

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213176Orig1Orig2s000

MULTI-DISCIPLINE REVIEW

Summary Review

Office Director

Cross Discipline Team Leader Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	New Drug Application
Application Number(s)	213176 – Original 1
Priority or Standard	Priority
Submit Date(s)	15 June 2020
Received Date(s)	15 June 2020
PDUFA Goal Date	15 February 2021
Division/Office	Division of Hematologic Malignancies II
Review Completion Date	04 February 2021
Established Name	Umbralisib
(Proposed) Trade Name	UKONIQ
Pharmacologic Class	PI3K inhibitor
Code name	Phosphatidylinositol 3-kinase inhibitor
Applicant	TG Therapeutics
Formulation(s)	Oral tablets - 200 mg strength
Dosing Regimen	800 mg orally once daily continuously
Applicant Proposed Indication(s)/Population(s)	Adult patients with marginal zone lymphoma who have received at least one prior anti-CD20-based regimen.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Adult patients with relapsed or refractory marginal zone lymphoma who have received at least one prior anti-CD20-based regimen.

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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

%CfB	percent change from baseline
ABL1	Abelson murine leukemia viral oncogene homolog 1
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ARA	acid-reducing agent
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma/serum concentration-time curve
AUC ₀₋₄₈	area under the plasma concentration-time curve from time zero to 48 hours post-dose
AUC _{0-inf}	area under the plasma concentration-time curve from time zero to infinity
AUC _{0-t}	area under the plasma/serum concentration-time curve from time zero to the time of the last quantifiable concentration
BM	bone marrow
BTK	Bruton's tyrosine kinase
C _{max}	maximum concentration
CD20	cluster of differentiation 20
CI	confidence interval
CK1ε	casein kinase 1 epsilon
CMC	chemistry, manufacturing, and controls
C _{min,ss}	minimum plasma concentration at steady state
CNS	central nervous system
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CV%	percentage coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DMF	drug master file
DOR	duration of response
DP	drug product
DS	drug substance
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group

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eGFR	estimated glomerular filtration rate
E-R	exposure-response
FDA	Food and Drug Administration
FL	follicular lymphoma
hERG	human ether-à-go-go-related gene
IC ₅₀	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IDB	integrated database
IND	Investigational New Drug
iNHL	indolent non-Hodgkin lymphoma
IRC	Independent Review Committee
ITT	intent-to-treat
MALT	mucosal-associated lymphoid tissue
MATE	multidrug and toxic compound extrusion transporter
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NDA	new drug application
NHL	non-Hodgkin lymphoma
OAT	organic anion transporter
OATP	organic anion transport protein
OCT	organic cation transporter
ORR	objective response rate
PBPK	physiologically-based PK
PD	progressive disease
PET-CT	positron emission tomography-CT
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PI3K α , β , γ , δ	phosphoinositide 3-kinase alpha, beta, gamma, and delta isoforms
PK	pharmacokinetic(s)
PP	per protocol
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
QD	once daily
QTc	corrected QT interval
QTcF	corrected QT interval by Fredericia
R ²	REVLIMID® (lenalidomide) in combination with rituximab

SAE	serious adverse event
SAP	statistical analysis plan
SLL	small lymphocytic lymphoma
SOC	system organ class
SPD	sum of the products of longest diameters
T _{max}	time to maximum concentration
TEAE	treatment-emergent adverse event
TTR	time to response
US	United States

1 Executive Summary

1.1. Product Introduction

Umbralisib is a phosphoinositide-3-kinase-delta (PI3K δ) inhibitor in development for the treatment of patients with hematologic malignancies. While both the gamma and the delta isoforms of PI3K are restricted to cells of hematopoietic origin, the delta isoform has the highest expression on leukocytes. Umbralisib also inhibits Casein Kinase 1 epsilon (CK1 ϵ) which regulates the non-canonical Wnt/planar cell polarity pathway. This pathway is involved in lymphoid malignancy pathogenesis via regulation of cell survival, proliferation, chemotaxis, and migration. Regulation of the Wnt/ β -catenin pathway also modulates T-cell transcription factor-1, which affects the development of regulatory T cells (Tregs). The Applicant purports that this support of regulatory T-cells is the mechanism by which T-reg clones are supported, and the development of immune-related toxicity may be potentially mitigated.

On 15 June 2020, TG Therapeutics submitted Part 2 of their rolling NDA 213176 submission under 21 CFR 314.50 and Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, seeking accelerated approval of umbralisib at the recommended dose of 800 mg by mouth daily for the following indication:

- Treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The efficacy of umbralisib is based on data from 69 patients with MZL from a cohort of the UTX-TGR-205 trial, an open-label, multi-center, single-arm, multi-cohort trial. Patients with MZL were required to have prior treatment with 1 or more lines of therapy, including at least 1 anti-

CD20-based regimen. The trial excluded patients with prior exposure to a PI3K inhibitor. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) based on the 2007 International Working Group criteria using computerized tomography (CT). Secondary endpoints included duration of response and progression-free survival.

Of the 69 patients with MZL [extranodal (N=38), nodal (N=20), and splenic (N=11)], the median age was 67 years (range: 34 to 88 years), 52% were female, 83% were White, 7% were Black, 3% were Asian, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), with 26% being refractory to their last therapy. The median follow-up time was 20.3 months (range 15.0 to 28.7 months). The ORR per IRC was 49% (95% CI: 37.0, 61.6), with 16% achieving a complete response. The median duration of response was not reached (95% CI: 9.3, not evaluable). Of the 34 patients that responded, 65% maintained a response at 6 months, 50% at 9 months, and 38% at 12 months.

The data in patients with MZL support the determination that umbralisib has clinically meaningful activity in adult patients with relapsed or refractory MZL. To support accelerated approval, the efficacy data is considered in the context of available therapy for patients with MZL in the 2nd line setting and beyond. Available therapy includes rituximab and the immunotherapy combination rituximab plus lenalidomide, which provides response rates ranging from 44% to 65% with associated durability (Table 1). Thus, the ORR of 49% with durability for umbralisib provides data to support a clinically meaningful therapeutic benefit in the context of available therapy for patients with relapsed or refractory MZL in the 2nd line setting and beyond. Therefore, the review team recommends accelerated approval of umbralisib for:

- Treatment of adult patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen.

Benefit-Risk Summary and Assessment

Umbralisib is a specific and orally bioavailable dual kinase inhibitor of phosphoinositide-3-kinase-delta (PI3K δ) and casein kinase 1 epsilon (CK1 ϵ).

Efficacy:

Efficacy of umbralisib in adult patients with previously treated marginal zone lymphoma (MZL) is based on the results from a single-arm cohort of Study UTX-TGR-205, a multicenter, single-arm, open-label, multi-cohort trial, which included 69 patients with MZL. The scheduled umbralisib dose was 800 mg by mouth daily until progressive disease or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) based on the 2007 International Working Group criteria using computerized tomography (CT). Among the 69 patients with MZL, the median follow-up time was 20.3 months (range 15.0 to 28.7 months). The ORR per IRC was 49% (95% CI: 37.0, 61.6], with 16% achieving a complete response. The median duration of response was not reached.

Safety:

The safety profile was supported by analysis of the 69 patients with marginal zone lymphoma from the study UTX-TGR-205 and a combined safety database of 371 patients with hematologic malignancies [marginal zone lymphoma (22%), follicular lymphoma (40%), diffuse large B-cell lymphoma or mantle cell lymphoma (20%), and other hematologic malignancies (18%)] who received umbralisib doses $\geq$ 800 mg daily.

In the 69 patients with MZL, the median duration of treatment was 9.4 months (range 5 days to 23 months) and the most common adverse events ($\geq$ 20% of patients) were increased creatinine, diarrhea-colitis, AST/ALT increased, fatigue, neutropenia, nausea, musculoskeletal pain, thrombocytopenia, cough, headache, rash, decreased appetite, upper respiratory tract infection, anemia, edema, and vomiting. Grade $\geq$ 3 adverse events occurred in 62% and those occurring in at least 5% of the MZL population included diarrhea-colitis, AST/ALT increased, and neutropenia. Adverse events that led to treatment discontinuation occurred in 23% of patients, most often due to AST/ALT increased and diarrhea-colitis.

The primary safety issues identified with umbralisib include serious, including fatal, infections and cutaneous reactions, and serious diarrhea or colitis, hepatotoxicity, and neutropenia. In the 371 patients with hematologic malignancies, 51% of patients

experienced a grade 3 or 4 toxicity, the most common including neutropenia (17%), diarrhea-colitis (8%), and increased AST/ALT (6%). Fifteen percent of patients discontinued umbralisib due to an adverse event, most often due to diarrhea-colitis and increased AST/ALT.

