinical Tests

The routine clinical testing of patients enrolled in the clinical trial appear adequate to assess the risks.

8.2.4 Safety Results

Table 36 presents a high-level summary of the safety results.

Table 36 Summary of Safety Results Study EZH-202

	Cohort 5 N=62 n=%
All-Grade TEAEs	62 (100)
Grade 3-4 TEAEs	30 (48)
Deaths due to TEAEs	0
Serious TEAEs (SAEs)	23 (37)
Treatment Discontinuation due to TEAEs	1 (1.6)
Dose interruption due to TEAEs	21 (34)
Dose reduction due to TEAEs	1 (1.6)

Source: Reviewer generated table from ADSL and ADAE datasets

Deaths

A total of seven deaths occurred within 30 days of the last dose of tazemetostat. All seven patients died due to disease progression. There were no patients who died due to an AE. During review of the death narratives, there were several cases in which a death was attributed to an AE by the investigator. However, the conclusion of this reviewer and the Applicant is that in all cases the AE was attributable to disease progression. Table 37 summarizes the causes of death in the Safety Set.

Table 37 Summary of Deaths

	EZH-202 Cohort 5 N=62 n=%
Deaths	7 (11)
Within 30 days of last dose	7 (11)
Disease progression	7 (11)
Adverse event	0

Source: reviewer generated table from ADSL dataset and narratives

Serious Adverse Events

Serious AEs (SAEs) occurred in 37% of patients. The most frequently occurring (≥2%) SAEs were hemorrhage, pleural effusion, skin infection, dyspnea, pain, and respiratory failure. Table 38 summarizes the serious AEs occurring up to 30 days in ≥1% of patients.

Table 38 Serious Adverse Events Study EZH-202

Adverse Event	**EZH-202 Cohort 5 N = 62**
Patients with Serious AEs	23 (37)
Hemorrhage[a]	6 (10)
Pleural effusion	3 (5)
Skin Infection[b]	2 (3.2)
Dyspnea[c]	2 (3.2)
Pain[d]	2 (3.2)
Respiratory failure[e]	2 (3.2)
Pyelonephritis	1 (1.6)
Biliary tract infection	1 (1.6)
Pneumonia	1 (1.6)

Adverse Event	EZH-202 Cohort 5 N = 62
Pulmonary embolism	1 (1.6)
Pneumothorax	1 (1.6)
Respiratory distress	1 (1.6)
Hypercapnia	1 (1.6)
Seizure	1 (1.6)
Aphasia	1 (1.6)
Brain edema	1 (1.6)
Abdominal pain	1 (1.6)
Dysphagia	1 (1.6)
Tracheal obstruction	1 (1.6)
Wound dehiscence	1 (1.6)
Bilirubin increased	1 (1.6)
Panic attack	1 (1.6)

Source: Reviewer generated table from ADSL and ADAE datasets
[a]Group hemorrhage includes PT terms pulmonary hemorrhage, wound hemorrhage, rectal hemorrhage, hemorrhage intracranial, cerebral hemorrhage, and hemoptysis
[b]Group skin infection includes PT terms skin infection and cellulitis
[c]Group dyspnea includes PT terms dyspnea and dyspnea exertional
[d]Group pain includes PT terms tumor pain, pain in extremity, non-cardiac chest pain, flank pain, back pain, arthralgia, bone pain, cancer pain, musculoskeletal pain, myalgia, and neck pain
[e]Group respiratory failure includes PTs respiratory failure and acute respiratory failure

Dropouts and/or Discontinuations Due to Adverse Effects

In general, there were few study drug modifications. AEs leading to study drug discontinuation and reduction occurred in one patient each and were due to altered mood and decreased appetite, respectively. A total of 21 (34%) patients had an AE that led to study drug interruption. The most frequently occurring were hemorrhage, alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased. All other AEs leading to dose interruption occurred in one patient each. Table 39 summarizes the AEs leading to dose modifications or discontinuations.

Table 39 Adverse Events Leading to Dose Modifications or Discontinuations, Study EZH-202

Dose Modifications	Cohort 5 N = 62
Dose Interruption due to AEs	21 (34)
Hemorrhage[a]	4 (6)
Alanine aminotransferase increased	2 (3)
Aspartate aminotransferase increased	2 (3)

Dose Modifications	Cohort 5 N = 62
Dose Reduction due to AEs	1 (2)
Decreased appetite	1 (2)
Drug Discontinuation due to AEs	
Altered mood	1 (2)

Source: Reviewer generated table from ADSL and ADAE datasets and patient narratives
[a]Group hemorrhage includes PT terms pulmonary hemorrhage, wound hemorrhage, rectal hemorrhage, hemorrhage intracranial, cerebral hemorrhage, and hemoptysis

Significant Adverse Events

On (b) (6), an event of T-lymphoblastic lymphoma (T-LBL) was observed in a pediatric patient on study EZH-102. A global halt of enrollment was placed on Study EZH-202 by the Applicant and the IND was placed on partial clinical hold by the FDA. Further review of the data by the Applicant also identified a case of secondary myelodysplastic syndrome (MDS). Based on these findings, the Applicant submitted protocol amendment 6 dated September 28, 2018, which added a description of the events as well as risk mitigation and monitoring required to minimize the risk of occurrence of these events in patients taking tazemetostat. Patients with prior history of T-LBL/T-ALL; thrombocytopenia, neutropenia, or anemia of Grade ≥3 (per CTCAE 4.03 criteria) or any prior history of myeloid malignancies, or had an abnormality known to be associated with MDS (e.g. del 5q, chr 7 abn) and myeloproliferative neoplasm (MPN) (e.g. JAK2 V617F) observed in cytogenetic testing and DNA sequencing were excluded from enrolling. As noted by the Applicant, all patients with epithelioid sarcoma analyzed in this review had been enrolled at the time of the addition of these exclusion criteria.

Because of the sentinel event, the Applicant identified secondary malignancies as an AESI. The AESIs were defined as MDS, MPN, acute myeloid leukemia (AML), and T-LBL/T-ALL. In the data reviewed as part of this application, at the adult target dose of 800 mg BID, there were 5 (0.7%) of 668 patients who experienced six cases of secondary malignancies. One of the five patients had MDS that transformed to AML. Across the development program for tazemetostat, 6 (0.7%) of 822 adult and pediatric patients developed a secondary malignancy. Overall, the time from initiation of tazemetostat to the secondary malignancy diagnosis ranged from 14 months to more than 4 years. All but one patient who developed a secondary malignancy had received prior chemotherapy. No patients with epithelioid sarcoma developed a secondary malignancy, though the FDA considers the risk applicable to all patients exposed to tazemetostat. Table 40 provides further information about the patients who developed a secondary malignancy.

Table 40 Secondary Malignancies Across the Tazemetostat Development Plan

Patient Age (years)/Sex	Initial Diagnosis	Prior Radiation	Prior Systemic Therapy	Prior Stem Cell Transplant	Secondary malignancy	Dose of Tazemetostat	Duration of Treatment Prior to Secondary Malignancy
61, male	Follicular lymphoma	Yes	6 chemotherapy regimens including doxorubicin, cyclophosphamide, and etoposide	Yes	MDS*	800 mg BID	15 months (Day 465)
69, male	DLBCL	No	2 chemotherapy regimens including doxorubicin and cyclophosphamide	No	MDS	800 mg BID	27 months (Day 843)
9, female	Chordoma	Yes	Doxorubicin, ifosfamide, pazopanib	No	T-LBL	900 mg/m^2	14 months
57, male	Rhabdoid sarcoma	Yes	No	No	AML	800 mg BID	Over 4 years (Day 1591)

Patient Age (years)/Sex	Initial Diagnosis	Prior Radiation	Prior Systemic Therapy	Prior Stem Cell Transplant	Secondary malignancy	Dose of Tazemetostat	Duration of Treatment Prior to Secondary Malignancy
68, male	Follicular lymphoma	No	2 prior regimens included chlorambucil, cyclophosphamide, doxorubicin, rituximab, VCR	No	AML	800 mg BID (dose reduced to 600 mg BID)	33 months (Day 786)
76, male	DLBCL	No	Rituximab, cyclophosphamide, doxorubicin, prednisone, VCR, carboplatin, cytarabine, dexamethasone	No	AML	800 mg BID	3 years 2 months (Day 1163)

Source: Reviewer generated table from patient narratives.
Abbreviations: MDS: myelodysplastic syndrome; BID: twice daily; DLBCL: diffuse large B-cell lymphoma; T-LBL: T-cell lymphoblastic lymphoma; AML: acute myeloid leukemia; VCR: vincristine.

The findings of secondary lymphoma and leukemia were also demonstrated in non-clinical toxicology studies. (Refer to Section 5 Nonclinical Pharmacology/Toxicology for further details). In the nonclinical toxicology studies performed by the Applicant, T cell lymphoma with concurrent leukemia led to multiple early deaths in both adult and juvenile animals. Dedicated carcinogenicity studies were not conducted with tazemetostat, but T-LBL occurred in juvenile and adult rats after ~9 or more weeks of tazemetostat administration during 13-week toxicity studies. Based on nonclinical studies in rats, the risk of T-LBL appears to be greater with longer duration of dosing. EZH2 gain-of-function mutations have been identified in patients with spontaneous MDS, T-ALL, and MPNs (Kim 2016), suggesting that the development of secondary malignancies may be an on-target effect of tazemetostat.

Reviewer's comment: *The exact mechanism by which tazemetostat leads to the development of secondary malignancies is unclear but is likely related to EZH2 and thus an on-target effect of tazemetostat.*

Treatment Emergent Adverse Events and Adverse Reactions

All patients in Cohort 5 experienced at least one treatment emergent adverse event. The most common AEs (occurring in ≥20%) of patients were pain, fatigue, nausea, decreased appetite, vomiting, and constipation. The most common Grade 3-4 AEs were anemia (13%), pain and weight decreased (7%); decreased appetite, dyspnea, hemorrhage and pleural effusion (5%).

Table 41 Treatment-Emergent Adverse Events Occurring in ≥10% Patients in Cohort 5, Study EZH-202

	COHORT 5 N = 62		
	All Grades	**Grade 3**	**Grade 4**
Patients with TEAEs	62 (100)	29 (47)	2 (3.2)
Pain[a]	32 (52)	4 (7)	0
Fatigue[b]	29 (47)	1 (1.6)	0
Nausea	22 (36)	0	0
Decreased appetite	16 (26)	3 (5)	0
Vomiting	15 (24)	0	0
Constipation	13 (21)	0	0
Hemorrhage[c]	11 (18)	1 (1.6)	2 (3.2)
Cough	11 (18)	0	0
Headache	11 (18)	0	0
Anemia	10 (16)	8 (13)	
Weight decreased	10 (16)	4 (7)	0
Dyspnea[d]	10 (16)	3 (5)	0

	COHORT 5 N = 62		
	All Grades	**Grade 3**	**Grade 4**
Diarrhea	10 (16)	0	0
Abdominal pain[e]	8 (13)	1 (1.6)	0
Pleural effusion	6 (10)	3 (5)	0
Peripheral edema	6 (10)	0	0
Dysgeusia	6 (10)	0	0
Hypertension	6 (10)	2 (3.2)	0

Source: Reviewer generated from ADAE and ADSL datasets
[a]Group pain includes PT terms tumor pain, pain in extremity, non-cardiac chest pain, flank pain, back pain, arthralgia, bone pain, cancer pain, musculoskeletal pain, myalgia, and neck pain
[b]Group fatigue includes PT terms fatigue, and asthenia
[c]Group hemorrhage includes PT terms pulmonary hemorrhage, wound hemorrhage, rectal hemorrhage, hemorrhage intracranial, cerebral hemorrhage, and hemoptysis
[d]Group dyspnea includes PT terms dyspnea, and dyspnea exertional
[e]Group abdominal pain includes PT terms abdominal pain, abdominal pain lower, and gastrointestinal pain

Reviewer's comment: Although tazemetostat has been generally well-tolerated across the development program as measured by the low frequency of dose reductions and drug discontinuations, it is not without risk. In a disease in which stable disease may be common for long periods of time even without treatment, treatment with a drug that causes even mild to moderate toxicity can adversely affect a patient's quality of life.

Laboratory Findings

The most frequent (occurred in ≥20%) laboratory abnormalities were hypertriglyceridemia, hyperglycemia, hypernatremia, hyperphosphatemia, hyperalbuminemia, and increased alkaline phosphatase. Table 42 summarizes the laboratory abnormalities during treatment and within the last 30 days of the last dose by worst grade.

Table 42 Treatment-Emergent Laboratory Parameters by Worst Grade Study Occurring in ≥10 % of Patients Study EZH-202

Laboratory Abnormality		**Cohort 5**	
	N	**All Grades N, (%)**	**Grade 3-4 N, (%)**
Chemistry			
Increased triglycerides	61	22 (36)	2 (3.3)
Increased glucose	61	20 (33)	1 (1.6)
Decreased sodium	60	18 (30)	1 (1.7)
Decreased phosphate	60	17 (28)	1 (1.7)
Decrease albumin	60	14 (23)	0

Laboratory Abnormality	N	Cohort 5	
		All Grades N, (%)	Grade 3-4 N, (%)
Increased alkaline phosphatase	60	14 (23)	1 (1.7)
Increased aspartate aminotransferase	57	10 (18)	2 (3.5)
Decreased potassium	60	12 (20)	1 (1.7)
Decreased calcium	61	10 (16)	0
Decrease glucose	61	10 (16)	0
Increased partial thromboplastin time	39	6 (15)	2 (5)
Increased alanine aminotransferase	59	8 (14)	2 (3.4)
Increased creatinine	52	6 (12)	0
Increased potassium	60	7 (12)	0
Hematology			
Decreased hemoglobin	61	30 (49)	9 (15)
Decreased lymphocytes	61	22 (36)	8 (13)
Decreased white blood cell count	58	11 (19)	0

Source: Reviewer generated from ADLB dataset

Vital Signs

Vital sign assessment was performed at baseline, every 2 weeks though week 9, and then every 4 weeks thereafter. Measurements included blood pressure, heart rate, temperature and respiratory rate.

Only one patient experienced a temperature ≥38°C. There were four (6.5%) patients who had an AE of pyrexia reported. No patients had a systolic blood pressure less than 80, and 5 patients experienced a systolic blood pressure greater than 160. One patient had the AE of hypotension and 6 patients had hypertension reported. A total of 29 patients had a heart rate ≥100; 14 patients experienced a heart rate ≤60. There was one patient with Grade 1 report of tachycardia.

Electrocardiograms (ECGs)

ECG were performed at Screening, at Day 1 and Day 15 of the first 2 cycles of therapy and then on Day 1 of every cycle thereafter. Abnormal ECGs were rare.

QT

Heart rate corrected QT interval as based on Fridericia's equation, Prolongation of QT was There was one person with prolonged QTc. There was one patient with the reported AE of Grade 1 QTC prolongation.

8.2.5 Analysis of Submission-Specific Safety Issues

Not applicable.

8.2.6 Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

Not applicable.

8.2.7 Safety Analyses by Demographic Subgroups

There were too few patients enrolled in the ES cohorts of Study EZH-202 to allow for conclusions regarding safety in different demographic subgroups. There were no clinically meaningful differences in safety based on age, sex, or race in the broader patient population of 668 adults treated with tazemetostat at the target dose (Target Dose Adult Population).

In the Target Dose Adult Population, 418 (63%) of patients were <65 years of age and 250 (37%) were ≥65 years. The incidence of individual TEAEs was generally similar between the two age groups as shown in Table 43.

Table 43 Treatment-Emergent Adverse Events Occurring in ≥10% Patients by Age Group, Target Dose Adult Population

Preferred Term	Age <65 years N=418 n (%)	Age ≥65 years N=250 n (%)	Total N=668 n (%)
Fatigue[a]	151 (36)	85 (34)	209 (31)
Nausea	123 (29)	54 (22)	177 (27)
Pain[b]	95 (23)	34 (14)	129 (19)
Vomiting	88 (21)	39 (16)	127 (19)
Diarrhea	64 (15)	45 (18)	109 (16)
Cough	70 (17)	36 (14)	106 (16)
Anemia	63 (15)	42 (17)	105 (16)
Decreased appetite	63 (15)	36 (14)	99 (15)
Dyspnea	65 (16)	24 (10)	89 (13)
Constipation	57 (14)	26 (10)	83 (12)
Thrombocytopenia	37 (9)	33 (13)	70 (11)
Abdominal pain	45 (11)	23 (9)	68 (10)

Source: Reviewer generated from ADAE and ADSL datasets
[a]Group fatigue includes PT terms fatigue and asthenia
[b]Group pain includes PT terms cancer pain and back pain

A summary of the most commonly reported TEAEs by sex is provided for the Target Dose Adult Population in Table 44. In the Target Dose Adult Population, 378 (57%) patients were male and 290 (43%) were female. The incidence of individual TEAEs was generally similar between males

and females, with a modestly higher incidence of nausea (mostly low Grade) in women.

Table 44 Treatment-Emergent Adverse Events Occurring in ≥10% Patients by Sex, Target Dose Adult Population

Preferred Term	Male N=378 n=%	Female N=290 n (%)	Total N=668 n (%)
Fatigue[a]	129 (34)	107 (37)	236 (35)
Nausea	76 (20)	101 (35)	177 (27)
Pain[b]	67 (18)	62 (21)	129 (19)
Vomiting	58 (15)	69 (24)	127 (19)
Diarrhea	59 (16)	50 (17)	109 (16)
Cough	59 (16)	47 (16)	106 (16)
Anemia	57 (15)	48 (17)	105 (16)
Decreased appetite	52 (14)	47 (16)	99 (15)
Dyspnea	52 (14)	37 (13)	89 (13)
Constipation	38 (10)	45 (16)	83 (12)
Thrombocytopenia	40 (11)	30 (10)	70 (11)
Abdominal pain	34 (9)	34 (12)	68 (10)

Source: Reviewer generated from ADAE and ADSL datasets
[a]Group fatigue includes PT terms fatigue and asthenia
[b]Group pain includes PT terms cancer pain and back pain

TEAEs are summarized by race in Table 45 for white vs non-white patients in the Target Dose Adult Population. In the Target Dose Adult Population, race was reported as white for 60% of patients, black/African American for 5%, Asian for 3%, and American Indian/Alaskan Native for <1%. For the remaining 32% of patients, race was reported as other/unknown. For both the white and non-white race groups in the Target Dose Adult population, fatigue was the most commonly reported TEAE (37% white vs 33% non-white patients).

Table 45 Treatment-Emergent Adverse Events Occurring in ≥10% Patients by Race, Target Dose Adult Population

Preferred Term	White N=402 n (%)	Non-White[a] N=266 n (%)	Total N=668 n (%)
Fatigue[b]	149 (37)	87 (33)	236 (35)
Nausea	123 (31)	54 (20)	177 (27)
Pain[c]	83 (21)	46 (17)	129 (19)
Vomiting	87 (22)	40 (15)	127 (19)
Diarrhea	74 (18)	35 (13)	109 (16)
Cough	68 (17)	38 (14)	106 (16)

Preferred Term	White N=402 n (%)	Non-White[a] N=266 n (%)	Total N=668 n (%)
Anemia	57 (14)	48 (18)	105 (16)
Decreased appetite	64 (16)	35 (13)	99 (15)
Dyspnea	52 (13)	37 (14)	89 (13)
Constipation	58 (14)	25 (9)	83 (12)
Thrombocytopenia	29 (7)	41 (15)	70 (11)
Abdominal pain	45 (11)	23 (9)	68 (10)

Source: Reviewer generated from ADAE and ADSL datasets
[a]Includes unknown
[b]Group fatigue includes PT terms fatigue and asthenia
[c]Group pain includes PT terms cancer pain and back pain

8.2.8 Specific Safety Studies/Clinical Trials

There were no studies conducted to evaluate a specific safety concern.

8.2.9 Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant did not conduct carcinogenicity studies.

Human Reproduction and Pregnancy

There were no pregnancies documented during this trial.

Pediatrics and Assessment of Effects on Growth

No adverse drug reactions regarding growth or that are otherwise specific to pediatric patients have been identified in pediatric studies of tazemetostat. Nonclinical toxicology studies revealed skeletal abnormalities in fetuses of pregnant rats and increased trabecular bone in juvenile animals exposed to tazemetostat. Refer to Section 5 for more details.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The applicant did not provide any reported cases of overdose of tazemetostat. No data were available on the potential for abuse or dependence. A formal study has not been conducted by the applicant to investigate withdrawal and/or rebound.

8.2.10 Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Not applicable.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in the clinical trial.

8.2.11 Integrated Assessment of Safety

Tazemetostat appears to be relatively well-tolerated. The most common (occurred in ≥20%) adverse events (AEs) experienced by patients enrolled in Cohort 5 were pain, fatigue, nausea, decreased appetite, vomiting, and constipation. A total of 48% of patients experienced a Grade 3 or 4 adverse reaction: the most common were anemia (13%), pain and decreased weight (7%), and three (4.8%) patients each with hemorrhage, decreased appetite, dyspnea, and pleural effusion. A total of 23 (37%) patients had a serious AE (SAE). SAEs that occurred in ≥ 2 patients were hemorrhage (10%), pleural effusion (5%), dyspnea, skin infection, respiratory distress, and pain (3.2%). There were no fatal adverse events attributable to tazemetostat. Although 34% of patients required a dose interruption for toxicity, dose reductions and discontinuations of tazemetostat for toxicity were rare.

An important risk of tazemetostat is the risk of secondary malignancies associated with its use. In the pooled safety population of 822 adults and pediatric patients with solid tumors or hematologic malignancies, 6 (0.7%) patients developed secondary MDS, AML, or T-LBL.

8.3 Statistical Issues

A modest ORR was observed in both Cohorts 5 and 6, with a pooled ORR across cohorts of 13% (95% CI: 7, 21). While Cohorts 5 and 6 were designed with different primary objectives, the eligibility criteria were similar. A key difference that may affect the efficacy of tazemetostat is INI1 status – patients enrolled in Cohort 5 were required to have loss of INI1, while patients in Cohort 6 were not required to have loss of INI1. The number of patients who retained INI1 in Cohort 6 was low (4/44), although 6 additional patients did not have INI1 testing available. As approximately 90% of ES patients have INI1 loss, it is likely that most or all of these 6 patients had INI1 loss. Taken together, these observations suggest that this key difference in cohorts is not likely to have a large effect on ORR, suggesting that pooling across cohorts may be appropriate. While the impact of difference in INI1 status is thought to be small, we note here that the indication sought is for unselected ES patients. Should INI1 status be confirmed to have an impact on ORR, the ORR observed in Cohort 6 may be more representative of the ORR expected in this unselected population than the ORR observed in Cohort 5.

Whether the pooled ORR from Cohorts 5 and 6 represents clinical benefit on its own is a matter of clinical interpretation. Interpretation of historical response rates of doxorubicin in patients with STS is confounded by different response criteria, lack of independent assessment of response, and differences in baseline characteristics. Thus, a direct comparison between the response rate of doxorubicin and that of tazemetostat is problematic. While tazemetostat has a numerically higher response rate than pazopanib for 2+ line patients (11% vs. 4%), pazopanib was approved based on an improvement in PFS vs. placebo. FDA does not consider time to

event endpoints to be interpretable in a single arm trial, and consequently improvement over pazopanib on this endpoint cannot be established using the available data.

The heterogeneity of STS is a crucial issue in the assessment of this application, as it is not currently known how outcomes for ES patients relate to those of non-ES STS patients. Retrospective data reviewed suggest that outcomes are similar, though the rarity of ES limits such comparisons. The Natural History Study was not adequately designed to serve as an external control arm or to establish the relationship of outcomes in ES patients to those in non-ES STS patients. The primary factors limiting interpretation of this study were 1) the use of rwORR, and the lack of understanding of how this endpoint is related to ORR as assessed by RECIST v1.1 and 2) a lack of a comparator arm.

8.4 Conclusions and Recommendations

Epithelioid sarcoma is a rare, subset of the broader STS patient population and represents a histologically unique tumor type. Available treatment options are inadequate with response rates less than 20% and no treatments that provide a survival advantage. In addition, the available treatments have significant toxicities. Newer therapies with improved benefit:risk profiles are greatly needed in this patient population for which 5-year survival in patients with metastatic disease is 0%. It is commendable that the Applicant put forth an effort to develop a drug in a rare patient population which are frequently overlooked when it comes to drug development.

The ORR observed across Cohorts 5 and 6 was modest, with limited information available to assess the durability of response.

The ORR for tazemetostat in patients with epithelioid sarcoma does not provide substantial evidence of a clinically meaningful improvement over available therapies for the effectiveness of tazemetostat 800 mg BID for the treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection (21 CFR 314.510 Subpart H).

The ORR of 15%, 11%, and 15% in Cohorts 5, 6 and pooled data, respectively, is low. This reviewer took into account other factors in assessing the ORR to determine if a clinical benefit could be identified to augment the low response rate. These other factors included duration of response, available therapies, tumor burden, and mechanism of action of the drug. Below are the reviewer's assessment of these and other factors:

- The 95% CI show that the true response rate may be as 7%. There is not enough evidence from a single study in addition to limited data with tazemetostat in other patient populations to be confident that the true ORR lies between 11% and 15%.
- In clinical trials in STS, ORR has not always translated into an improvement in survival or PFS. Although the Applicant has a confirmatory study planned, enrollment has yet to begin. The assumption that tazemetostat will yield an improvement in PFS of 7 months

may be overly optimistic and thus the trial may be underpowered to show an effect on PFS.