Benefit-Risk:

In the single-arm cohort with 69 patients with MZL, patients had to of received prior treatment with 1 or more lines of therapy, including at least 1 anti-CD20-based regimen. The median number of prior systemic therapies was 2 (range 1 to 6) with 22% refractory to their last therapy. The ORR of 49% with associated durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk for these patients. To support accelerated approval, the efficacy data is considered in the context of available therapy for patients with MZL in the 2nd line setting and beyond. Available therapy includes rituximab and the immunotherapy combination rituximab plus lenalidomide, which provides response rates ranging from 44% to 65% with associated durability (Table 1). Thus, the ORR of 49% with durability for umbralisib provides data to support a clinically meaningful therapeutic benefit in the context of available therapy for patients with relapsed or refractory MZL in the 2nd line setting and beyond. Therefore, the benefit-risk of umbralisib is deemed favorable to support accelerated approval under 21 CFR 314.510 Subpart H for the following indication:

- Treatment of adult patients with relapsed or refractory marginal zone lymphoma who have received at least one prior anti-CD20-based regimen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Approximately 7,500 cases of marginal zone lymphoma (MZL) are diagnosed each year in the United States. Patients with relapsed or refractory MZL are considered incurable. • The course of MZL is characterized by remitting and relapsing phases, and though most patients respond to initial chemo-immunotherapy, they will require multiple therapeutic regimens over the course of their disease.	MZL is a serious and life-threatening disease.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Median survival, regardless of therapy is generally between 8 and 12 years.	
Current Treatment Options	- Treatment options for relapsed and refractory MZL include chemotherapy, immunochemotherapy, and anti-CD20 monoclonal antibodies. - Numerous patients with relapsed or refractory MZL cannot tolerate intensive chemotherapy due to age or comorbidities.	New treatments are needed for patients with relapsed or refractory MZL, including chemotherapy-free treatments.
Benefit	- Umbralisib was administered at 800 mg orally once daily - Study UTX-TGR-205 was an open-label, multicenter, single-arm multi-cohort trial which included 69 patients with relapsed or refractory MZL. - Overall response rate (ORR) per independent review committee was 49% (95% CI: 37.0, 61.6], with 16% achieving a complete response. The median duration of response was not reached.	Based on ORR with durability, umbralisib has clinically meaningful activity in patients with relapsed or refractory MZL who have received at least one prior anti-CD20-based regimen.
Risk and Risk Management	- In the 69 patients with MZL treated with umbralisib 800 mg daily: - The median duration of treatment was 9.4 months (range 5 days to 23 months) - The most common adverse events (≥20% of patients) were increased creatinine, diarrhea-colitis, AST/ALT increased, fatigue, neutropenia, nausea, musculoskeletal pain, thrombocytopenia, cough, headache, rash, decreased appetite, upper respiratory tract infection, anemia, edema, and vomiting.	The safety profile of umbralisib is acceptable in the intended patient population. The USPI includes warnings and precautions for infections, neutropenia, diarrhea or colitis, hepatotoxicity, and severe cutaneous reactions.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Grade ≥ 3 adverse events occurred in 62% and those occurring in at least 5% of the MZL population included diarrhea-colitis, AST/ALT increased, and neutropenia. - Adverse events that led to treatment discontinuation occurred in 23% of patients, most often due to AST/ALT increased and diarrhea-colitis.	

1.3. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
☐	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.)	

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☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Section 2.1 Analysis of Condition]
☐	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 was not submitted in the application, but was considered in this review.	

- **Patients experience data was not submitted as part of this application.**

X

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Marginal zone lymphoma (MZL) is the second most common form of indolent non-Hodgkin lymphoma (iNHL), accounting for 5% to 15% of all non-Hodgkin lymphoma (NHL) (Zucca et al. 2020), with an estimated 7,500 new United States (US) cases annually (Leslie et al. 2019). MZL arises from B lymphocytes at the margins or edges of lymph nodes and various tissues, including the stomach, salivary glands, thyroid gland, eyes, lungs, and spleen (Zucca et al. 2020). There are 3 subtypes of MZL: splenic, nodal, and mucosal-associated lymphoid tissue (MALT), which respectively comprise 20%, 10%, and 70% of MZL cases (Zucca et al. 2020). While all 3 subtypes arise from memory B lymphocytes originating in the marginal zone of lymphoid follicles, they exhibit distinct genetic mutations, anatomical presentation, and response to therapies (Zinzani 2012).

B-cell activating autoimmune conditions, chronic infectious pathogens (such as *Helicobacter pylori*), and genetic variation in the major histocompatibility complex have been implicated in the etiology of MZL (Zucca et al. 2020). *H. pylori* and hepatitis C virus are precursors to many instances of gastric MALT-MZL and splenic MZL (Zucca et al. 2014), respectively, warranting antibiotic (Strati et al. 2019) and antiviral (Arcaini et al. 2014) therapy. Despite these attempts to eradicate the underlying pathogen and mitigate chronic inflammation, MZL often becomes antigen-independent (Zucca et al. 2014) and a majority of patients will relapse, necessitating subsequent therapy (Zinzani 2012, Strati et al. 2019).

The clinical disease characteristics of MZL vary depending on the subtype and lymphoma site of origin (Denlinger et al. 2018). For patients with extranodal MZL or MALT MZL, the disease is commonly limited to the site of origin, with rare peripheral lymph node and bone marrow (BM) involvement. For patients with splenic MZL, splenomegaly without lymphadenopathy is the hallmark clinical feature, with most patients exhibiting BM and blood involvement (Rosand et al. 2018). Most patients with nodal MZL present with non-bulky disseminated peripheral, abdominal, and thoracic lymph node involvement with B symptoms (i.e., fever, night sweats, and weight loss) and elevated lactate dehydrogenase levels commonly observed; BM involvement can occur, but peripheral blood involvement and cytopenias are rare (Rosand et al. 2018). Although the clinical manifestations vary, chronic activation of the B-cell receptor, which provides proliferation and survival signals, has been implicated in the pathogenesis of B cell lymphoproliferative disorders in general, including MZL (Noy et al. 2017).

The FDA's Assessment:

The FDA agrees with the Applicant's position.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Currently, no standard-of-care treatment exists for first-line or relapsed/refractory MZL, and treatments vary depending on the MZL subtype, clinical manifestations, etiology, lymphoma site of origin, patient's age, and overall health (Denlinger et al. 2018, Lymphoma Research Foundation 2018, Rosand et al. 2018). Accordingly, consensus guidelines (National Comprehensive Cancer Network [NCCN 2020]) offer a variety of options for first-line therapy of MZL with chemoimmunotherapy regimens including bendamustine plus rituximab or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with milder regimens suggested for patients who are elderly or infirm, including rituximab monotherapy. Second-line and subsequent therapeutic options include repeat chemoimmunotherapy, lenalidomide+rituximab, ibrutinib, radioimmunotherapy, phosphoinositide 3-kinase (PI3K) inhibitors, or rituximab monotherapy. The only fully approved therapy for previously treated MZL is REVLIMID® (lenalidomide) in combination with rituximab (R²). Table 1 summarizes the Food and Drug Administration (FDA)-approved treatment options in the MZL relapsed setting.

Table 1: Summary of FDA Approved Treatment Options in the MZL Relapsed Setting

Product Name(s)	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Lenalidomide (REVLIMID®) in combination with a rituximab product	Treatment of adult patients with previously treated MZL in combination with a rituximab product	May 2019/ Full approval	20 mg PO QD on Days 1-21 of repeated 28-day cycles for up to 12 cycles	AUGMENT study: Median PFS: + rituximab= 20.2 months (95% CI: 16.0, NR); vs. + placebo= 25.2 months (95% CI: 11.1, NR); HR=1.00 (95% CI: 0.47, 2.13) ORR: + rituximab= 65% (95% CI:	Embryo-fetal toxicity, hematologic toxicity, venous and arterial thrombo-embolism, Hepato-toxicity, severe cutaneous reactions, TLS, impaired stem cell mobilization, hypersensitivity, second primary

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Product Name(s)	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
				45%, 81%) vs. + placebo=44% (95% CI:36%, 62%) MAGNIFY study: ORR=51% (95% CI: 36, 66)	malignancies, tumor flare, serious and fatal cardiac adverse reactions
Ibrutinib (IMBRUVICA®)	Treatment of adult patients with MZL who require systemic therapy and who have received at least 1 prior anti-CD20-based therapy	January 2017/ Accelerated Approval based on ORR	560 mg PO QD	Based on Phase II, open-label, single arm study: median follow-up=19.4 months , ORR=46.0% (95% CI: 33.4%, 59.1%); CR=3.2%; PR=42.9%	Hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, TLS, embryo-fetal toxicity

Abbreviations: CI, confidence interval; CR, complete response; FDA, Food and Drug Administration; FL, follicular lymphoma; ORR, overall response rate; PO, oral; PR, partial response; QD, once daily; TLS, tumor lysis syndrome.
Source: Leonard et al 2019, Drugs@FDA

Despite the various treatment options available, MZL remains an incurable, life-threatening condition. Limitations of initial therapeutic approaches, such as surgical intervention, radiation therapy, radioimmunotherapy, and chemoimmunotherapy, include surgical complications and development of secondary malignancies. Furthermore, none of these strategies are capable of completely eradicating MZL, which results in relapse and necessitates subsequent lines of therapy. In the relapsed setting, R² is the only full FDA-approved treatment; however, this combination did not improve outcomes and resulted in shorter progression-free survival (PFS) compared to rituximab alone among MZL patients (Thieblemont et al. 2019). Ibrutinib received accelerated approval; however, it failed to generate deep remissions, with only 3% of patients achieving a complete response (CR) (IMBRUVICA® package insert 2019). While there are various interventions in the frontline setting, treatments for relapsed/refractory MZL are largely investigational. This scarcity of treatment options for relapsed/refractory MZL patients represents a high unmet medical need.

The FDA's Assessment:

The FDA disagrees with the Applicant's assertion that lenalidomide in combination with rituximab did not provide an improvement in clinical outcomes for patients with relapsed or refractory MZL. For patients with MZL, the combination of lenalidomide and rituximab was evaluated in the AUGMENT and MAGNIFY trials (Table 1). In AUGMENT, there were 31 patients with MZL who received lenalidomide in combination with rituximab and 32 patients who received rituximab plus placebo. Notably in AUGMENT, patients with rituximab refractory disease were ineligible. For the 31 patients receiving the combination, the ORR was 65% (95% CI: 45%, 81%) with a median duration of response of 17.4 months (95% CI: 13.2, not evaluable). For the 32 patients receiving rituximab plus placebo, the ORR was 44% (95% CI: 26%, 62%) with a median duration of response not reached (95% CI: 8.4, not evaluable). In the MAGNIFY trial, 45 patients with MZL received lenalidomide in combination with rituximab. In MAGNIFY, patients with rituximab refractory disease were eligible and 41% of the 45 patients with MZL had rituximab refractory disease. In the 45 patients, the ORR was 51% (95% CI: 36%, 66%) and the median duration of response was not reached (95% CI: 8, not evaluable) with a median follow-up of 11.5 months. For the combination of lenalidomide and rituximab, the response rates of 51% to 65% with associated durability are supportive of a clinically meaningful benefit in patients with MZL.

For the time-to-event outcomes, such as progression-free survival (PFS), the limited number of patients with MZL in the AUGMENT and MAGNIFY trials preclude any meaningful interpretation of the PFS outcomes and should be considered exploratory and descriptive.

The FDA considers lenalidomide in combination with rituximab available therapy for patients with relapsed or refractory MZL. To support accelerated approval, the data with umbralisib in patients with MZL was required to demonstrate a clinically meaningful therapeutic benefit in the context of available therapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Umbralisib is a new molecular entity and is not currently marketed in any country. New Drug Application (NDA) 213176 is submitted for accelerated approval of single agent umbralisib for the treatment of adult patients with MZL who have received at least 1 prior anti-cluster of differentiation 20 (CD20)-based regimen.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

Date	Event Summary
10 January 2020	Presubmission of Part 1 of 2 of NDA 213176
20 December 2019	FDA Granted Rolling Review of NDA 213176
16 September 2019	Type B meeting – Breakthrough Therapy to discuss the format and content of NDA 213176
10 June 2019	Type B meeting – Breakthrough Therapy meeting to discuss the overall development plan of single agent umbralisib in MZL intended to support consideration for an accelerated approval opportunity
11 April 2019	Orphan Drug Designation granted to umbralisib for treatment of MZL (extranodal #19-6874, nodal #19-6875, and splenic #19-6800)
17 January 2019	Breakthrough Therapy Designation granted for treatment of adult patients with MZL who received at least one prior anti-CD20-based regimen
13 August 2018	Type B meeting – CMC to discuss the CMC umbralisib development program
18 April 2018	Type C meeting– Guidance to discuss the nonclinical and clinical pharmacology program for umbralisib

Date	Event Summary
03 January 2018	Type B meeting – End-of-Phase 1 meeting to discuss the ongoing study UTX-TGR-205 a
23 September 2015	IND (b) (4) was activated and opened in the United States
28 December 2012	IND 116762 was activated and opened in the United States
05 April 2012	IND (b) (4) was activated and opened in the United States

Abbreviations: CMC, Chemistry, Manufacturing, and Controls; FDA, Food and Drug Administration; FL, follicular lymphoma; IND, Investigational New Drug; MZL, marginal zone lymphoma.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

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

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were requested for two clinical sites in the U.S. with the highest accrual for Study UTX-TGR-205, along with inspection of the Applicant, TG Therapeutics. The clinical sites included 1) Site HOB - MD Anderson (Felipe Samaniego, MD; Houston, TX), which enrolled 24 patients and 2) Site CLA - Levine Cancer Institute (Nilanjan Ghosh, MD; Charlotte, NC), which enrolled 19 patients. Based on the clinical site inspections, the study data from the clinical sites were considered reliable. Additionally, the Applicant was inspected concerning its oversight of Study UTX-TGR-205. Based on the inspection, the Applicant's oversight of the clinical trial and the quality of conducting the study were determined to be adequate. The audited study data submitted to the Agency was deemed acceptable in support of the NDA application, in compliance with Good Clinical Practice.

4.2. Product Quality

Umbralisib tosylate is a small chiral BCS class II molecule that is produced as a single enantiomer that is manufactured by Alembic Pharmaceuticals Limited, India, as a single enantiomer in a linear, two-stage synthesis. The drug product is presented as a 200 mg immediate-release tablet for oral administration. It is a green film-coated, oval-shaped tablet,

debossed with “L474” on one side and plain on the other.

The recommended starting dose for the drug product is 800 mg orally, once daily until disease progression or unacceptable toxicity.

Based on the information provided by the Applicant, the Office of Product Quality (OPQ) has determined that the data is adequately supportive and the potential risks to patient safety, product efficacy, and product quality are mitigated appropriately. Therefore, OPQ recommends approval of umbralisib and grants a (b) (4) month retest for the drug substance and a 36-month shelf-life for the drug product when stored in HDPE bottles at 20°C and 25°C (68°F to 77°F).

4.3. **Clinical Microbiology**

The data to support the microbiology assessment were adequate and there were no issues from a microbiology standpoint.

4.4. **Devices and Companion Diagnostic Issues**

Not applicable

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Umbralisib (also known as RP-5264, TGR-1202, (b) (4), and RP-5307) is a small molecule inhibitor of phosphoinositide-3-kinase delta (PI3K δ) and casein kinase 1 epsilon (CK1 ϵ). The targets mediate tumor-progressive signaling in a variety of hematologic malignancies.

Umbralisib binds to human PI3K δ and CK1 ϵ with dissociation constants (K_d) of 6.2 nM and 180 nM, respectively. A screen of 442 kinases incubated with 1 μ M of umbralisib showed that the phosphorylated Abelson murine leukemia viral oncogene homolog 1 containing the mutation F317I (ABL1 (F317I)-phosphorylated) kinase was inhibited at levels comparable to CK1 ϵ . In vitro growth-inhibitory activity was assessed in a panel of 13 human leukemia and lymphoma cell lines. Growth inhibitory (GI₅₀) values ranged from 0.6 to 66 μ M after the cells were treated for 72 or 96 hours with umbralisib. The test article also inhibited cytokine-mediated adhesion and migration in vitro.

The in vivo antitumor activity of umbralisib was evaluated in a MOLT-4 xenograft model. MOLT-4 tumor-bearing mice were dosed orally with umbralisib at 150 mg/kg/day for 25 days, with the measurement of tumor growth continuing until 41 days after dosing initiation. The test article dosing group had tumors growing at a slower rate than the control group tumors.

Safety pharmacology studies assessed the effects of umbralisib on cardiovascular, central nervous system (CNS), and respiratory function. Umbralisib had no toxicologically-significant effects on cardiovascular function in a cardiovascular study in dogs, and had no effects on neurobehavioral function or temperature in mice. Respiratory function was affected by umbralisib with decreases in tidal volume as much as 24%, respiration rate as much as 38%, and minute volume as much as 46% observed in respiratory studies conducted in mice administered a single umbralisib dose of 50 to 500 mg/kg.

The oral bioavailability of umbralisib in mice and dogs were 47% and 34% respectively for the 2 species. A mass balance study in male mice demonstrated that 89% and 5% of umbralisib is excreted in feces and urine, respectively. Umbralisib metabolism was evaluated in vitro with liver microsomes. After 60 minutes of incubation with mouse, dog, and human liver microsomes, 75%, 77%, and 86% respectively of umbralisib remained.

The repeat-dose studies in mice and dogs referenced above were conducted to assess the general toxicity of umbralisib. The drug was administered once daily for 26 weeks in mice and

39 weeks in dogs, with the doses and durations informed by the experience of the 13-week repeat-dose studies in both species. The studies were conducted using the oral route of administration, which is consistent with the intended clinical route of administration. There were several unscheduled deaths in the mouse study, while dose reductions and dosing holidays were applied to the dog study. Drug-related findings included decreased white blood cells (WBCs) and differentials, increased liver weights and alkaline phosphatase (ALP) levels, and lymphoid depletion.

In the 26-week mouse study, umbralisib was administered by oral gavage at 30, 100, and 300 mg/kg/day with 4 weeks of recovery. Umbralisib-induced mortality was observed in the study with half of all observed mortalities and unscheduled euthanasia's occurring in the 300 mg/kg dose group. The exact causes of death in these animals were undetermined. In the surviving animals, toxicities included reduced lymphocyte levels, increased liver weights and ALP levels, and inflammatory findings. In the 39-week dog study, dogs were initially dosed orally with umbralisib at 10, 30, or 100 mg/kg/day, but doses were reduced to 8, 20, and 50 mg/kg/day due to notable weight loss as the study proceeded. The high-dose group (100/50 mg/kg/day) also had a dosing holiday due to continued weight loss. Reduced RBCs, hemoglobin, hematocrit, and reticulocyte levels were observed in all umbralisib-dosed conditions. Microscopic findings were limited to decreased cellularity in the lymph nodes and the thymus. Additional findings of decreased weight and the presence of debris in the lumen, and tubular degeneration and atrophy in the testes were noted in the 13-week repeat-dose study in dogs.

A combined male and female fertility study was conducted in mice with umbralisib administered once daily at doses of 50, 150, or 300 mg/kg/day, starting 28 days prior to pairing and through mating in males and starting 14 days prior to pairing through Gestation Day (GD) 7 in females. Umbralisib-related findings included reduced testis and epididymis weights, and reduced sperm count and motility in the mid- and high-dose groups. Findings in female mice included increased post-implantation loss and increased resorption. Exposure at 150 mg/kg/day is approximately 1.3 times the recommended human clinical dose based on the toxicokinetic (AUC) values.

In an embryo-fetal development study, daily oral administration of umbralisib at 100, 200, or 400 mg/kg/day to pregnant mice on GD 6-15 resulted in increased litter losses, visceral findings and fetal skeletal abnormalities in all dose groups. Malformations noted were increased frequency of cleft palates in the mid- and high-dose groups and low incidence nasopharyngeal fistula (one fetus) at high dose. The 100, 200, and 400 mg/kg groups had exposures that were 0.9, 1.4, and 2.4 times the exposures at the recommended clinical dose based on AUC. In an embryo-fetal development study in female rabbits, daily administration of umbralisib at 30, 100, or 300 mg/kg/day on GD 6-19 resulted in maternal toxicity characterized by a 50% reduction in food intake and an 8% reduction in body weight by the end of the dosing period.