- The ORR across Cohorts 5 and 6 and the pooled analysis is similar to patients with soft tissue sarcoma treated with available therapies and therefore, a clinically meaningful improvement over available therapies does not exist.
- The ORR across Cohorts 5 and 6 and the pooled data are similar to what is reported in the literature for patients with epithelioid sarcoma treated with available therapies. The Applicant suggested that patients with epithelioid sarcoma may respond differently to available therapies but this does not appear to be supported by the data reviewed.
- Although the duration of response appears promising, there is too little data from this study and too little data on response durability for doxorubicin and pazopanib to accurately determine whether tazemetostat confers more durable responses than those of available therapy. It will be important for the Applicant to continue to follow more patients and for longer follow-up time to more accurately assess the DOR.
- Tumor burden was modest and tumor volume reduction was also modest. There was no quality of life data collected to demonstrate and improvement in the way a patient feels or functions. Patient reported outcome data should be collected during the confirmatory study.
- The mechanism of action as being a targeted therapy postulated by the Applicant does not correlate to a high response rate that is typically seen with other targeted therapies, raising the possibility that the target of tazemetostat is less relevant to the biology of epithelioid sarcoma than had previously been postulated.
- Treatment with tazemetostat is generally well-tolerated, although secondary malignancies are a risk factor.

According to FDA's Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics (2014), accelerated approval may be considered for a drug that treats a serious condition AND generally provides a meaningful advantage over available therapies AND demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on an intermediate clinical endpoint. Assessing the totality of the data, this reviewer does not recommend accelerated approval as the evidence does not meet the regulatory requirements for accelerated approval. Specifically, there are insufficient data to conclude that tazemetostat confers a meaningful advantage over available therapies with respect to ORR and DOR, or that its effect on ORR and DOR is reasonably likely to predict clinical benefit. In addition, there were no other endpoints assessed on this study that could be used to support demonstration of a clinical benefit.

X

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9 Advisory Committee Meeting and Other External Consultations

An Advisory Committee (AC) meeting was held on December 18, 2019. The committee discussed whether the evidence from Cohorts 5 and 6 of EZH-202 is sufficient to establish the benefit of tazemetostat in patients with epithelioid sarcoma, then voted unanimously (11-0) that the demonstrated benefit of tazemetostat outweighs the risks of the drug in the proposed indication.

During the discussion, the committee members focused on the assertions by sarcoma specialists in the room that metastatic epithelioid sarcoma is a steadily progressive disease, that prolonged periods of stable disease are typically not observed, and that available therapies do not yield durable responses. While the committee acknowledged that the response rate was low, the vote seemed to be influenced by the occurrence of prolonged response to tazemetostat in a few patients, by the number of patients who experienced some period of stable disease on tazemetostat, and by the rarity of the disease and lack of satisfactory therapies. The committee members asserted that the drug appeared well-tolerated and that the risk of secondary malignancies was not a concern in this patient population. Two of the committee members said that they favored an approval in patients who had failed their initial treatment regimen, the remainder did not object to an approval that is agnostic of line of therapy.

10 Pediatrics

There were a total of three pediatric patients enrolled in study EZH-202, all were 16 years of age. None of these patients experienced an objective response. Study EZH-202 did not include sufficient numbers of pediatric patients with epithelioid sarcoma to determine whether they respond differently from patients ≥18 years of age. FDA considered that since tazemetostat had been studied in patients with epithelioid sarcoma as young as 16, and the clinical pharmacology team considered the proposed dose to be supported in patients aged ≥ 16, the FDA recommended extension of the indication down to age 16.

The safety and effectiveness of tazemetostat in pediatric patients aged less than 16 years have not been established.

11 Labeling Recommendations

11.1 Prescription Drug Labeling

The table below (Table 46Table 46) summarizes changes to the proposed prescribing information (PI) made by FDA. See the final approved prescribing information for TAZVERIK (tazemetostat) accompanying the approval letter for more information.

Table 46: Highlights of Significant Labeling Changes (High-Level Changes and Not Direct

Section	Proposed Labeling	Approved Labeling
Full Prescribing Information		
Indications and Usage	…	Specified age groups in indication and usage statement as recommended in the guidance on the indications and usage section of labeling. Expanded indication to include pediatric patients 16 years and older based on the available data in pediatric patients 16 years and older.
Dosage and Administration Dosage Modifications for Adverse Reactions	Included text to describe dosage modifications for adverse reactions	Modified to provide tabular summary of dosage modifications for adverse reactions.
Dosage and Administration Dosage Modifications for Drug Interactions	…	Added dosage modifications for (b) (4) (b) (4) moderate CYP3A inhibitors.
Dosage Forms and Strengths	(b) (4)	Omitted (b) (4) based on recommendations in MAPP 5021.1 (rev.1).
Warnings and Precautions	Included (b) (4)	(b) (4) W&P for secondary malignancies, based on the recommendations in the guidance for W&P, contraindications and boxed warning sections of labeling (b) (4) Described the incidence in pooled safety population. Added a W&P for embryofetal toxicity based on the nonclinical studies demonstrating that tazemetostat can cause embryo-fetal harm.
Adverse Reactions	Listed the potentially serious adverse reactions in Clinical Trials Experience (6.1)	Moved to Adverse Reactions (6) based on recommendations in guidance for adverse reactions section of labeling, which states that all serious and otherwise important adverse reactions described in greater detail in other

	[redacted] (b) (4)	labeling sections should be identified and cross references in Adverse Reactions. Revised to describe the safety population of 62 adults and pediatric patients 16 years and older with metastatic or locally advanced epithelioid sarcoma who received the recommended dosage. Included overall exposure to tazemetostat for 6 months and one year and a description of serious adverse reactions, dosage modifications and most common adverse reactions.
	Described limited number of adverse reactions and laboratory abnormalities [redacted] (b) (4)	Expanded list to include adverse reactions and laboratory abnormalities that occurred above a specified rate [redacted] (b) (4) as the safety of tazemetostat was evaluated in a single arm trial. Modified tables to group by body system or category and list the body system/category and individual adverse reactions or abnormalities within each body system/category in decreasing order based on regulation 21 CFR 201.57(c)(7). Added clinically relevant adverse reactions that occurred below the specified rate in the table.
Drug Interactions	Included a description of effect of tazemetostat on CYP3A4 substrates [redacted] (b) (4) .	Added a description of the effect of strong and moderate CYP3A inhibitors and inducers on the pharmacokinetics of tazemetostat and provided dosage modifications. Omitted the [redacted] (b) (4) and modified the information regarding a drug interaction with CYP3A4 substrates based on the available clinical pharmacology data.
Specific Populations Lactation	Recommended avoid breastfeeding during treatment and for [redacted] (b) (4) after the final dose.	Modified to avoid breastfeeding during treatment and for 1 week after the final dose based on the elimination half-life.
Specific Populations Pediatric Use	…	Modified to include description of the evidence used to support an indication in pediatric patients 16 years and older.

		Added a description of the juvenile animal toxicity data based on nonclinical findings.
Specific Populations Geriatric Use	Included description of exposure and safety in (b) (4)	Modified to include statement about efficacy in geriatric patients compared to younger adults based on regulation 21 CFR 201.57(c)(11).
Clinical Pharmacology Pharmacokinetics	Included (b) (4)	Omitted (b) (4) and added a description of effect of renal and hepatic function on pharmacokinetics.
Clinical Studies	Included (b) (4)	Omitted (b) (4)

PLLR = pregnancy and lactation labeling final rule; W&P = Warnings and Precautions

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS program is not considered necessary for approval of this application.

13 Postmarketing Requirements and Commitment

If the application is approved, the review team recommends the following postmarketing requirements (PMRs) and postmarketing commitment (PMC).

Clinical post-marketing requirements:

1. Submit the final results from a randomized confirmatory trial in patients with epithelioid sarcoma to confirm clinical benefit and provide additional efficacy data that may inform product labeling for tazemetostat.

   Draft Protocol Submission: 07/2019
   Final Protocol Submission: 09/2019
   Trial Completion: 03/2029
   Final Report Submission: 11/2029

2. Submit the final report and datasets for the final analysis of overall response rate and duration of response for clinical trial EZH-202 titled, "A Phase II, Multicenter Study of the EZH2 Inhibitor Tazemetostat in Adult Subjects With INI1-Negative Tumors or Relapsed/Refractory Synovial Sarcoma" to verify and confirm clinical benefit of tazemetostat, that may inform product labeling. An additional 25 patients from Cohort 6 beyond those included in the original NDA submission will be evaluated and all responding patients will be followed for at least 12 months from the onset of response.

   Draft Protocol Submission: 03 /2020
   Final Protocol Submission: 05/2020
   Trial Completion: 12/2022
   Final Report Submission: 06/2023

3. Conduct cumulative, integrated safety analyses after 5 and 10 years of follow-up from an adequate number of patient enrolled in clinical trials to characterize the risk of acute myeloid leukemia, myelodysplastic syndrome, T-lymphoblastic lymphoma, and other secondary malignancies in patients receiving TAZVERIK; include incidence rates, time to onset, predisposing factors, and outcomes. These safety evaluations will be adequate to inform labeling of patient populations at highest risk and to provide evidence-based monitoring recommendations.

   Draft Protocol EZH-301 Submission: 07/2019
   Final Protocol EZH-301Submission: 09/2019
   Planned first patient enrolment: 12/2019
   Cutoff for Interim (5 year) Integrated Safety Analysis: 12/2024
   Report Submission: 03/2025
   Cutoff for Final (10 year) Integrated Safety Analysis: 12/2029
   Report submission: 03/2030

Clinical pharmacology post-marketing requirements:

1. Conduct a pharmacokinetic and safety study in cancer patients with moderate or severe hepatic impairment investigating the effects of hepatic impairment (based on the NCI Organ Dysfunction Working Group (ODWG) criteria) on the repeat dose pharmacokinetics of tazemetostat compared to cancer patients with normal hepatic function. This study will assess the magnitude of increased tazemetostat exposure and determine appropriate dosing recommendations of tazemetostat for patients with moderate or severe hepatic impairment.

Draft Protocol Submission:	08/2019
Final Protocol Submission:	01/2020
Trial Completion:	07/2022
Final Report Submission:	01/2023

2. Conduct a cross-over study in patients with cancer investigating the effects of itraconazole, a strong CYP3A inhibitor, on the repeat dose pharmacokinetics of tazemetostat to assess the magnitude of increased tazemetostat exposure and to determine appropriate dosing recommendations for tazemetostat when it is administered concomitantly with strong CYP3A inhibitors.

Draft Protocol Submission:	06/2020
Final Protocol Submission:	09/2020
Study/Trial Completion:	12/2022
Final Report Submission:	06/2023

Clinical pharmacology post-marketing commitment:

1. Conduct a cross-over study in patients with cancer investigating the effects of rifampin, a strong CYP3A inducer, on the repeat dose pharmacokinetics of tazemetostat to assess the magnitude of decreased tazemetostat exposure and to determine appropriate dosing recommendations for tazemetostat when it is administered concomitantly with strong CYP3A inducers.

Draft Protocol Submission:	06/2020
Final Protocol Submission:	09/2020
Study/Trial Completion:	12/2022
Final Report Submission:	06/2023

14 Division Director (DHOT)

X NOT APPLICABLE

John Leighton, PhD
Director, Division of Hematology, Oncology, and Toxicology

15 Division Director (OCP)

X

Nam Atiqur Rahman, PhD
Director, Office of Clinical Pharmacology

16 Division Director (OB) Comments

X

Rajeshwari Sridhara, PhD
Director, Office of Biometrics

17 Division Director (Clinical) Comments

While I share many of the review team's concerns regarding the clinical effects of tazemetostat in the indicated population, in the final analysis, I am recommending (accelerated) approval of NDA 211723 for the treatment of patients with metastatic or locally advanced epithelioid sarcoma (ES) who are not eligible for curative surgery. This recommendation considers the data package included in the application, multiple discussions with the review team and OCE/OOD, and the discussion of the application at the Oncologic Drugs Advisory Committee (ODAC) meeting, including the perspectives of sarcoma specialists, and the 11 to 0 vote in favor of tazemetostat. Although I had concerns regarding some of the conclusions or interpretations of the data during the AC (see below), I did not question the actual data and ultimately respect the decision of the AC. As such, this approval recommendation (and underlying uncertainties) is only promulgated based on the (many) unique circumstances regarding this specific application

and should not be interpreted that similar results will be sufficient for approval in other applications.

I will briefly summarize my thoughts regarding this application using the benefit-risk framework outlined in Section 1.2 of this review, focusing of the major issues I considered in my decision

Epithelioid sarcoma (ES) is a rare and aggressive tumor

ES is an extremely rare cancer with approximately 125 cases in the US per year with fewer that are unresectable or metastatic. Accordingly, conducting clinical trials and identifying new effective therapies can be difficult for patients with ES. As stated above in this review, the expected 5 year survival rate of patients with ES is 0. Indeed, during the Oncologic Drugs Advisory Committee (ODAC) discussion, and as stated above in this review, Committee members focused on the assertions by sarcoma specialists (either on the Committee or representing the Applicant) in the room that metastatic epithelioid sarcoma is an extremely rare and rapidly progressive disease and that prolonged periods of stable disease are typically not observed.