Fetal weights were lower in the high-dose group. Elevated fetal abnormalities were noted in the mid- and high-dose groups compared to the concurrent controls, although the levels were considered within the normal range for this strain of rabbit. The 30, 100, or 300 mg/kg/day doses resulted in exposures that were 0.03, 0.08, and 0.03 times the exposures at the recommended clinical dose based on AUC. There was high inter-animal variability in the toxicokinetic values in this study within each dose group, reduced exposures at high dose, and lack of dose-dependence in exposures observed in rabbits.

Umbralisib was not mutagenic in the in vitro bacterial reverse mutation test or clastogenic in either the in vitro chromosomal aberrations assay or in the in vivo bone marrow micronucleus assay in mice. No carcinogenicity studies have been conducted or are warranted to support the marketing of umbralisib for the current indications.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of umbralisib for the proposed indications.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

The following NDAs and Drug Master Files (DMFs) are referenced in this application:

Investigational New Drug (IND) (b) (4), IND 116762, IND (b) (4), DMF (b) (4), DMF (b) (4), and DMF (b) (4).

5.3. Pharmacology

Primary pharmacology

FDA's Assessment:

In vitro and in vivo pharmacology studies conducted with umbralisib assessed the mechanism of action and the pharmacological activity. The binding affinity for CK1 ϵ and PI3K was determined with a competitive binding assay based on phage display (Study # TGT027-01-S-00001). Umbralisib was incubated with CK1 ϵ and PI3K variants α , β , δ , and γ for an hour at room temperature prior to an assessment of binding affinity (Kd). The resulting Kds were 180 nM for CK1 ϵ and 6.2 for PI3K δ . The Kds for the other PI3K variants were in the μ M range.

Inhibitory activity of umbralisib

Umbralisib Kd (nM)					
Kinase	CK1 ϵ	PI3K α	PI3K β	PI3K δ	PI3K γ
	180	>10000	>10000	6.2	1400

The selectivity of umbralisib was determined by evaluating its binding to a panel of 442 kinases that included PI3K variants and CK1 ϵ (Study # INO006-01-P-00001). Using the same platform that determined the K_d for umbralisib, the test article was incubated with the panel of kinases at 1 μ M for an hour at room temperature prior an assessment of binding inhibition normalized to control conditions. Beyond the intended targets, phosphorylated Abelson murine leukemia viral oncogene homolog 1 containing the mutation F317I (ABL1 (F317I)-phosphorylated) was the only kinase in the panel that was inhibited by the test article at levels beyond the 65% threshold. With an inhibition level of 72%, ABL1 was inhibited at levels comparable to CK1 ϵ , which had an inhibition level of 73% in the same assay.

The in vitro inhibitory effect of umbralisib on malignant cell proliferation was evaluated with a panel of 13 leukemia and lymphoma cell lines (RPMI-8226, U266B1, MM1.S, MM1.R, DLBCL, Toledo, Daudi, Raji, CCRF-CEM, MOLT-4, U937, THP-1, and Jurkat. Study # IVT-5264-LCA-01). Umbralisib was incubated with the cell lines for 72 or 96 hours at 37°C. Growth was determined with a 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and normalized to untreated conditions. Growth inhibitory (GI₅₀) values ranged from 14.9 μ M (Daudi, a Burkitt's lymphoma cell line) to 0.58 μ M (Toledo, a DLBCL/non-Hodgkin's lymphoma cell line).

In vitro proliferation inhibitory activity of umbralisib

Cell line	Disease origin	GI ₅₀ (μ M)
RPMI-8226	Myeloma	65.56
U266B1		0.61
MM1.S		3.16
MM1.R		2.59
DLBCL	DLBCL	3.14
Toledo		0.58
Daudi	Burkitt's lymphoma	14.90
Raji		4.66
CCRF-CEM	ALL	6.15
MOLT-4		1.33

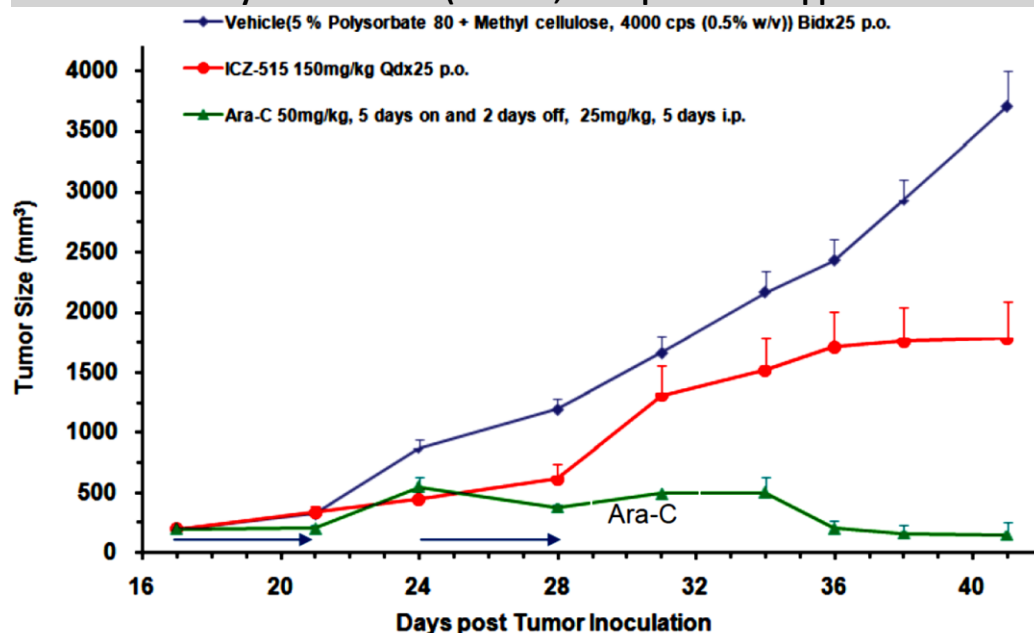
Cell line	Disease origin	GI ₅₀ (μM)
U937	Histiocytic lymphoma	3.64
THP-1	AML	1.94
Jurkat	ALL	1.87

To determine if umbralisib inhibits cell adhesion (Study # VT-5264-VCAD-29), Daudi cells were treated with the test article at 1 μM for an hour prior to a brief plating on VCAM- and CXCL12- or CCL19-coated plates with centrifugation at room temperature. The plates were washed and the remaining cells were fixed and stained prior to plate reading for absorbance at 570 nm. Umbralisib inhibited CXCL12-mediated adhesion by 50% and CCL19-mediated adhesion by 70%.

Umbralisib inhibition of cell migration was also evaluated with Daudi cells (Study # IVT-5264-VC MIG-28). The cells were added to VCAM-coated migration chamber inserts which were then added to chambers containing CXCL12, CXCL13, or CCL19, with umbralisib at 1 μM for 5 hours at room temperature. Cells that migrated to the underside of the migration chamber insert were stained prior to plate reading for absorbance at 570 nm. Umbralisib inhibited CXCL12- and CCL19-mediated migration by 70% and CXCL13-mediated migration by 80%.

Umbralisib's in vivo antitumor activity was evaluated in a Molt-4 xenograft model (Study # Incozen-CP-P006). The Molt-4 cell line was established subcutaneously in female NOD/SCID mice prior to oral dosing with umbralisib at 150 mg/kg for 25 days. Tumors were measured 3 times per week and the mice were weighed weekly. The tumor volumes were determined and normalized to the untreated condition. A group of mice were dosed with Ara-C as a dosing control with known antitumor effects on the model. The animals were euthanized on day 41. Umbralisib-dosed animals had reduced tumor growth rates compared to untreated animals.

Antitumor activity of umbralisib (ICZ-515; excerpted from Applicant's submission)



Secondary Pharmacology

The Applicant's Position:

Umbralisib demonstrated selectivity against a panel of 442 kinases in a KINOMEScan™ competition binding assay. At a fixed concentration of 1 μ M, umbralisib inhibited ligand binding of only 3 kinases at greater than the 65% inhibition cutoff: PI3K δ (100% inhibition), casein kinase 1 epsilon (CK1 ϵ) (73% inhibition), and phosphorylated Abelson murine leukemia viral oncogene homolog 1 (ABL1)(F317I)-phosphorylated (72% inhibition).

The FDA's Assessment:

The FDA agrees with the Applicant that umbralisib at a concentration of 1 μ M inhibited 3 out of 442 kinases at levels greater than 65%. One of the 3 kinases, ABL1(F317I), is not an intended target and was inhibited at levels comparable to CK1 ϵ at the concentration tested.

Safety Pharmacology

The Applicant's Position:

In a cell-based human ether-à-go-go-related gene (hERG) assay, the IC₅₀ for umbralisib was found to exceed 100 μ M (highest tested concentration), a concentration which is beyond the relevant human concentrations of umbralisib in the circulation. In electrocardiogram (ECG) evaluations in dogs, oral doses of umbralisib up to 250 mg/kg (equivalent to 5,000 mg/m² or

9,722 mg in a 70 kg human) did not result in any changes in cardiovascular parameters. In a central nervous system (CNS) evaluation in mice, after a single dose of umbralisib at doses up to 300 mg/kg (equivalent to 900 mg/m² or 1707 mg in a 70 kg human), there were no changes in functional observational battery observations. In mice, after a single dose of umbralisib at doses up to 500 mg/kg (equivalent to 1,500 mg/m² or 2917 mg in a 70 kg human), there were dose-dependent decreases in tidal volume, respiration rate, and minute volume, which were considered minimal and non-adverse.

The FDA's Assessment:

The FDA agrees with the Applicant's summary for safety pharmacology. Additional details regarding the safety pharmacology assessments are provided below.

A. Central Nervous System

CD-1 mice that were part of the 26-week GLP toxicology study were subjected to a CNS functional observation battery (FOB). The animals were dosed with umbralisib daily with 30, 100, or 300 mg/kg. Overall, umbralisib had no significant effects on neurobehavioral function at doses up to 300 mg/kg.

B. Respiratory

In a study evaluating the effects on respiratory function (Study # 037274), CD-1 mice were administered a single oral dose of umbralisib (50, 150, or 500 mg/kg) or vehicle (0.5% methylcellulose and 10% PS80 in water). Respiratory measurements including tidal volume, respiratory rate, and derived minute volume, were taken at 0.25 through 8 hours after dosing. Compared to control conditions, umbralisib caused a 24% decrease in tidal volume at the high dose by the end of the testing period and transient decreases in respiratory rate (lowest of 36% and 38% at 1 hour for the 50 and 150 mg/kg groups, and 24% at 1.75 hours for the 500 mg/kg) and tidal volume at all doses tested (lowest of 11% at 2.25 hours for the 50 mg/kg group, and 15% at 4.25 hours for the 150 mg/kg group). Minute volumes in the umbralisib-treated conditions were at their relative lowest between 1 and 2 hours after dosing, with maximum differences of 43% and 47% for the 50 and 150 mg/kg groups at 1 hour, and 39% for the 500 mg/kg group at 1.75 hours.

C. Cardiovascular

An in vitro hERG channel inhibition study (Study # CYP0358-R10) with hERG-expressing cells incubated with umbralisib at concentrations up to 100 µM showed that the test article had an IC₅₀ greater than the highest dose tested. In vivo cardiovascular assessments were conducted as part of a 13-week repeat dose general toxicology study in dogs. ECG examinations showed that umbralisib at doses 30, 100, or 250 mg/kg did not result in any umbralisib-related effects on CV system parameters.

5.4. ADME/PK

The Applicant's Position:

After a single oral dose, umbralisib absorption was faster in mice, with a time to maximum concentration (T_{max}) of 0.5 hours, compared to 2, 7, and 3 hours in rats, dogs, and monkeys, respectively. The absolute oral bioavailability, ranked from highest to lowest, was >100% in rats, 51.4% in dogs, 46.8% in mice, and 30.3% in monkeys. Following repeat oral administration to mice and dogs, the systemic exposures generally increased in a less-than-dose proportional manner over a dose range of 30 to 750 mg/kg/day in mice and 30 to 500 mg/kg/day in dogs. Little to no drug accumulation occurred in mice or rats, but 2- to 13-fold drug accumulation was apparent in dogs. No consistent sex-related effects were apparent in any animal species tested. Plasma protein binding of umbralisib ranged from 99.7% to 99.8% in animals and humans. In mice, umbralisib was widely distributed, with the highest concentrations in the gastrointestinal, metabolic/excretory, fatty, secretory, and endocrine tissues and the lowest concentration in brain, demonstrating penetration of umbralisib occurred in richly perfused organs, while passage to the CNS was limited. There was no meaningful ocular distribution. Fecal elimination was the primary excretion pathway.

The FDA's Assessment:

The FDA generally agrees with the Applicant's statement. See the review below for additional details regarding the PK studies.

Type of Study	Major Findings
Absorption	
Single dose Bioavailability study of ICZ-515 in Beagle Dogs (DMPK-ICZ-515-PK-04&25)	Beagle dogs were given single oral and IV doses of 1 mg/kg and 30 mg/kg. • Oral bioavailability was 33.52% (different from the levels stated by the Applicant above). • T_{max} was 0.7.0 hours. • $T_{1/2}$ was 37.13 hours.
Pharmacokinetic Study of RP5307 (PTSA salt of RP5264) after Single Oral and Intravenous Administration to Balb/C Mice (DMPK-5307-PK-13)	Male balb/C mice were given single oral and IV doses of 20 and 1 mg/kg, respectively. • Oral bioavailability was >47%. • T_{max} was 0.5 hours. • $T_{1/2}$ was 2.4 hours.
Distribution	

Type of Study	Major Findings					
Mass Balance in Male CD-1 Mice and Tissue Distribution by Quantitative Whole Body Autoradiography in Male C57BL/6 Mice Following a Single Oral Administration of [14C]TGR-1202 (C18008)	Tissue	Mean mouse tissue Concentration (µg/g or µg/mL) of umbralisib Over Time				
		1 hr	2 hrs	24 hrs		
	Plasma	10.7	14.6	2.29		
	Heart	48.0	51.0	2.92		
	Liver	122	144	31.1		
	Spleen	21.6	32.9	1.99		
	Lung	22.0	25.8	1.78		
	Kidney	46.9	76.5	5.63		
	Brain	10.3	19.8	0		
	Stomach	626	372	6.14		
	Small Intestine	1304	699	39.0		
	Testicle	7.55	21.1	1.80		
	Fat	108	182	9.24		
	Muscle	15.4	27.0	1.05		
	Thymus	20.1	29.6	1.57		
	Skin	11.7	16.3	2.61		
Metabolism						
In Vitro Intrinsic clearance of RP5264 in Mouse, Rat, Dog, Monkey and Human Liver Microsomes (DMPK-5264-MS-02)	Time (minutes)	Umbralisib metabolic stability in liver microsomes (%)				
		Mouse	Rat	Dog	Monkey	Human
	0	100	100	100	100	100
	15	96.87	70.14	94.31	98.48	97.95
	30	84.70	57.96	90.10	90.95	95.85
	45	77.36	52.44	82.73	82.41	92.03
	60	74.47	42.67	76.94	76.83	85.83
Excretion						
Mass Balance in Male CD-1 Mice and Tissue Distribution by Quantitative Whole Body Autoradiography in Male C57BL/6 Mice Following a Single Oral Administration of [14C]TGR-1202 (C18008)	[14C]Umbralisib Recovery %					
	Urine	Feces	Cage Rinse/Wash			
	4.21	88.79	0.7			
TK data from general toxicology studies						
A 26-week Study of TGR-1202 by Oral Gavage in Mice with a 28-day Recovery Period (20150163)	Mice:	- Higher exposures in females compared to males - Higher exposures on day 182 compared to day 1				

Type of Study	Major Findings																																																																					
A 39-week Study of TGR-1202 by Oral Capsule in Dogs with a 28-day Recovery Period (20150164)	• T_{max} increases at high dose in males, indicating potential for saturation of absorption at high doses • Less than dose-proportional increases in exposures, particularly at higher doses, also suggesting saturation of absorption																																																																					
	Dogs: • Variable exposures between males and females • T_{max} increases at high doses, indicating potential for saturation of absorption at high doses																																																																					
	<table><tr><th colspan="6">Umbralisib TK Parameters in 26-Week Repeat-Dose Study in Mice</th></tr><tr><th>Dose (mg/kg/d)</th><th>Study Day</th><th>Sex</th><th>C_{max} (ng/mL)</th><th>T_{max} (h)</th><th>AUC_{0-t} (h*ng/mL)</th></tr><tr><td rowspan="4">30</td><td rowspan="2">1</td><td>M</td><td>5170</td><td>1</td><td>29400</td></tr><tr><td>F</td><td>6040</td><td>1</td><td>37700</td></tr><tr><td rowspan="2">182</td><td>M</td><td>8290</td><td>1</td><td>55400</td></tr><tr><td>F</td><td>7520</td><td>1</td><td>67700</td></tr><tr><td rowspan="4">100</td><td rowspan="2">1</td><td>M</td><td>17900</td><td>1</td><td>129000</td></tr><tr><td>F</td><td>19000</td><td>1</td><td>152000</td></tr><tr><td rowspan="2">182</td><td>M</td><td>20600</td><td>1</td><td>140000</td></tr><tr><td>F</td><td>22000</td><td>1</td><td>281000</td></tr><tr><td rowspan="4">300</td><td rowspan="2">1</td><td>M</td><td>20400</td><td>4</td><td>309000</td></tr><tr><td>F</td><td>22000</td><td>1</td><td>332000</td></tr><tr><td rowspan="2">182</td><td>M</td><td>30500</td><td>4</td><td>334000</td></tr><tr><td>F</td><td>41000</td><td>1</td><td>553000</td></tr></table>	Umbralisib TK Parameters in 26-Week Repeat-Dose Study in Mice						Dose (mg/kg/d)	Study Day	Sex	C _{max} (ng/mL)	T _{max} (h)	AUC _{0-t} (h*ng/mL)	30	1	M	5170	1	29400	F	6040	1	37700	182	M	8290	1	55400	F	7520	1	67700	100	1	M	17900	1	129000	F	19000	1	152000	182	M	20600	1	140000	F	22000	1	281000	300	1	M	20400	4	309000	F	22000	1	332000	182	M	30500	4	334000	F	41000	1	553000
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5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Umbralisib was well tolerated after a single dose, with a maximum tolerated dose (MTD) of <1000 mg/kg/day in mice and >2000 mg/kg/day in rats. The tolerability, potential toxicities, target organs, and toxicokinetics of umbralisib were evaluated in repeat-dose toxicity studies up to 26 weeks in mice and 39 weeks in dogs. Umbralisib was generally well tolerated through acute, subchronic, and chronic dosing; test article-related mortality occurred at ≥ 100 mg/kg/day in mice (equivalent to 300 mg/m² or 584 mg in a 70 kg human), and adverse clinical findings necessitating dose reductions occurred at ≥ 10 mg/kg/day in dogs (equivalent to 200 mg/m² or 389 mg/kg in a 70 kg human) when administered chronically.