When reviewing the Applicant's natural history study (and FDA's review of the data in Section 19.1, below), while this (i.e., rapidly progressive) may be an accurate description of the clinical course for the vast majority of patients with ES, the data suggest that there also may be a limited number of patients whose survival is longer than was described during the ODAC. For example, in the Applicant's KM curve of 66 patients (page 69 of Module 2.7.3) receiving first-line systemic chemotherapy in the historical study, 18 patients were alive at 100 weeks and seven were alive at 200 weeks. This information suggests that at least in some patients with unresectable or metastatic ES, the pace of the disease may differ than what was described for the entire population of patients with metastatic ES, and may provide context regarding the stability in tumor growth claims that were discussed during the AC.

Risks and Benefit of tazemetostat

I agree with the statement above in Section 1 of this review that, although used clinically, doxorubicin and pazopanib appear to be unsatisfactory therapies in patients with ES. These drugs have been investigated in unselected sarcoma trials with few enrolled patients with ES; therefore, it is difficult to ascertain the effects of these drugs in patients with ES, though some reports describe anti-tumor responses which generally appear to be of short duration. Furthermore, even if there are some patients who live longer than average, there is no conclusive evidence that this is due to treatment with either doxorubicin or pazopanib or combination therapy with an anthracycline and ifosfamide (or other drug). Based on these considerations, I agree that patients with unresectable or metastatic ES have a life-threatening disease and have an unmet medical need.

I agree with the statement in Section 1 of this review that the overall safety profile of tazemetostat appeared acceptable for the treatment of a serious and life-threatening

condition. Reported adverse events included pain, fatigue, and gastrointestinal toxicities. Toxicities were generally manageable with dose interruption; and dose modifications or discontinuations due to toxicity were rare. Overall, the safety profile of tazemetostat was assessed both in patients with ES and in a broader patient pool of 668 patients who received the 800 mg twice daily dose of tazemetostat. The greatest uncertainty regarding risk stems from the lack of a control arm in the ES cohorts. Therefore, it cannot be determined what proportion of adverse events were caused by tazemetostat versus the patients' underlying disease, considering that pain and fatigue commonly occur in patients with cancer.

Based on the totality of non-clinical and clinical data, I agree that treatment with tazemetostat probably confers a risk of secondary hematologic malignancies. Although significant if it occurs, this risk may be less relevant in patients with a rare, aggressive, and incurable condition with few treatment options like unresectable or metastatic ES. This risk may be weighed differently in other clinical settings such as if use would be considered in the adjuvant setting or for the treatment of cancers with a longer life expectancy.

As is stated above in Section 1 of this review, the efficacy of tazemetostat is based on an open-label, single-arm cohort (Cohort 5) of a multi-center study (EZH-202) in patients INI1-negative, metastatic, relapsed or refractory epithelioid sarcoma that demonstrated an overall response rate (ORR) of 15% (95% CI: 7, 26). Supportive data from Cohort 6 and pooled efficacy data from Cohorts 5 and 6 demonstrated similar results, with ORRs of 11% (95% CI: 4, 25) and 13% (95% CI: 7, 21), respectively. The lower bound of the associated confidence interval implies that the true ORR may be as low as the single digits. In my opinion, this represents a modest clinical effect.

Response rate is an imperfect marker for clinical benefit in patients with cancer considering that some drugs can have lower response rates that are associated with beneficial effects on PFS or OS (e.g., pazopanib in sarcoma or TAS-102 in CRC) and other therapies can have effects on ORR that do not translate into benefit. A challenge for patients with ES, given the rarity of the disease, is the difficulty in conducting randomized trials to demonstrate a clear benefit (for example, on OS). Such trials, depending on the anticipated effect size, might take 10 or more years to conduct. Although ORR can be an imperfect intermediate endpoint, FDA has considered certain effects on ORR as representing clinical benefit, particularly for targeted drugs that confer a very high ORR with long duration. Traditional approvals have been granted, for example, to crizotinib for ROS-1-positive NSCLC and avapritinib for PDGFR exon 18 mutant GIST. Depending on the context, FDA has also granted accelerated approval for other drugs based on effects on (durable) ORR.

Ultimately, in Cohorts 5 and 6 of Study EZH-202, observed confirmed responses (i.e., tumor shrinkage per RECIST) occurred in a limited number of patients (13% in the pooled analysis). I agree that tumor shrinkage is unlikely to occur in the absence of therapy in patients with ES. Although the potential exists that tazemetostat may cause disease stabilization, and therefore provide benefit to a greater number of patients (e.g., pazopanib's effect in unselected sarcoma), this cannot be adequately assessed in a single arm trial.

For me, it was difficult to determine, and I was conflicted whether, based on the objective data presented in this application, the observed clinical effect on ORR (with associated duration) did in fact change the natural history of this disease in patients enrolled in the EZH-202 study (or whether the observed effect would be reasonably likely to effect such a change in the natural history of the disease). Ultimately, this topic was presented at the advisory committee which voted unanimously that the drug provided for a favorable risk-benefit profile and that tazemetostat would be beneficial for patients with ES as this is a rare disease that is difficult to treat and does not have many options for treatment. In addition to observed responses, durability of response is encouraging; however, there is uncertainty regarding the effect based on the limited number of patients responding.

Therefore, with reservations, I will recommend (accelerated) approval of this application. This decision is made for tazemetostat considering the following specific contextual factors: extremely rare condition (fewer than 150 cases in US per year); poor prognosis of underlying condition; no known clearly effective drugs for this condition; and reasonably favorable toxicity profile given the life-threatening nature of metastatic ES. Tazemetostat may also be unique in that increased activity has been reported in another potential condition of use (as presented in the AC: ORR of 69% for patients with EZH2 mutation-positive follicular lymphoma; and 35% for patients with wild-type EZH2 follicular lymphoma). If confirmed, these data at least show biological effects of tazemetostat occur in a second cancer (noting that biology may differ between ES and follicular lymphoma).

The Applicant plans to initiate a confirmatory trial designed to assess for an effect on PFS when tazemetostat is administered in combination with doxorubicin; however, this study has not been initiated. Given the rarity of the disease, the possibility exists that this trial will not be completed. Therefore, uncertainty regarding the clinical effects of this drug may persist indefinitely following approval, which is a real concern. If approved, I do hope that patients benefit; however, I am concerned that there will be an “opportunity cost” to the action (e.g., fewer patients initially seek clinical trials due to the availability of this therapy). Such an opportunity cost could, in theory, delay discovery or study of other therapies for patients with ES.

If approved, it will be important for the manufacturer, in advertising or other presentations, to accurately describe the effects of the drug as well as limitations of the data to ensure that patients and their treating oncologists can make the best treatment decision (e.g., whether to take tazemetostat, receive an alternative regimen, or to enroll into a clinical trial). For example, statements regarding effects on OS or disease stabilization should not be made based on cross study comparisons of non-randomized trial data to data from natural history studies (the validity of such comparisons may be further limited by small sample sizes, differences in when and where patients were identified, missing data, etc.).

Steven Lemery

Steven Lemery, MD, MHS

Acting Director, Division of Oncology 3

18 Office Director (or designated signatory authority) Comments

After consideration of the FDA Review documents, selected documents submitted to the NDA, ODAC materials, discussions with the review team, and discussion at the December 18, 2019 ODAC, I conclude that the application for tazemetostat meets the statutory standards for marketing approval under 21 CFR 314, subpart H, with consideration of the principles described in 21 CFR 312, subpart E, for the following indication:

> treatment of adults and pediatric patients aged 16 years and older with metastatic or locally advanced epithelioid sarcoma not eligible for complete resection.

Major uncertainties identified by the FDA Clinical Review for the tazemetostat application are (1) the clinical meaningfulness of a modest objective response rate (ORR) with limited information on the duration of responses (DOR) and (2) whether tazemetostat represents a therapeutic meaningful advantage—in the context of qualifying criteria for accelerated approval—for the proposed indication given the prior FDA approvals of doxorubicin and pazopanib for the broader STS population.

Epithelioid sarcoma is a rare, aggressive sarcoma that has been historically categorized within the broader group of soft tissue sarcoma (STS), a heterogeneous compilation of histological distinct diseases brought together in drug development programs based, in part, on mesenchymal derivation, rarity of any one subtype and associated challenges for dedicated study, and, until recently, little molecular insights for understanding pathogenesis of individual subtypes. With molecular characterization of histologic subtypes of STS such as epithelioid sarcoma, individual diseases are beginning to be categorized not only on histology but also unifying genetic aberrations. For example, in epithelioid sarcoma, 90% or more of patients harbor tumors with nuclear loss of INI-1 by IHC. There are an estimated 125 new patients per year in the U.S. diagnosed with epithelioid sarcoma with half of patients having metastatic disease at diagnosis. Patients with metastatic disease have a poor prognosis—median survival is approximately 12 months with a 0% reported 5-year survival. There are no FDA approved therapies for the epithelioid sarcoma indication. The treatment effects of FDA approved drugs for treatment of patients in the broader category of STS—doxorubicin and pazopanib—are modest in general and are largely uncertain in patients with epithelioid sarcoma based on the reasons described in the FDA clinical review. Taken together, patients with metastatic epithelioid sarcoma represent a population with a high unmet medical need.

Tazemetostat is a small molecule inhibitor of EZH2, a methyltransferase that is part of a complex implicated in repression of cell differentiation genes. INI1 is part of a complex that antagonizes EZH2—loss or dysfunction of INI can lead to aberrant EZH2 activity or expression and oncogenic dependence on EZH2.

The primary trial supporting approval, Study EZH-202, NCT02601950), is a multi-center, single-arm, open-label, multi-cohort trial evaluating tazemetostat in patients with unresectable or

metastatic epithelioid sarcoma. In the primary efficacy cohort (Cohort 5) of Study EZH-202, the primary endpoint was objective response rate as assessed by an independent review committee per RECIST v1.1 and duration of response. Cohort 5 of EZH-202 demonstrated a confirmed ORR of 15% (95% confidence interval: 7, 26) among the 62 patients with unresectable or metastatic epithelioid sarcoma. Among the nine patients with a response, responses were ongoing for 5 of the 9 patients at the time of data cutoff and 6 of the 9 patients had a duration of response of at least 6 months (duration of responses ranging from 4 to 24+ months). The results in a similar cohort of patients (n=44) with unresectable or metastatic epithelioid sarcoma (Cohort 6) was supportive of the ORR and DOR results observed in Cohort 5.

In general, the safety evaluation indicates that tazemetostat appears to be well tolerated by patients with epithelioid sarcoma with adverse events managed by dose interruption (34%) and supportive care. Adverse events leading to discontinuation (1.6%) or dose reduction (1.6%) of tazemetostat are uncommon. Oncologists are well versed in the management of the most common (≥20% incidence) adverse events observed with tazemetostat—pain, fatigue, nausea, decreased appetite, vomiting, and constipation. The major safety risk of tazemetostat is the rare (<1%) risk of secondary malignancies with myelodysplastic syndrome, acute myeloid leukemia, and T-cell lymphoblastic lymphoma, which were observed in the overall drug development program.

The FDA convened the Oncologic Drugs Advisory Committee (ODAC) on December 18, 2019, to discuss the benefit-risk of tazemetostat in this rare disease given the modest ORR observed in Cohorts 5 and 6 of Study EZH-202 and uncertainties surrounding the clinical meaningfulness of this magnitude of ORR and DOR, i.e., a pooled ORR of 13% (95% CI: 7, 21) and duration of responses ranging from 3.5 to at least 24 months (response was ongoing). The ODAC members, including 3 temporary voting members with specific expertise in epithelioid sarcoma (patient representative and 2 clinicians), were unanimous in their vote that the benefits outweighed the risks in this population (11- “yes”; 0 – “no”). In the discussion, the ODAC members commented that the magnitude and durability of objective responses observed with tazemetostat represented clinically meaningful efficacy in patients with metastatic epithelioid sarcoma, as this is a rare disease that is characterized by relentless progression and unresponsiveness to FDA approved therapies for STS, such as doxorubicin and pazopanib. The sentiment of the ODAC discussion also was supportive of the FDA and the Applicant assessments that the safety risks of tazemetostat, including the risk of secondary malignancy, are acceptable in patients with metastatic epithelioid sarcoma given the serious and life-threatening nature of this disease.

While the FDA clinical review team was not unanimous in the recommendation for approval of this application, I concur with Dr. Lemery, Division Director (Acting) of the Division of Oncology 3, that this application meets the statutory standards for accelerated approval. The approval action reflects a long-standing commitment by FDA to regulatory flexibility regarding the evidence required to support approval for the treatment of serious or life-threatening diseases with limited therapeutic options. In regulations, 21 CFR 312, subpart E, for patients with serious

and life-threatening diseases, FDA has determined that "that it is appropriate to exercise the broadest flexibility in applying the statutory standards, while preserving appropriate guarantees for safety and effectiveness." This is based on the knowledge that for serious and life-threatening illnesses, physicians and patients are willing to accept greater risks or side effects from treatments. Additionally, this framework recognizes that the benefits of the drug need to be evaluated in context of the severity of the disease being treated.