The liver was identified as the main target organ in mice and the gastrointestinal tract in dogs. Increased liver weights were observed in all studies in mice for the high-dose groups, but these findings did not correlate with increases in liver enzymes, and liver histopathology findings were minimal to mild. Another major finding was damage to the non-glandular stomach mucosa after subchronic and chronic administration, but the clinical relevance of these findings in humans cannot be determined, as humans do not have a non-glandular stomach. Other findings in mice included decreases in leukocytes and lymphocytes and increases in cholesterol that were considered minimal, non-adverse, or related to the pharmacologic action of umbralisib. All findings in mice were reversible upon treatment cessation. None of these findings were observed in dogs upon treatment with umbralisib. In dogs, diarrhea, body weight reductions, and decreased food consumption were noted in all studies and increased in severity and frequency in a dose-dependent manner. Dogs with body weight loss and decreased food consumption were offered canned food to increase appetite and food consumption. Dose holidays and dose reductions were necessitated during chronic administration due to low body condition scores. There were no gross pathology or histopathology findings that correlated to the clinical signs. Clinical pathology showed minor changes in metabolic parameters that were considered secondary to the clinical findings. There were no other adverse findings upon umbralisib treatment in dogs.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment; see additional information provided below for the 26-week and 39-week repeat-dose toxicity studies in mice and dogs, respectively.

Study title/Study number: A 26-week Study of TGR-1202 by Oral Gavage in Mice with a 28-day Recovery Period/20150163

NDA Multi-disciplinary Review and Evaluation NDA 213176
UKONIQ (umbralisib)

Key Study Findings

- There were 20 unscheduled deaths, with all but 1 occurring in the umbralisib-dosed groups and half occurring in the high-dose group. While umbralisib induced mortality occurred in a dose-dependent manner, the deaths were due to undetermined causes.
- Principle hematology findings included reduced lymphocyte levels in mid-dose and high-dose male and female animals.
- Hepatotoxicity: Liver weights, ALP levels, and microscopic signals (minimal necrosis, inflammation, and hypertrophy) were increased in umbralisib-dosed animals.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (control), 30, 100, or 300 mg/kg/day (umbralisib batch # TGR1202/II/A422/10). Administered once daily.

Route of administration: Oral gavage

Formulation/Vehicle: 0.5% (w/v) methylcellulose and 10% (v/v) Tween 80 in deionized water

Species/Strain: CD-1 mice

Number/Sex/Group: Terminal: 20
Recovery: 6

Age: 7 to 8 weeks

Deviation from study protocol affecting interpretation of results: None that affected the overall interpretation of the study findings nor compromised the integrity of the study.

Observations and Results: changes from control

Parameters	Major findings
Mortality	There were 20 unscheduled deaths during the study. Control: One control group female mouse was found dead on day 177. LD: A total of 5 animals died or were euthanized with 3 of the 5 animals dying due to housing-related incidents unrelated to umbralisib. The other 2 were females euthanized on day 72. These animals exhibited ulcerative dermatitis, which was determined as the cause of death. MD: A total of 4 animals died. Two of the 4 animals died due to housing-related incidents unrelated to umbralisib. The other 2 were females found dead on days 50 and 164. These animals had no macroscopic findings and microscopic findings, including inflammatory signals in the liver and lymph nodes, were not considered causal to their deaths by the Applicant's pathologist. HD: 10 animals died prematurely. One animal died due to housing-related incidents unrelated to umbralisib. Two animals, a male and a

NDA Multi-disciplinary Review and Evaluation NDA 213176
UKONIQ (umbralisib)

Parameters	Major findings																																											
	female, exhibited ulcerative dermatitis while another 2 males contracted urogenital infections that resulted in septicemias. Five females found dead on days ranging from 42 to 164 had deaths that could not be ascribed to a specific cause; none had macroscopic observations. Cortical adrenal hyperplasia was the most common organ microscopic signal in these animals.																																											
Clinical Signs	Clinical signals were generally unremarkable. Notable clinical observations <table><tr><th rowspan="3">Observations</th><th colspan="4">Dose (mg/kg/day)</th></tr><tr><th>0</th><th>30</th><th>100</th><th>300</th></tr><tr><th colspan="4">Number of animals affected (M/F)</th></tr><tr><td>Abnormal gait</td><td>0/0</td><td>0/0</td><td>0/0</td><td>2/0</td></tr><tr><td>Hunched posture</td><td>1/1</td><td>1/0</td><td>0/0</td><td>3/0</td></tr><tr><td>Fur staining, yellow</td><td>1/0</td><td>4/0</td><td>4/0</td><td>3/0</td></tr><tr><td>Fur, ungroomed</td><td>1/0</td><td>0/0</td><td>2/1</td><td>3/0</td></tr><tr><td>Decreased activity</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/2</td></tr><tr><td>Cold to touch</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/2</td></tr></table>	Observations	Dose (mg/kg/day)				0	30	100	300	Number of animals affected (M/F)				Abnormal gait	0/0	0/0	0/0	2/0	Hunched posture	1/1	1/0	0/0	3/0	Fur staining, yellow	1/0	4/0	4/0	3/0	Fur, ungroomed	1/0	0/0	2/1	3/0	Decreased activity	0/0	0/0	0/0	0/2	Cold to touch	0/0	0/0	0/0	0/2
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Neurobehavioral Observations	A functional observational battery was conducted on the first dosing day. There were generally no umbralisib-related differences that were outside of the reasonable range for the strain. There was a notably elevated left pinna reflex in all umbralisib-dosed male and female groups.																																											
Body Weights/food consumption	Unremarkable																																											
Ophthalmoscopy	Unremarkable																																											
Respiratory Rate	Unremarkable																																											
Hematology	Hematology changes by the end of the dosing period included significantly lower lymphocyte levels in MD and HD males with notably reduced levels in females at all doses. At the MD and HD, reduced levels were noted in WBC, basophil, leukocyte, hemoglobin, and hematocrit levels. These values reversed by the end of the recovery period.																																											

Hematology values at the end of the dosing period									
Value	Unit (% of control)	Control		30 mg/kg/day		100 mg/kg/day		300 mg/kg/day	
		M	F	M	F	M	F	M	F
White blood cells (WBC)	10 ³ /μL	5.9	6.2	5.6 (-4.6)	4.7 (-24.3)	4.6 (-22.3)	4.4 (-29.4)	4.4 (-24.4)	3.9 (-38.3)
Lymphocytes (LYMPH)		4.3	5.1	4.3 (1.5)	3.7 (-28.6)	2.9 (-32.9)	3.4 (-34.5)	3.1 (-27.8)	2.7 (-47.7)
Eosinophils (EOS)		0.17	0.16	0.13 (-25.6)	0.13 (-18.9)	0.14 (-18.4)	0.07 (-55.6)	0.11 (-34.3)	0.09 (-44.9)
Basophils (BASO)		0.016	0.03	0.018 (9.4)	0.02 (-37.5)	0.011 (-29.7)	0.01 (-58.3)	0.009 (-45.3)	0.02 (-47.6)
Red blood cells (RBC)	10 ⁶ /μL	9.2	9.2	8.9 (-3.0)	8.9 (-2.8)	9.1 (-4.4)	9.0 (-2.2)	8.9 (-3.3)	8.9 (-3.0)

NDA Multi-disciplinary Review and Evaluation NDA 213176
UKONIQ (umbralisib)