Additionally, as described in FDA Guidance[1], the accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to:

> . . . a product for a serious or life-threatening disease or condition . . . upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, *taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments.*

Furthermore, this FDA Guidance affirms flexibility concerning the implications of available therapy on granting accelerated approval. For example, a meaningful therapeutic advantage may exist in the absence of demonstration of a direct efficacy or safety advantage, such as therapy with a novel mechanism of action in a setting where available therapy provides modest responses or significant heterogeneity in the responses.

In conclusion, tazemetostat demonstrates a favorable benefit-risk profile with a clinically meaningful, albeit modest treatment effect on ORR with prolonged durations of response in the context of acceptable safety risks for the indicated population, and the application meets the statutory standards for accelerated approval under 21 CFR 314, subpart H. Objective response rate with prolonged durations of response is a commonly used intermediate endpoint to support accelerated approval of Oncology drugs—including for several applications with ORRs and DOR of similar magnitude as that demonstrated with tazemetostat for patients with unresectable or metastatic epithelioid sarcoma—and in some circumstances regular approval (depending on the magnitude of treatment effect, rarity of the patient population, and/or supporting information in a particular disease). Based on the statistical and clinical considerations of this application as described in the review, there is uncertainty surrounding the magnitude of ORR and DOR of tazemetostat in patients with epithelioid sarcoma as well as the relationship of these treatment effects to ultimate clinical benefit. With the principles described in 21 CFR 312.80, greater uncertainty of the magnitude of treatment effects of tazemetostat, in the context of the known safety profile, is acceptable based on the rarity and nature of metastatic epithelioid sarcoma as a serious and life-threatening disease with no effective treatment options. As a condition of the accelerated approval, the applicant will verify and describe the clinical benefit of tazemetostat in one or more trials [see Section 13]. FDA

[1] FDA Guidance for Industry *Expedited Programs for Serious Conditions – Drugs and Biologics*, May 2014.

approval of tazemetostat represent a new therapeutic option with a novel mechanism of action for treatment of the patients with unresectable or metastatic epithelioid sarcoma.

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Marc Theoret, MD
Deputy Director (Acting), Office of Oncologic Diseases

19 Appendices

19.1 Statistical Appendix

Natural History Study
EZH-1001 was a multi-center, non-interventional retrospective chart review study conducted in patients 10 years of age or older with histologically confirmed locally advanced unresectable or metastatic ES, who initiated systemic therapy between January 1, 2000 and December 31, 2017. Patient medical charts from five academic cancer centers (i.e., study sites) in the US were screened, reviewed, and abstracted by site research personnel. The following centers were included:

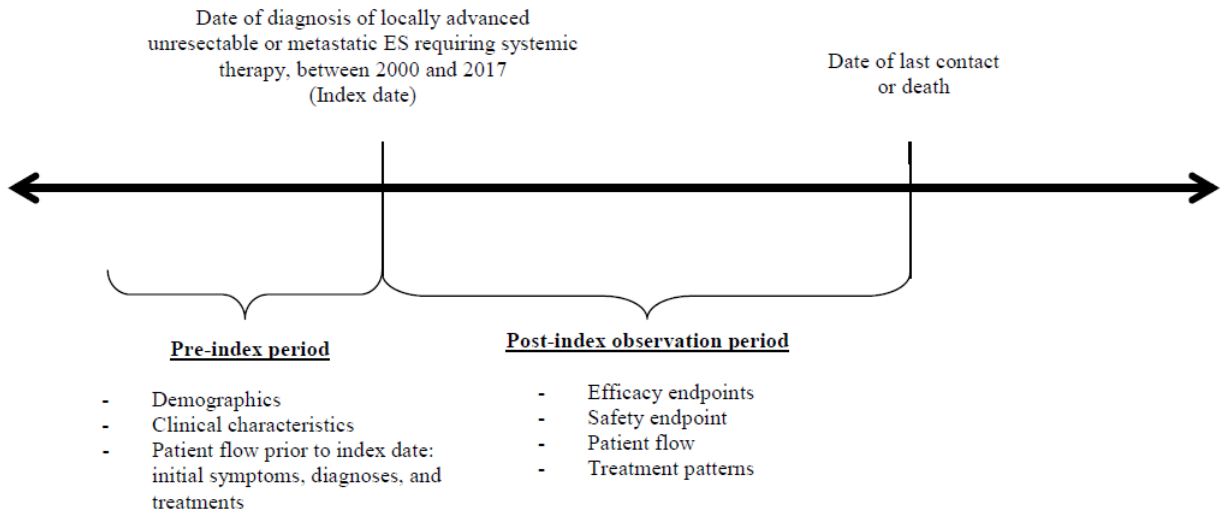
- Dana Farber Cancer Institute, Boston, MA
- Memorial Sloan Kettering Cancer Center, New York, NY
- MD Anderson Cancer Center, Houston, TX
- University of Michigan Comprehensive Cancer Center, Ann Arbor, MI
- University of Colorado Cancer Center, Denver, CO

The following inclusion criteria were used for selecting patients for the study:

- Diagnosed with histologically confirmed, locally advanced unresectable or metastatic ES requiring systemic therapy during between January 1, 2000 and December 31, 2017. The date of the confirmed locally advanced unresectable or metastatic ES diagnosis is designated as the index date.
    - Patients may have a date of ES diagnosis at an earlier stage prior to 2000 and still be eligible for the study.
- Initiation of treatment with any systemic anti-cancer therapy for the treatment of their locally advanced unresectable or metastatic ES during between January 1, 2000 and December 31, 2017
- At least 10 years of age at the index date

In eligible patients, the index date was defined as the date of diagnosis with histologically confirmed locally advanced unresectable or metastatic ES requiring systemic therapy. The study design is shown in Figure 25.

Figure 25: Study Design of EZH-1001



Source: Figure 1 of the EZH-1001 CSR, pg. 25.

In addition, patients were not required to be confirmed INI1(-) for inclusion in this study, but at the site level, the priority for recruitment were given to patients who are confirmed to be INI1(-) based on past immunohistochemistry stains.

The primary endpoint was real world ORR (rwORR) as recorded in clinician notes and radiology reports. Verbatim responses were categorized into clinician-assessed complete response, clinician-assessed less-than-complete response, etc. Real-world overall response rate is defined as the proportion of patients who have a documented radiological scan showing clinician-assessed complete response or less-than-complete response, of any duration, defined for each regimen and by line. No formal power calculations were performed. Epizyme stated in the protocol that they anticipated between 70 and 100 patients would meet eligibility criteria to be enrolled for chart review.

Secondary endpoints included real world duration of response (rwDOR) and overall survival.

Epizyme specified in the protocol that they would collect the following demographic patient characteristics: year of birth, gender, race/ethnicity, survival status and survival assessment date(s), and date of death and causes of death if patient is deceased. Epizyme also collected other baseline characteristics, such as clinical symptoms prior to diagnosis of ES, time from first onset of symptoms to presentation to first health care provider, tumor size, histologic grade, etc.

Interaction with FDA

On 02/11/2019, Epizyme submitted the results of EZH-1001. After reviewing the results, FDA communicated the following comments regarding the design of the study in meeting minutes dated 05/13/2019:

> *The following additional comments are regarding the protocol and results of the Natural History Study, submitted under SDN 253. While these comments are intended to enhance the interpretability of the data from the Natural History study, the FDA considers rwORR not comparable to ORR as assessed on a clinical trial, and considers cross-trial comparisons of time-to-event endpoints not valid. It is thus unlikely that a response to these comments will result in FDA agreement that the ES Natural History Study can be used as a "control arm" for the purposes of regular approval.*
>
> *The protocol for the natural history study does not provide adequate detail regarding quality of data, validity of endpoint assessments, and design choices, rendering the results of the study uninterpretable. For general principles regarding observational studies, please refer to "Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data" which can be accessed at https://www.fda.gov/downloads/drugs/guidances/ucm243537.pdf*
>
> *An observational study whose intent is to serve as an historical control for single arm data should be designed such that the patient populations to be compared in the analyses are as similar as possible. The following differences call into question the validity of the reported historical study for this purpose:*
>
> - *Difference in age used for inclusion criteria. Study EHZ-202 enrolls patients 18 years of age or older, while the historical study enrolls patients 10 years of age and older.*
> - *Difference in years during which patients received treatment. Study EHZ-202 was initiated in 2015, but the historical study included patients from 2000-2017.*
> - *The role of INI-1 in the study designs. All patients are screened for INI1 status for entry into EHZ-202. However, it is unclear how many of the patients eligible for inclusion in the Natural History Study were screened for INI1 status. Furthermore, INI1 status is likely to be associated with 1) the time during the study period at which each center started testing for INI1 status and 2) general practices within each center. Epizyme should summarize the differences in baseline characteristics and outcomes between patients for whom INI1 status is known and patients for whom INI1 status was not captured.*
>
> *The protocol should justify choosing different eligibility criteria and give rationale for why the resulting populations may be assumed to be similar in spite of differences retained.*

In addition to differences in eligibility criteria, many inclusion criteria used for EHZ-202 are not addressed in the design of the historical study, further limiting interpretability. For instance, patients enrolled in EHZ-202 must have completed prior cancer therapy(ies) prior to enrollment. The protocol for the historical study should clarify which, if any, prior cancer therapies should be discontinued before selection into the study. Furthermore, the protocol should define the minimum length of the pre-index period in which such information can be assessed for each patient.

The historical study does not specify any methods to evaluate potential confounding variables in the resulting data set. Because patient characteristics are likely to be different in the historical study compared to those in EHZ-202, comparisons between the two data sets may not accurately reflect the treatment effect of tazemetostat in reference to standard of care. In general, such analyses should be specified before looking at the data to reduce biases resulting from post-hoc inferences…

…The design of the Natural History Study is inadequate to provide evidence that outcomes in patients with ES are different than outcomes in patients with non-ES soft-tissue sarcomas.

Study Results

Demographics

Table 47presents the demographics of the patients selected for EZH-1001.

Table 47: Demographics of Patients Included in EZH-1001

	Overall
n	74
Age (median [range])	33.1 [10.6, 76.3]
Sex (%)	
Female	21 (28)
Male	53 (72)
Ethnicity (%)	
Hispanic or Latino	4 (5)
Not Hispanic or Latino	44 (59)
Unknown	26 (35)
Race (%)	
Unknown	9 (12)
Asian	5 (7)

	Overall
Black or African American	5 (7)
Native Hawaiian or Other Pacific Islander	1 (1)
White	54 (73)
Study Site Identifier (%)	
1-Dana Farber Cancer Institute	19 (26)
2-Memorial Sloan Kettering Cancer Center	22 (30)
3-Md Anderson Cancer Center	23 (31)
4-University of Michigan Comprehensive Cancer Center	9 (12)
5-University of Colorado Cancer Center	1 (1)

Source: Reviewer's analysis.

Baseline Characteristics

Table 48Table 48 presents the baseline characteristics of patients include in EZH-1001.

Table 48: Baseline Characteristics of Patients Included in EZH-1001

	Overall
n	74
Longest diameter of primary tumor at baseline (mean (sd))	69.4 (95.0)
Longest diameter of primary tumor at baseline, grouped	
0-5 cm	55 (98)
5-10 cm	1 (2)
>10 cm	0 (0)
Stage of disease at baseline (%)	
Stage i	2 (3)
Stage Ii	4 (5)
Stage Iii	3 (4)
Stage Iv	26 (35)
Unknown / not Sure	39 (53)
ES Subtype (%)	
Classic-Type (also Called Distal)	8 (11)
Other	1 (1)

	Overall
Proximal-Type	46 (62)
Unknown/ not Sure	19 (26)
INI1 status (%)	
Negative Reactivity	34 (46)
Positive Reactivity	1 (1)
Not Tested or Unknown	39 (53)
SURGERY (%)	
No	19 (26)
Yes	55 (74)

Reviewer's comment: Note that the disease burden at baseline is similar to patients studied in EZH-202. In particular, the longest diameter of the primary tumor is 0-5 cm for the majority of patients.

Table 49Table 49 presents a summary of the treatment regimens for all patients included in EZH-1001. The most frequently used regimens for first-line patients were anthracycline-based regimens, while the most frequently used regimens for second-line patients were gemcitabine-based regimens.

Table 49: Summary of Treatment Regimens for Patients Included in EZH-1001

	First-line	Second-line
n	74	47
Regimen (%)		
Anthracycline-based Regimen	39 (53)	8 (17)
Gemcitabine-based Regimen	18 (24)	21 (45)
Pazopanib	4 (5)	4 (9)
Other	13 (18)	14 (30)

Source: Reviewer's analysis.

Pazopanib was approved for second-line STS on 04/26/2012. To assess the utilization of this treatment, we repeated the above analysis, excluding all records prior to the approval of pazopanib. These results are presented in Table 50.

Table 50: Summary of Treatment Regimens Used After 04/26/2012 for Patients Included in EZH-1001

	First-line	Second-line
n	29	22
TREATMENT (%)		
Anthracycline-Based Regimen	14 (48)	3 (14)
Gemcitabine-Based Regimen	8 (28)	8 (36)
Pazopanib	4 (14)	4 (18)
Other	3 (10)	7 (32)

Source: Reviewer's analysis.

Efficacy Results – Primary Endpoint

Table 51 presents the applicant's analysis of real-world ORR from EZH-1001.

Table 51: Real-World ORR Results from EZH-1001

Response Measure	First-Line N=74	Second-Line N=46	Second and Later Lines [a] N=96
Real-world best overall response, n (%)			
Complete response [b]	3 (4.1)	0 (0.0)	0 (0.0)
Less-than-complete response [c]	8 (10.8)	5 (10.9)	9 (9.4)
Stable disease [d]	22 (29.7)	17 (37.0)	30 (31.3)
Progressive disease [e]	22 (29.7)	7 (15.2)	19 (19.8)
With decision to discontinue therapy	21 (28.4)	6 (13.0)	17 (17.7)
With decision to continue therapy for clinical benefit	1 (1.4)	1 (2.2)	2 (2.1)
No documented scans	19 (25.7)	17 (37.0)	38 (39.6)
Real-world overall response rate [f]			
n (%)	11 (14.9)	5 (10.9)	9 (9.4)
95% CI	(7.7, 25.0)	(3.6, 23.6)	(4.4, 17.1)

a. Analysis of second and later lines includes all patients who received second-line therapy and above. N represents the total number of lines of therapy rather than the number of patients. Lines of therapy contributed by the same patient are assumed to be independent. 46 patients received second-line therapy, 19 patients received third-line therapy, 15 patients received fourth-line therapy, 9 patients received fifth-line therapy, 5 patients received sixth-line therapy, and 2 patients received seventh-line therapy.
b. Complete response was defined as no clinical evidence of disease.
c. Less-than-complete response was defined as clinically significant tumor shrinkage.
d. Stable disease was defined as minimal increases or decreases in size of tumor.
e. Progressive disease was defined as clinically significant increase in tumor size.

Source: Table 8 of the EZH-1001 CSR, pg. 50.

Reviewer's comment: It is not known how real-world ORR is associated with ORR as measured per RECIST v1.1 in a clinical trial. The only conclusion one can draw from the response results is that ES patients typically derive some marginal level of response benefit from commonly-used

therapies. It is impossible to assess whether the responses observed are different than patients with non-ES STS, given the limitations in interpreting real-world ORR and the absence of such patients from EZH-1001.

The reviewer also notes that the "second-line" patients referred to in the results above are qualitatively different than first-line patients, in that they progressed and were re-treated while at the aforementioned centers, whereas the first-line patients were likely not treated at these centers prior to first-line treatment.

Efficacy Results – Secondary and Other Endpoints

Table 52 presents the applicant's analysis of OS from EZH-1001.

Table 52: Overall Survival Results from EZH-1001

Status	First-Line N=66	Second-Line N=44
Number of events, n (%)	54 (81.8)	36 (81.8)
Number of patients censored, n (%)	12 (18.2)	8 (18.2)
Overall survival (weeks) [a]		
Min	2.1	5.1
25th percentile	34.6	28.9
95% CI of 25th percentile	(26.9, 42.3)	(8.9, 35.9)
Median	66.3	43.3
95% CI of median	(49.6, 94.1)	(33.6, 78.3)
75th percentile	146.4	143.4
95% CI of 75th percentile	(94.1, 206.6)	(68.3, 218.6)
Max	529.6	401.1
Overall survival at intervals defined by weeks		
Overall survival at 16 weeks [b]		
n (%)	60 (92.4)	36 (84.1)
95% CI	(82.7, 96.8)	(69.5, 92.1)
Overall survival at 24 weeks [b]		
n (%)	57 (87.8)	34 (81.7)
95% CI	(77.0, 93.7)	(66.7, 90.4)
Overall survival at 32 weeks [b]		
n (%)	49 (78.3)	28 (69.6)
95% CI	(66.1, 86.5)	(53.4, 81.1)
Overall survival at 56 weeks [b]		
n (%)	32 (55.3)	17 (45.6)
95% CI	(42.1, 66.6)	(29.7, 60.2)

Overall survival at intervals defined by months		
Overall survival at 6 months [b]		
n (%)	56 (86.2)	34 (81.7)
95% CI	(75.2, 92.6)	(66.7, 90.4)
Overall survival at 12 months [b]		
n (%)	36 (62.2)	17 (45.6)
95% CI	(49.0, 72.8)	(29.7, 60.2)
Overall survival at 24 months [b]		
n (%)	18 (33.2)	11 (31.6)
95% CI	(21.5, 45.4)	(17.7, 46.6)

a. Overall survival was defined as time from initiation of therapy to death from any cause. Patients who initiated tazemetostat after first-line during the study period were censored at the date of initiation of tazemetostat, whether they had a death event or not. Patients who did not have a death event were censored at the date of last contact. Patients were excluded from this analysis due to unknown treatment initiation dates. Summary statistics were calculated with Kaplan-Meier analysis and 95% CIs using complementary log-log method.

b. Time-point estimates were calculated with Kaplan-Meier analysis and 95% CIs using complementary log-log method.

CI = confidence interval; max = maximum; min = minimum.

Source: Adapted from Table 16 of the EZH-1001 CSR, pg. 83.

<u>Reviewer's comment</u>: In general, time-to-event endpoints are not interpretable in single-arm trials. Furthermore, the limited sample size, time of study, and difference in treatment strategies preclude meaningful comparisons of OS between EZH-202 and EZH-1001.

19.2 References

Asano N, Yoshida A, Ogura K, et al. Prognostic Value of Relevant Clinicopathologic Variables in Epithelioid Sarcomas: A Multi-Institutional Retrospective Study of 44 Patients. Ann Surg Oncol. (2015);22(8):2624-2632.

Aster, JC, Blacklow, SC, Pear, WS. Notch Signaling in T cell lymphoblastic Leukaemia/Lymphoma and other haematological Malignancies. J Pathology Jan; (2011);223(2):262-273.

Chase DR, Enzinger FM. Epithelioid sarcoma. Diagnosis, Prognostic indicators, and Treatment. The American Journal of Surgical Pathology. 91985);9(4):241-63.

Doxorubicin USPI:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/062921s022lbl.pdf

Eisenhauer, EA, Therasse P, Bogaerts J, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (version 1.1). European Journal of Cancer (2009);45:228-247.

Jones RL, Constantinidou A, Olmos D, et al. Role of Palliative Chemotherapy in Advanced Epithelioid Sarcoma. Am J Clin Oncol (2012);35(4):351-357.

Judson, I, Verweij, J, Gelderblom H, et al. Doxorubicin Alone Versus Intensified Doxorubicin Plus ifosfamide for First-Line Treatment of Advanced or Metastatic Soft-Tissue Sarcoma: A Randomised Controlled Phase 3 trial. The Lancet Oncol. (2014);15: 415-423.

Kadoch, C, Crabtree, GR. Reversible disruption of mSWI/SNF (BAF) complexes by the SS18-SSX oncogenic fusion in synovial sarcoma. (2013)

Kadoch, C, Copeland, RA, Keilhack, H. PRC2 and SWI/SNF chromatin remodeling complexes in health and disease. Biochemistry (2016);55:1600-1641.

Kim KH, Kim W, Howard TP, et al. SWI/SNF-mutant Cancers Depend on Catalytic and Non-Catalytic Activity of EZH2. Nat Med. (2015);21:1491–1496.

Kim, W, Bird, GH, Neff, T, et al. Targeted Disruption of the EZH2–EED Complex Inhibits EZH2-Dependent Cancer. Nature chemical. (2013);9:64.

Kim, KH, Roberts, CW. Targeting EZH2 in cancer. Nat. Med (2016);22(2):128-34.

Nakayama RT, Pulice JL, Valencia AM, et al. SMARCB1 is required for widespread BAF complex-mediated activation of enhancers and bivalent promoters. Nat Genet. (2017);Nov;49(11):1613-1623.

Ntziachristos P, Tsirigos A, Van Vlierberghe P, et al. Genetic inactivation of the polycomb

repressive complex 2 in T cell acute lymphoblastic leukemia. Nat Med (2012);18: 298–301.

Pazopanib USPI:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022465s-010S-012lbl.pdf

Pink D, Richter S, Gerdes S, et al. Gemcitabine and docetaxel for epithelioid sarcoma: results from a retrospective, multi-institutional analysis. Oncology (2014); 87(2):95-103.

Seddon, B, Strauss, SJ, Whelan J, et al. Gemcitabine and Docetaxel Versus Doxorubicin as First-Line Treatment in Previously Untreated Advanced Unresectable or Metastatic Soft-Tissue Sarcomas (GeDDiS): A Randomised Controlled Phase 3 Trial. The Lancet Oncol. (2017);18:1397-1410.

SEER (2019): https://seer.cancer.gov/statfacts/html/soft.html

Spillane AJ, Thomas M, and Fisher C. Epithelioid Sarcoma: The Clinicopathological Complexities of This Rare Soft Tissue Sarcoma. Annals of Surgical Oncology. (2000);7(3):218-225.

Tap, WD, Papai Z, Van Tine, BA, et al. Doxorubicin Plus Evofosfamide Versus Doxorubicin Alone in locally Advanced, Unresectable or Metastatic Soft-Tissue Sarcoma (TH CR-406/SARC021): An International, Multicentre, Open-Label, Randomised Phase 3 Trial. The Lancet Oncol. (2017);18:1089-1103.

Tap, WD, Wagner, AJ, Papai, Z, et al. ANNOUNCE: A Randomized, Placebo (PBO)-Controlled, Double-Blind, Phase (Ph) III Trial of Doxorubicin (Dox)+ Olaratumab Versus Dox+ PBO in Patients (pts) with Advanced Soft tissue Sarcomas (STS). ASCO (2019):LBA3-LBA3.

Thway K, Jones RL, Noujaim J, et al. Epithelioid sarcoma: diagnostic features and genetics. Advances in Anatomic Pathology (2016); 23(1):41-9.

Touati, N, Schöffski, P, Litière, et al. European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Experience with Advanced/Metastatic Epithelioid Sarcoma Patients Treated in Prospective Trials: Clinical Profile and Response to Systemic Therapy. Clinical oncology, (2018);30(7):448-454.

Van Der Graaf, WT, Blay, JY, Chawla, SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a Randomised, Double-Blind, Placebo-Controlled Phase 3 Trial. The Lancet. (2012);379:1879-1886.

Wilson, BG, Wang, X, Shen, X, McKenna, ES, Lemieux, ME, Cho, YJ, Koellhoffer, EC, Pomeroy SL, Orkin, SH, Roberts, CW. Epigenetic antagonism between polycomb and SWI/SNF complexes during oncogenic transformation. Cancer Cell. (2010);18:316–328.

19.3 Financial Disclosures

Covered Clinical Study (Name and/or Number): Study EZh-202 and E7438-G000-101

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 349		
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: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

19.4 OCP Appendices (Technical documents supporting OCP recommendations)

19.4.2 Bioanalytical

Plasma and urine concentrations of tazemetostat and its major metabolites (EPZ-6930, EPZ006931 and EPZ034163) were determined in the clinical pharmacology and safety/efficacy studies. Summary of the bioanalytical methods used for quantitation of tazemetostat and its metabolites in clinical studies are listed in Table 53, including two methods for plasma sample analysis and one method for urine sample analysis

The two bioanalytical assays for human plasma samples were developed and validated separately at (b) (4) (validation report number: (b) (4)) or (b) (4) (validation report number: 151136VSMB_ECM) and used across different studies. In Method 151136VSMB_ECM, EPZ-6438, EPZ-6930, EPZ006931, and EPZ034163 are isolated from human plasma samples (20 µL) using a protein precipitation extraction procedure and then analyzed by turbo ion spray liquid chromatography/tandem mass spectrometry (LC/MS/MS) using AB SCIEX API 4000. In Method (b) (4), EPZ-6438 and EPZ-6930 in plasma were similarly extracted and quantified using TurboIonSpray Applied Biosystems API5000. No formal cross-validation between the two methods were performed to assess the assay comparability. Cross-study comparison showed comparable tazemetostat exposure between study E7438-G000-101 using method (b) (4) and EZH-105 using method 151136VSMB_ECM at 400 mg BID tazemetostat.

EPZ-6438 and EPZ-6930 were found to be stable in human plasma for up to 368 days at -20°C and -80°C as determined by Method (b) (4); and long-term stability up to 239 days at -20°C and -70°C were also demonstrated for EPZ-6438, EPZ-6930, EPZ006931 and EPZ034163 using Method 151136VSMB_ECM.