Parameters	Major findings																																																													
Clinical Chemistry	In males, increases in ALP, creatinine, cholesterol, and albumin levels were observed in all umbralisib-dosed groups. In females, increases in MD and HD females were observed in urea nitrogen, creatinine, triglycerides, and albumin. These normalized by the end of the recovery period.																																																													
Clinical chemistry parameters at the end of the dosing period																																																														
Value	Unit (% of control)	Control		30 mg/kg/day		100 mg/kg/day		300 mg/kg/day																																																						
		M	F	M	F	M	F	M	F																																																					
Alkaline phosphatase (ALP)	U/L	34.5	67.0	41.3 (19.8)	48.8 (-27.2)	43.5 (26.1)	62.9 (-6.1)	56.0 (62.3)	63.9 (-4.7)																																																					
Urea nitrogen (UREAN)	mg/dL	20.5	15.4	17.7 (-13.8)	14.7 (-4.6)	22.6 (10.2)	16.9 (9.7)	22.3 (8.9)	22.9 (48.4)																																																					
Creatinine (CREAT)	mg/dL	0.11	0.10	0.14 (31.3)	0.10 (0.0)	0.15 (36.4)	0.15 (50.0)	0.19 (71.7)	0.21 (114.3)																																																					
Cholesterol (CHOL)	mg/dL	169	118	202 (19.5)	134 (13.5)	217 (28.2)	136 (15.1)	229 (35.5)	170 (43.9)																																																					
Triglycerides (TRIG)	mg/dL	148	93.1	155 (4.6)	104.6 (12.4)	191 (29.1)	144.7 (55.4)	244 (65.1)	186.7 (100.6)																																																					
Albumin (ALB)	g/dL	2.9	1.6	3.2 (11.9)	1.6 (-2.7)	5.2 (9.7)	1.7 (1.5)	5.2 (9.2)	1.7 (0.5)																																																					
Gross Pathology		Unremarkable																																																												
Organ Weights		Increases (20-51%) in liver weights relative to brain weights were observed in MD and HD males and females. These changes reversed by the end of the recovery period.																																																												
Histopathology		Microscopic findings were noted in the liver and spleen, principally in males where increased liver hypertrophy was noted at all doses. These findings were not observed following the recovery period. Selected liver and spleen parameters at the end of the dosing period <table><tr><th rowspan="3">Observations</th><th colspan="4">Dose (mg/kg/day)</th></tr><tr><th>0</th><th>30</th><th>100</th><th>300</th></tr><tr><th colspan="4">Number of animals affected (M/F)</th></tr><tr><td>Number examined</td><td>20/19</td><td>17/18</td><td>18/18</td><td>17/14</td></tr><tr><td>Liver necrosis: minimal</td><td>1/2</td><td>1/4</td><td>1/1</td><td>6/1</td></tr><tr><td>Liver hypertrophy: Minimal</td><td>0/0</td><td>5/1</td><td>7/1</td><td>9/1</td></tr><tr><td> Mild</td><td>0/0</td><td>4/0</td><td>7/1</td><td>5/0</td></tr><tr><td>Liver inflammation: Minimal</td><td>1/4</td><td>8/9</td><td>7/5</td><td>2/7</td></tr><tr><td>Spleen hematopoiesis: Minimal</td><td>0/0</td><td>0/0</td><td>3/0</td><td>1/0</td></tr><tr><td> Mild</td><td>0/1</td><td>0/0</td><td>1/0</td><td>1/1</td></tr><tr><td> Moderate</td><td>1/0</td><td>0/0</td><td>0/0</td><td>1/0</td></tr></table>								Observations	Dose (mg/kg/day)				0	30	100	300	Number of animals affected (M/F)				Number examined	20/19	17/18	18/18	17/14	Liver necrosis: minimal	1/2	1/4	1/1	6/1	Liver hypertrophy: Minimal	0/0	5/1	7/1	9/1	Mild	0/0	4/0	7/1	5/0	Liver inflammation: Minimal	1/4	8/9	7/5	2/7	Spleen hematopoiesis: Minimal	0/0	0/0	3/0	1/0	Mild	0/1	0/0	1/0	1/1	Moderate	1/0	0/0	0/0	1/0
Observations	Dose (mg/kg/day)																																																													
	0	30	100	300																																																										
	Number of animals affected (M/F)																																																													
Number examined	20/19	17/18	18/18	17/14																																																										
Liver necrosis: minimal	1/2	1/4	1/1	6/1																																																										
Liver hypertrophy: Minimal	0/0	5/1	7/1	9/1																																																										
Mild	0/0	4/0	7/1	5/0																																																										
Liver inflammation: Minimal	1/4	8/9	7/5	2/7																																																										
Spleen hematopoiesis: Minimal	0/0	0/0	3/0	1/0																																																										
Mild	0/1	0/0	1/0	1/1																																																										
Moderate	1/0	0/0	0/0	1/0																																																										
Toxicokinetics		Toxicokinetic parameters for the end of the dosing period																																																												

Parameters	Major findings				
	Dose (mg/kg/day)	C _{max} (ng/mL)		AUC _{0-t} (ng.h/mL)	
		M	F	M	F
	30	8290	7520	55400 (0.39X*)	67700 (0.48X*)
	100	20600	22000	140000 (0.99X*)	281000 (2.0X*)
	300	30500	41000	334000 (2.4X*)	553000 (3.9X*)
*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC ₀₋₂₄ was 141 µg (141000ng)*h/mL)					

LD: low dose; MD: mid dose; HD: high dose

Study title/Study number: A 39-week Study of TGR-1202 by Oral Capsule in Dogs with a 28-day Recovery Period/20150164

Key Study Findings

- Due to weight loss and thin appearance, most notably in the mid- and high-dose animals, all umbralisib-dosed groups had dose modifications. High-dose animals received 2 dose modifications, a dosing holiday, and early euthanization on day 183 (week 26).
- Hematology signals included reduced RBC, hemoglobin, hematocrit, and reticulocytes in all umbralisib-dosed conditions.
- Microscopic findings included decreased cellularity in the lymph nodes and thymus.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (control), 10, 30, or 100 mg/kg/day (umbralisib batch # TGR1202/II/A422/10). Administered once daily. LD, MD, and HD groups were reduced to 8, 20, and 50 mg/kg/day, respectively, on day 127 (week 18). HD recovery group dogs were dosed with 20 mg/kg/day from day 183 (week 26) to day 273 (week 39).

Route of administration: Oral capsule

Formulation/Vehicle: Empty capsule

Species/Strain: Beagle dogs

Number/Sex/Group: Terminal: 4
Recovery: Control: 2; HD: 3

Age: 6 months

Deviation from study protocol affecting interpretation of results:	None that affected the overall interpretation of study findings nor compromised the integrity of the study.

Observations and Results: changes from control

Parameters	Major findings																											
Mortality	HD terminal study animals were euthanized early on day 183 (week 26) due to poor condition (principally thin appearance and liquid feces).																											
Clinical Signs	MD and HD animals were determined to be thin or extremely thin during dosing day 95 (week 13) and were given canned food to encourage weight gain by increased food consumption. Food consumption increased but weight gain remained at lower levels than controls. MD and HD animals also had liquid feces. HD animals were given dosing holidays from day 12 and all dose levels were reduced. Clinical signals reversed by the end of the dosing holiday and recovery period.																											
Body Weights	Described in the clinical signs section. Body weight by day 126 (week 18) <table><tr><th>Condition (mg/kg/day)</th><th colspan="2">Control</th><th colspan="2">10/8</th><th colspan="2">30/20</th><th colspan="2">100/50/20</th></tr><tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr><tr><td>Body weight (Kg)</td><td>9.4</td><td>9.0</td><td>9.1</td><td>8.8</td><td>8.9</td><td>8.0</td><td>8.6</td><td>7.6</td></tr></table>	Condition (mg/kg/day)	Control		10/8		30/20		100/50/20		Sex	M	F	M	F	M	F	M	F	Body weight (Kg)	9.4	9.0	9.1	8.8	8.9	8.0	8.6	7.6
Condition (mg/kg/day)	Control		10/8		30/20		100/50/20																					
Sex	M	F	M	F	M	F	M	F																				
Body weight (Kg)	9.4	9.0	9.1	8.8	8.9	8.0	8.6	7.6																				
Food consumption	Increased in HD groups and unremarkable in the LD and MD groups due to feeding of umbralisib-dosed groups with canned food.																											
Ophthalmoscopy	Unremarkable																											
ECG	Unremarkable																											
Respiratory Rate	Unremarkable																											
Hematology	Hematology changes by week 39 included lower basophil (BASO), RBC, hemoglobin, and hematocrit levels in MD and HD males and HD females. These signals demonstrated reversibility by the end of the recovery period.																											
Hematology values by day 274 (week 39)																												
Value	Unit (% of control)	Control		10/8 mg/kg/day		30/20 mg/kg/day		100/50 mg/kg/day																				
		M	F	M	F	M	F	M	F																			
RBC	10 ⁶ /μL	7.1	6.5	6.2 (-12.8)	6.0 (-7.6)	6.0 (-15.2)	6.0 (-7.2)	6.4 (-8.7)	6.3 (-3.2)																			
HGB	g/dL	15.6	14.9	14.0 (-10.5)	13.5 (-9.5)	13.3 (-14.7)	14.1 (-5.4)	14.5 (-7.2)	13.5 (-9.6)																			
HCT	%	46.5	44.1	41.3 (-11.3)	40.2 (-8.8)	39.7 (-14.6)	41.4 (-6.1)	42.5 (-8.7)	39.7 (-10.1)																			
Clinical Chemistry	Clinical chemistry signals were mild, variable, and reversible. Increased ALT, decreased albumin, and decreased total protein levels were noted in the HD group by the end of the treatment period.																											

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Clinical chemistry parameters by day 274 (week 39)																																												
Value	Unit (% of control)	Control		10 mg/kg/day		30 mg/kg/day		100 mg/kg/day																																				
		M	F	M	F	M	F	M	F																																			
Alanine aminotransferase (ALT)	U/L	33.3	22.0	44.0 (32.0)	22.5 (2.3)	33.0 (-1.0)	26.0 (18.2)	48.0 (44.0)	35.5 (61.4)																																			
Cholesterol (CHOL)	mg/dL	137	188	155 (13.0)	180 (-4.1)	151 (3.6)	183 (-2.7)	130 (-5.1)	198 (5.6)																																			
Total protein (TPROT)	g/dL	5.5	5.3	5.2 (-5.8)	5.1 (-3.6)	4.8 (-11.7)	5.0 (-6.9)	4.8 (-12.2)	4.8 (-9.7)																																			
Triglyceride (TRIG)	mg/dL	27.5	32.7	25.8 (-6.4)	34.5 (5.6)	28.5 (3.6)	32.5 (-0.5)	29.5 (7.3)	32.5 (-0.5)																																			
Albumin (ALB)	g/dL	3.3	3.4	3.1 (-7.3)	3.3 (-1.2)	2.9 (-11.8)	3.2 (-6.4)	2.8 (-15.6)	2.9 (-13.9)																																			
Gross Pathology			Unremarkable																																									
Organ Weights			Dose-dependent decreases in thymus weight (absolute and % of body or brain weight) were noted at the terminal sacrifice. This finding reversed by the end of the recovery period. Thymus weights by terminal euthanasia day (183/274) <table><tr><td>Group (mg/kg)</td><td colspan="2">10/8</td><td colspan="2">30/20</td><td colspan="2">100/50/20</td></tr><tr><td>Weight % of control</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr><tr><td>Absolute</td><td>2.8</td><td>-6.7</td><td>-17.6</td><td>-28.1</td><td>-46.6</td><td>-44.8</td></tr><tr><td>% Body weight</td><td>5.3</td><td>-3.8</td><td>-16.4</td><td>-18.5</td><td>-37.1</td><td>-21.2</td></tr><tr><td>% Brain weight</td><td>3.0</td><td>-8.8</td><td>-24.9</td><td>-29.8</td><td>-45.9</td><td>-47.9</td></tr></table>							Group (mg/kg)	10/8		30/20		100/50/20		Weight % of control	M	F	M	F	M	F	Absolute	2.8	-6.7	-17.6	-28.1	-46.6	-44.8	% Body weight	5.3	-3.8	-16.4	-18.5	-37.1	-21.2	% Brain weight	3.0	-8.8	-24.9	-29.8	-45.9	-47.9
Group (mg/kg)	10/8		30/20		100/50/20																																							
Weight % of control	M	F	M	F	M	F																																						
Absolute	2.8	-6.7	-17.6	-28.1	-46.6	-44.8																																						
% Body weight	5.3	-3.8	-16.4	-18.5	-37.1	-21.2																																						
% Brain weight	3.0	-8.8	-24.9	-29.8	-45.9	-47.9																																						