Table 53: Summary of bioanalytical methods used in tazemetostat clinical program

Matrix	Analyte	Method validation study report	Bioanalytical Laboratory	Calibration Range (ng/mL)	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
Plasma	Tazemetostat (E7438, EPZ-6438)	(b) (4)	(b) (4)	1.00-1000	1.00	≤±8.8% (intra-run); ≤±5.0% (inter-run)	≤11.8% (intra-run); ≤9.3% (inter-run)
		151136VSMB_ECM		1.00-2000	1.00	-6.0 to 10.0% (intra-run); -2.0 to 6.0% (inter-run)	≤15.1% (intra-run); ≤10.3% (inter- run)
	EPZ-6930 (ER-897387)	(b) (4)		1.00-1000	1.00	≤±9.0% (intra-run); ≤±3.0% (inter- run)	≤10.3% (intra-run); ≤8.8% (inter-run) [solvent 2]

		151136VSMB_ECM	(b) (4)	1.00-2000	1.00	0.4 to 17.0% (intra- run); 2.0 to 12.0% (inter- run)	≤6.9% (intra- run); ≤7.4% (inter- run)
	EPZ006931	151136VSMB_ECM		1.00-2000	1.00	-5.3 to 12.0% (intra- run); -0.5 to 7.0% (inter- run)	≤15.5% (intra- run); ≤13.3% (inter- run)
	EPZ034163	151136VSMB_ECM		1.00-2000	1.00	-6.7 to 11.0% (intra- run); -0.4 to 8.0% (inter- run)	≤13.1% (intra- run); ≤10.6% (inter- run)
Urine	Tazemetostat (E7438, ER-581982-06)	(b) (4)		1.00-1000	1.00	Not available	Not available

Source: Summary of Biopharmaceutical Studies and Associated Analytical Methods (M2.7.1), Table 17 and method validation reports for 151136VSMB_ECM and (b) (4)

The performance of the bioanalytical methods in individual clinical studies is summarized in Table 54.

Table 54: Summary of Bioanalytical Method Performance for Analysis of Clinical Study Samples

Study	Bioanalytical Laboratory	Bioanalytical Method	Bioanalysis Report	Analyte	Biological Matrix	LLOQ (ng/mL)	Accuracy (%RE)	Precision (%CV)
E7438-G000-101	(b) (4)	(b) (4)		EPZ-6438	Plasma	1.00	-0.4 to 1.5%	≤ 8.4%
				EPZ-6930	Plasma	1.00	0.9 to 5.0%	≤ 7.4%
				EPZ-6438	Urine	1.00	-0.3% to 11.0%	≤ 8.6%
EZH-105		151136VSMB_ECM	161297ASMB_ECM_INTERIM	EPZ-6438	Plasma	1.00	-3.2 to 6.0%	≤ 10.3%
		151136VSMB_ECM		EPZ-6930	Plasma	1.00	2.0 to 12.0%	≤ 7.4%
		151136VSMB_ECM		EPZ006931	Plasma	1.00	-0.5 to 7.0%	≤ 13.3%
		151136VSMB_ECM		EPZ034163	Plasma	1.00	-0.4 to 8.0%	≤ 10.6%
EZH-202		(b) (4)	(b) (4) 1	EPZ-6438	Plasma	1.00	1.6%-2.7%	≤ 8.7%
				EPZ-6930	Plasma	1.00	-0.6%-3.8%	≤ 6.8%
EZH-203		151136VSMB_ECM	160331ASMB_ECM	EPZ-6438	Plasma	1.00	-4.0% to -1.2%	≤ 6.4%
				EPZ-6930	Plasma	1.00	-4.0% to -2.3%	≤ 8.5%
				EPZ006931	Plasma	1.00	-6.7% to 2.3%	≤ 9.5%
				EPZ034163	Plasma	1.00	-5.1% to -2.0%	≤ 9.2%
EZH-103		(b) (4)	(b) (4) 1	EPZ-6438	Plasma	1.00	5.4%-10.2%	≤ 5.0%
				EPZ-6930	Plasma	1.00	1.0%-10.3%	≤ 6.4%

Source: Module 2.7.1 Summary of Biopharmaceutical Studies and Associated Analytical Methods, Table 18 and respective study bioanalysis reports.

19.4.3 Pharmacometrics

Key Review Question:
Do E-R relationships for efficacy and safety support an 800 mg BID dose regimen of tazemetostat in patients with metastatic or locally advanced epithelioid sarcoma who are not eligible for curative surgery?
A positive trend for exposure-efficacy was observed in the pivotal study EZH-202 cohort 5 in 59 patients. However, multivariate logistic regression modeling, including baseline EOG score, body weight and prior lines of systemic therapy as potential risk factors, did not identify a significant relationship between tazemetostat exposure and efficacy (ORR and DCR). Furthermore, this positive exposure efficacy relationship was not observed in 42 patients in cohort 6 of study EZH-202.

A positive relationship between tazemetostat exposure and treatment-emergent Grade 3 and above adverse event was observed. However, the risk to toxicities is expected to be low over the exposure range at 800 mg BID dosage regimen based on the pooled safety data from Studies E7438-G000-101 Part 1, EZH-105 and EZH-202. Pre-clinical studies suggest that secondary malignancy seems to be related with high dose (1600mg BID). In addition, there is limited experience for safety on higher dose too. The occurrence of T-LBL might be confounded by age. Thus the overall benefit of efficacy and safety in higher dose is uncertain.

Overall the proposed dosing regimen of 800 mg BID is acceptable for the epithelioid sarcoma population.

19.4.4 Population PK Model

The Population PK model is generally acceptable. Co-administration of PPI during the treatment will increase clearance by 9% by modified pop-PK model. However, caution needs to be taken in interpretation of population PK results as the PPI dosing records were not well documented. Baseline factors such as, BSA, AST, albumin, creatinine clearance and bilirubin status are identified as the significant covariates for clearance, but their effects are unlikely to be clinically significant.

19.4.5 Exposure Response Relationship for Efficacy

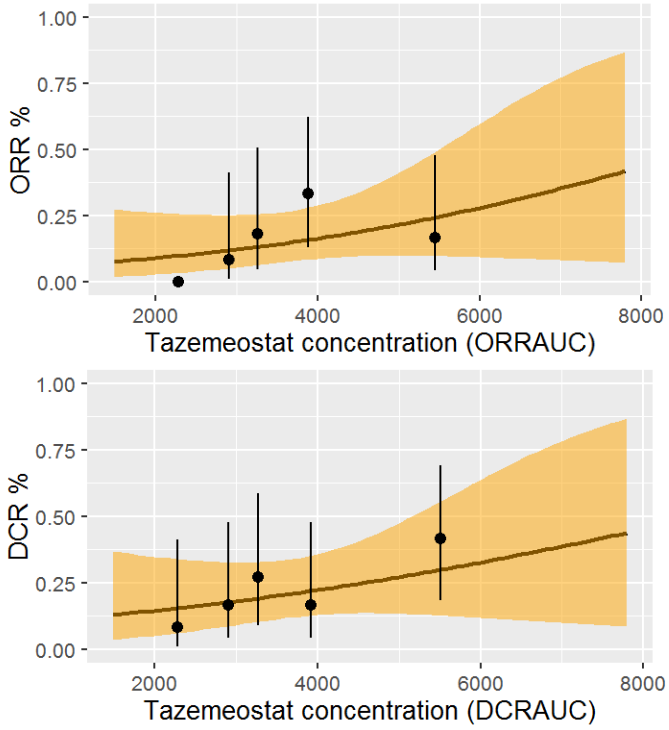
Sixty-two patients with metastatic or locally advanced epithelioid sarcoma (ES-STS) who are not eligible for curative surgery from the pivotal study EZH-202 were included in the exposure-response analysis of efficacy outcomes. Three patients were excluded in the primary analysis pool since their ages are below 16. Overall response rate per investigator and IRC are shown in Table 55. All patients involved in exposure-efficacy analysis received oral doses of tazemetostat at a dosing regimen of 800-mg bid.

Table 55: Overall Response Rate Based on Investigator and IRC Assessment

	Investigator Assessment N=62	IRC Assessment N=62
ORR (CR+PR)	9 (15%)	9 (15%)
CR	0	1 (2%)
PR	9 (15%)	8 (13%)

The PK exposure for tazemetostat was summarized as ORRAUC (mean dose AUC for dose interval up until disease progression after objective response). The efficacy of tazemetostat, measured as overall response rate (ORR) and disease control rate (DCR) per investigator and IRC (Table 56). Logistic regression was conducted. There is a positive trend between exposure versus ORR and DCR (Figure 26 and Table 56). Baseline ECOG, baseline body weight (BW) and lines of therapy had been incorporated into logistic regression and only body weight showed a statistic significant negative trend (Table 56). Further exploratory univariant and bivariant subgroup analysis was conducted.

Figure 26: Exposure-Response for Efficacy by Logistic Regression



Source: FDA reviewer's analysis. Solid line is the logistic regression of the predicted ORR per investigator (upper panel) or IRC (lower panel). 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 100 mg BID. Exposure-response analyses showed no correlation between PK exposure (maximum plasma concentration [Cmax] or AUC over 2 dosing intervals [AUC0-24]) and overall response rate (ORR).

Table 56: Estimated Parameters in Logistic Regression for ER Relationship for Efficacy

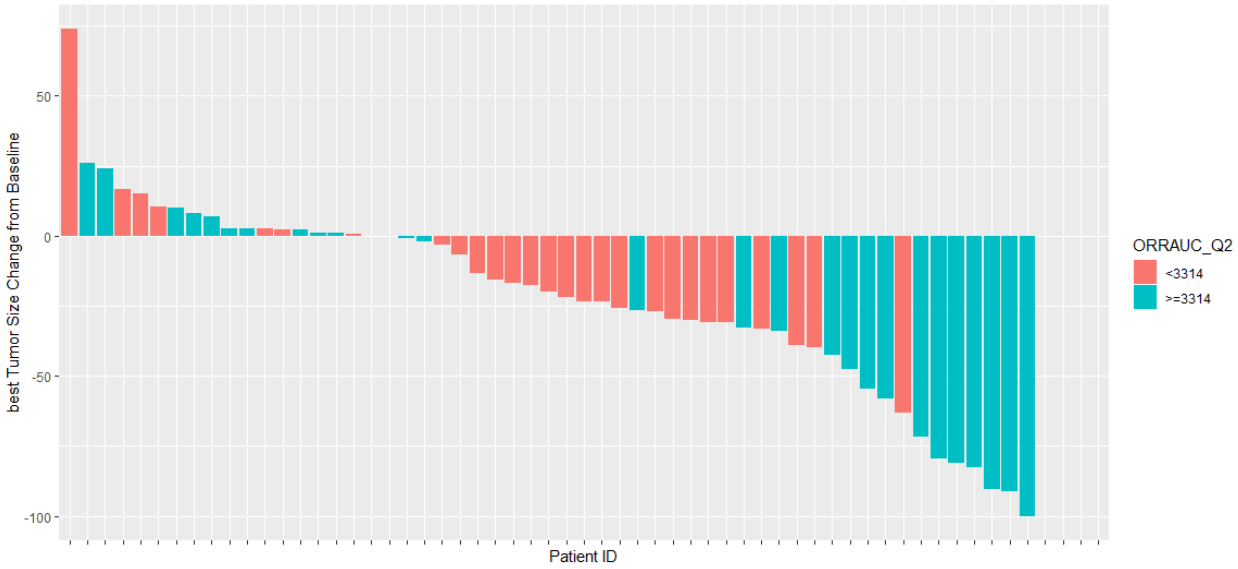
		Estimate	Std. Error	P value
ORR per IRC ~ AUC	Intercept	1.83	2.47	0.459
	Exposure Slope	0.00039	0.00034	0.249
	Ecog	-0.36	0.661	0.59
	Lines of Therapy	-0.14	0.21	0.493
	Baseline Body Weight	-0.065	0.03	0.037*
DCR per IRC~ AUC	Intercept	-1.07	1.8	0.554
	Exposure Slope	0.00031	0.00029	0.28
	Ecog	-0.79	0.60	0.189
	Lines of Therapy	-0.11	0.21	0.592
	Baseline Body Weight	-0.012	0.017	0.508

Source: FDA's analysis * body weight is treated as continuous variant. Lines of therapy is treated as continuous variance.

Notably, when patients were divided by two exposure subgroups with the median exposure which is 3314 ug-day/mL, there is only 1 responder out of 30 patients in the lower half group and the duration of response DOR is 175 days. This DOR is shorter than median DOR in the 9 responders (16 months ranged from 4-24 months). Moreover, for the 3 pediatric patients had exposure under 3314 ug-day/ml and there is no responder.

Further exposure subgroup analysis was conducted with waterfall plot (Figure 27). Higher exposure patients showed a better best tumor reduction rate per IRC. This result is consistent with overall response rate, higher exposure patients showed a better chance to be a responder however low exposure patients are more likely to be steady state if their tumor shrink.

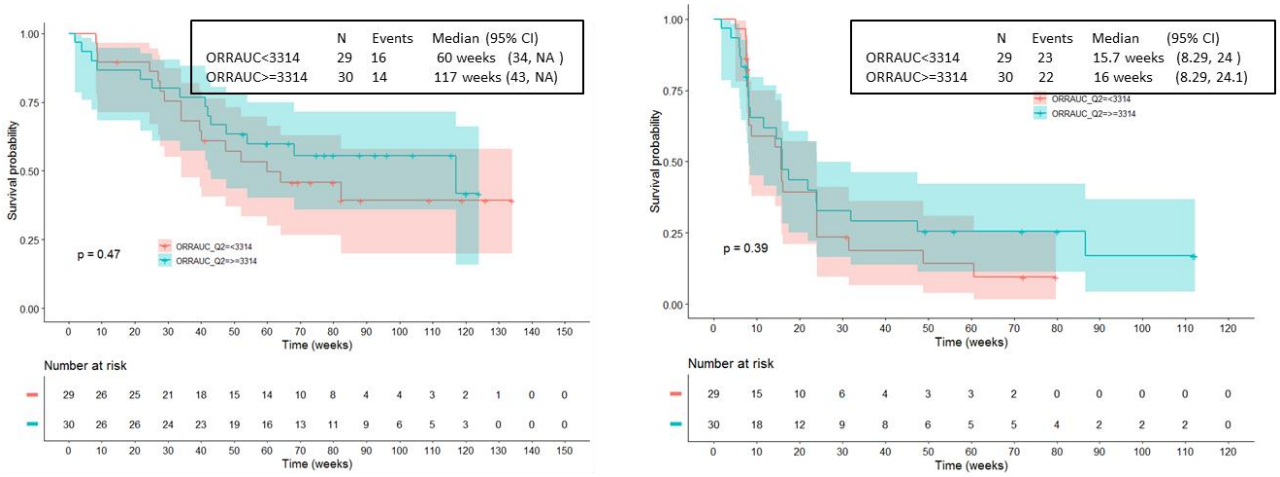
Figure 27: Best Tumor Size Change From Baseline per IRC stratified by Exposure Subgroup in Study EZH-202 Cohort 5



Source: FDA's Analysis. Waterfall plot stratified by exposure subgroups. Patients with exposure less than

The overall survival and progress free survival subgroup analysis are shown in Figure 28. The trend is consistent with ORR and DCR, showing better efficacy in terms of OS and PFS in higher exposure patients. However, the result was considered inconclusive given the small number of at risk population at the the terminal phase of curves.

Figure 28: KM curves for OS (Left) and PFS (Right) in ES-STS Patients Treated with Tazemetostat in Study EZH-202 Cohort 5



Source: FDA's Analysis.

Exploratory Analysis of Confounding Factors

To further examine the potential effect of the confounding factors, bivariate descriptive analysis was conducted and results were summarized below. Within the caveat of very limited data available, there was a numerical trend of better efficacy in higherexposure subgroup when stratified by lines of therapy (Table 57) , baseline ECOG (Table 58), body weight subgroup (Table 59) and hepatic function (Table 60). Body weight also appeared to affect ORR responseNevertheless, the small number of events in each subgroup analysis preclude a definitive assessment. Furthermore, multivariate logistic regression modeling, including baseline ECOG score, body weight and prior lines of systemic therapy as potential risk factors, did not identify a significant relationship between tazemetostat exposure and efficacy (ORR and DCR).

Table 57: Better Efficacy in Higher Exposure Subgroup Stratified by Lines of Therapy

Prior lines of radiotherapy	Exposure Ug-day/mL	Exposure Median (range)	N	Responder (ORR%)	DCR%	Median DOR (days)
0	<3314	2569 (1553, 3212)	15	0	1 (6.7)	-
	>=3314	4202 (3369, 5760)	11	3 (27.3)	3 (27.3)	224
1	<3314	2775 (2240, 3186)	9	1 (11.1)	2 (22.2)	175
	>=3314	4291 (3315, 7747)	11	3 (27.3)	4 (36.4)	288
2	<3314	2895 (2661, 3025)	3	0	1 (33.3)	-
	>=3314	4444 (3960, 5661)	4	2 (50)	2 (50)	300.5
3	<3314	2687 (2294, 3080)	2	0	0	-
	>=3314	3417 (3322, 3513)	2	0	0	-
4	>=3314	3373	1	0	0	-
13	>=3314	7380	1	0	0	-

Source: FDA's Analysis.

Table 58: Better Efficacy in Higher Exposure Subgroups Stratified by Baseline ECOG

ECOG Baseline	Exposure Ug-day/mL	Exposure Median (range)	N	Responder (ORR)	DCR	Median DOR (days)
0	<3314	2838 (1553, 3186)	15	1 (6.7)	4 (26.7)	175
	>=3314	4103 (3322, 5661)	19	4 (21.1)	5 (26.3)	308.5
1	<3314	2941 (2267, 3212)	11	0	0	-
	>=3314	4234 (3315, 7380)	9	4 (44.4)	4 (44.4)	255.5
2	<3314	2294 (2240, 2377)	3	0	0	-
	>=3314	5656 (3564, 7747)	2	0	0	-

Source: FDA's Analysis.

Table 59: Better Efficacy in Higher Exposure Subgroups Stratified by Body Weight Subgroups

Body Weight Baseline	Exposure Ug-day/mL	Exposure Median (range)	N	Responder (ORR)	DCR	Median DOR (days)
< 80kg	<3314	2858 (2267, 3212)	18	1 (5.5%)	2 (11%)	175
	>=3314	4234 (3369, 7747)	19	7 (36.8%)	7 (36.8%)	288
>= 80kg	<3314	2498 (1553, 3063)	11	0	2 (18.2%)	-
	>=3314	3558 (3315, 5661)	11	1 (9%)	2 (18.2%)	113

Source: FDA's Analysis.

Table 60: Better Efficacy in Higher Exposure Subgroup Stratified by Hepatic Functions

Hepatic Functions	Exposure Ug-day/mL	Exposure Median (range)	N	Responder (ORR)	DCR	Median DOR (days)
Normal	<3314	2866 (1834, 3080)	16	0	2 (12.5%)	-
	>=3314	4000 (3314, 7747)	23	7 (30.4%)	7 (30.4%)	224
Mild	<3314	2661 (1553, 3212)	13	1 (7.7%)	2 (15.4%)	175
	>=3314	4291 (3322, 5513)	7	1 (14.3%)	2 (28.6%)	488

Source: FDA's Analysis.

Additional Evidence in Cohort 6 (based on data cut-off at September 17, 2018)

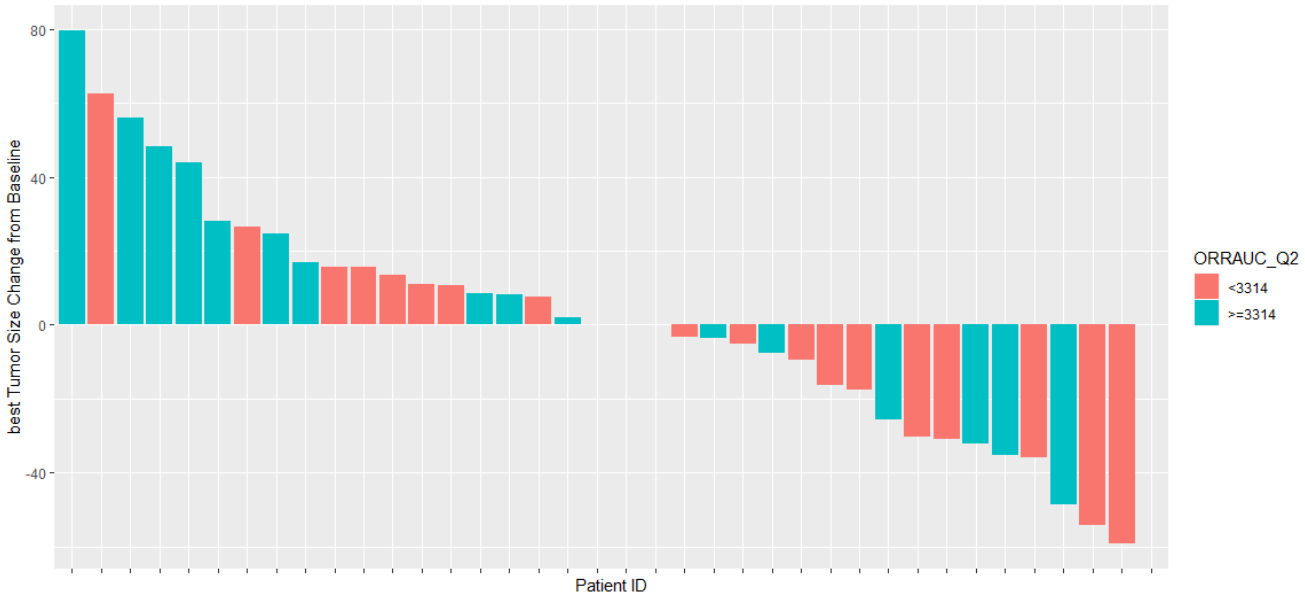
Additional 42 patients with epithelioid sarcoma in study EZH-202 cohort 6 was analysis although efficacy data was not mature. A comparison between cohort 5 and cohort 6 was conducted in Table 61: Comparison of ORR in Cohort 5 vs. Cohort 6. Best tumor size change from baseline per investigator is available and analysis by exposure subgroup (Figure 29). No positive trend was found in higher exposure subgroup. Cohort 6 analysis was conducted with early cut-off data at September 17, 2018, consisitent observation was found with updated dataset at Oct 2019.

Table 61: Comparison of ORR in Cohort 5 vs. Cohort 6

	EZH-202 COHORT 5 N=62	EZH-202 COHORT 6 N=42
ORR (%)	15	5
95% CI	(7, 26)	(0, 16)
CR n, (%)	1 (13)	0
PR n, (%)	8 (13)	2 (5)
DOR (months) (range)	16 (4, 24+)	NE (2+, 6+)
Median Follow-up (range)	8 (0.2, 32)	6 (0.2, 11)

Source: FDA's analysis

Figure 29: Best Tumor Size Change from Baseline per investigator stratified by Exposure Subgroup in Study EZH-202 Cohort 6



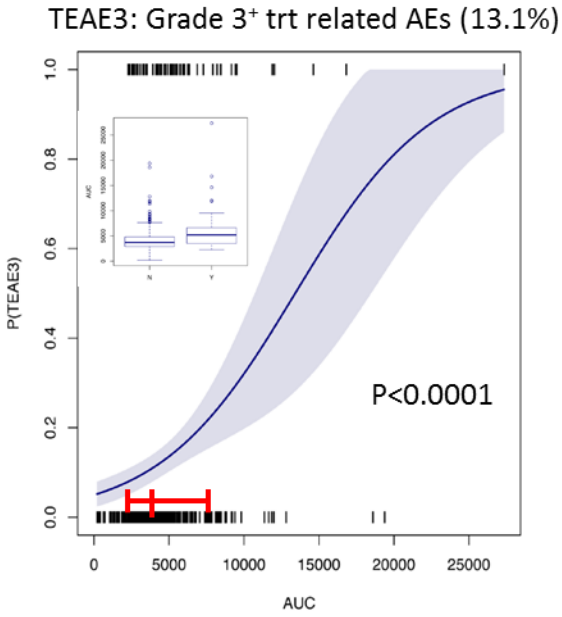
Source: FDA's Analysis.

In conclusion, the exposure-response analyses indicated a trend of positive exposure-response relationship for efficacy. However, the present evidence was inconclusive supporting the additional benefit at higher dosage than the proposed 800 mg BID regimen.

19.4.6 Exposure Response Relationship for Safety

A significantly positive exposure-safety relationship was observed for the grade 3 or above treatment-emergent adverse event (Figure 30). ER for safety was conducted in 458 patients with 60 patients had grade 3 or higher TEAE3.

Figure 30: Exposure Safety Relationship for treatment related Grade 3 and higher TEAE



Source: Sponsor's Analysis.

Secondary malignancy and death are considered as adverse event of special interest (AESI). Exposures in patients with secondary malignancy and death are listed in Table 62Table 62. T-LBL and MDS patients received 1600mg BID dose. The event of secondary malignancy may limit the possibility of dose escalation.

Table 62: Exposure in Patients with AESI

AESI	USUBJID	DOSE	AUC
T-LBL	-	900mg/m^2 (equal to 1600mg)	-
MDS	(b) (6)	1600mg	4706
		1600mg	4011
Death			
acute respiratory failure		800mg	2300
bronchopneumonia		1600mg	4351
intestinal perforation		800mg	2673
respiratory distress		800mg	4739
respiratory failure		800mg	2479
pneumonia			-
Unknown (<30 days)			-
intestinal obstruction (<30 days)			-

Source: FDA's analysis

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Signing for Dr. Ward by proxy. Her comments and recommendations are in the unireview.

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