Histopathology	Decreased cellularity observed in the lymph nodes and thymus was determined to be attributable to the administration of umbralisib . These findings were not observed following the recovery period.				
	Selected microscopic parameters at the end of the dosing period				
	Observations	Dose (mg/kg/day)			
		0	30	100	300
		Number of animals affected (M/F)			
	Number examined	4/4	4/4	4/4	4/4
	GALT decreased cellularity:				
	Minimal	0/0	1/1	3/4	1/0
	Mild	0/0	0/0	0/0	1/1
	Moderate	0/0	0/0	0/0	2/3
	Mandibular lymph node decreased cellularity:				
	Minimal	0/0	1/1	0/3	0/0
	Mild	0/0	1/1	4/1	4/4
	Mesenteric lymph node decreased cellularity:				
	Minimal	0/0	3/1	1/3	1/0
Mild	0/0	0/0	1/1	2/3	
Moderate	0/0	0/0	0/0	0/1	
Thymus decreased cellularity:					
Minimal	1/1	0/1	1/0	0/0	
Mild	1/0	0/0	2/0	1/2	
Moderate	1/0	2/0	0/0	0/1	
Marked	0/0	0/0	0/0	2/0	
Adrenal gland cytoplasmic zona fasciculata vacuolation:					
Minimal	2/3	2/2	1/2	1/0	
Mild	0/0	0/2	0/0	3/3	
Adrenal gland cortex atrophy:					
Moderate	0/0	0/0	0/0	0/1	
Toxicokinetics	Toxicokinetic parameters for day 91 (week 13)				
	Dose (mg/kg/day)	C _{max} (ng/mL)		AUC ₀₋₂₄ (ng.h/mL)	
		M	F	M	F
	10	3530	2500	61500 (0.44X*)	38800 (0.28X*)
	30	8750	8410	185000 (1.3X*)	177000 (1.3X*)
	100	13900	12800	293000 (2.1X*)	280000 (2.0X*)
	*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC ₀₋₂₄ was 141 µg (141000ng)*h/mL)				

LD: low dose; MD: mid dose; HD: high dose

Additional toxicology studies

Below is a summary of the 13 week toxicology study in dogs, titled "TGR-1202: 13-Week Oral Toxicity Study in Dogs with a 30-Day Dose-Free Recovery" (Study 034717):

Beagle dogs (3/sex/group) were administered umbralisib orally at doses of 0, 30, 100, or 250 mg/kg/day for 13 weeks. There were no test article-related mortalities. Treatment with umbralisib resulted in:

- GI toxicities as presented with soft, mucoid, and/or liquid feces, and emesis.
- Hematological changes included reductions in RBC parameters (hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration).
- Notable but reversible changes in clinical chemistry parameters were most evident in the HD group, with reductions in total protein, albumin, globins, electrolytes, cholesterol, and triglycerides. These changes may be the secondary effect of the clinical changes (weight loss, emesis, reduced food intake).
- Lower thymus and spleen weights with microscopic observations of thymic atrophy and lymphoid depletion of lymph nodes
- Lowered weights in the testes and epididymides. MD and HD males displayed testicular changes that included degeneration, multinucleated giant cells, vacuolation, and sloughed cells in the tubular lumen within the seminiferous epithelium.

5.5.2. Genetic Toxicology

The Applicant's Position:

Umbralisib was negative for mutagenic potential in an in vitro Ames assay at concentrations up to 5000 µg/plate and in an in vitro micronucleus assay. In vivo mutagenicity was also assessed in vivo after dosing CD-1 mice with 2 oral gavage doses of umbralisib up to 1000 mg/kg administered once daily. No increases in the scored micronuclei of reticulocytes in treated mice compared to control mice were detected under the study conditions.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Additional details regarding the studies are provided in the review below.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Reverse Mutation Assay/ AF33EJ.502ICH. (b) (4)

Key Study Finding:

- Umbralisib did not increase the number of revertant colonies in tester strains with or without metabolic activation.
- Precipitate was observed at ≥1000 µg per plate and toxicity resulting in a reduction in revertant count was observed at 5000 µg per plate.

GLP compliance: Yes.

Test system: Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537, and Escherichia Coli strain WP2 uvrA in the presence or absence of rat liver S9 extract (at concentrations up to 5000 µg/plate).

Study is valid: Yes.

In Vitro Assays in Mammalian Cells

Study title/number: In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells/AF33EJ.361ICH. (b) (4)

Key Study Finding:

- Umbralisib did not induce chromosome aberrations in TK6 cells with or without metabolic activation.

GLP compliance: Yes.

Test system: The TK6 human lymphocytic cell line +/- S9 activation. Drug concentrations of umbralisib were 15 to 75 µg/mL for 4 hours of incubation in both the S9-activated and non-activated conditions, and 5 to 50 µg/mL for 27 hours of incubation in the non-activated condition.

Study is valid: Yes.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: In Vivo Mammalian Micronucleus Assay in Mice with Flow Cytometric Analysis in Peripheral Blood Reticulocytes/AF33EJ.123M021FLPBICH. (b) (4)

Key Study Finding:

- Umbralisib did not increase the frequency of micronucleated polychromatic erythrocytes in mice after oral administration.

GLP compliance: Yes.

Test system: CD-1 mice were administered 2 oral doses of umbralisib 24 hours apart at doses ranging from 75 mg/kg to 1000 mg/kg. Necropsies were conducted 48 hours after the second dose.

Study is valid: Yes.

5.5.3. Carcinogenicity

The Applicant's Position:

In accordance with the International Council for Harmonisation (ICH) guideline ICH S9 (2009), no carcinogenicity studies have been conducted because umbralisib is intended for use in patients with advanced cancer.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

The potential for umbralisib exposure to impact male and female fertility parameters and pregnancy parameters was evaluated in mice at doses up to 300 mg/kg/day. In male mice, umbralisib administration at 300 mg/kg/day (equivalent to 900 mg/m² or 1707 mg in a 70-kg human) for 4 weeks resulted in reduced testis weights accompanied by reduced sperm count and motility. The magnitude of these changes was small and did not impact overall male reproductive health.

The potential for umbralisib exposure to impact maternal health, pregnancy parameters, and embryonic development was evaluated in embryo-fetal development studies in mice and rabbits. In mice, doses ≥ 200 mg/kg (equivalent to ≥ 600 mg/m² or ≥ 1138 mg in a 70 kg human) administered during the period of organogenesis resulted in no effects on maternal health but impacted pregnancy parameters (resorptions and post-implantation losses) and the developing fetus (increased incidence of cleft palate, nasopharyngeal fistula, and minor skeletal abnormalities). Treatment-related findings included an increase in the number of litters that exhibited 100% resorptions and post implantation resorption; and external (cleft palate), visceral (nasopharyngeal fistula), and skeletal fetal abnormalities. In rabbits, doses of 300 mg/kg (equivalent to 3600 mg/m² or 6774 mg in a 70 kg human) administered during the period of organogenesis resulted in maternal toxicity of reduced body weights and food consumption with no other reported findings on pregnancy and fetal development in rabbits.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment. The FDA's review of the fertility and early embryonic development study in mice and embryo-fetal development studies in mice and rabbits is provided below.

Fertility and Early Embryonic Development

Study title/ number: TGR-1202: Study of Fertility and Early Embryonic Development in the CD-1 Mouse by Oral Gavage Administration/YC15PK

- There were notable reductions in testis and epididymis weights in all umbralisib-dosed groups, reduced sperm counts in the 150 and 300 mg/kg/day groups, and reduced sperm motility in the 300 mg/kg/day group. These reductions were within historic ranges.
- Increased resorption and post-implantation loss were observed in the mid-dose group.
- While the fertility index is comparable to, or is higher than, the values in the concurrent control group, the low number of pregnancies in the concurrent control group makes it difficult to make a conclusion on the fertility index for umbralisib-treated animals
- The doses of 50, 150, and 300 mg/kg/day doses resulted in exposures that were 0.7, 1.3, and 1.9 times the clinical exposure at the recommended dose of 800 mg/day.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes.

Methods

Dose and frequency of dosing:

0, 150, 300 mg/kg/day

Males: From 4 weeks (28 days) prior to mating, through mating until sacrifice.

Females: From 2 weeks (14 days) prior to mating through gestation day (GD) 7. Sacrificed on GD 13.

Route of administration:

Oral gavage.

Formulation/Vehicle:

10 % (v/v) polysorbate 80 in 0.5 % (w/v) methylcellulose (400 cp), in deionized water

Species/Strain:

Mice/CD-1

Number/Sex/Group:

22

Satellite groups:

4 spare animals/sex

Study design:

Mice were paired 1:1 for 14 days or until evidence of mating (presence of a copulatory plug or sperm in the vaginal smear).

Deviation from study protocol

affecting interpretation of results:

No

Observations and Results

Parameters	Major findings
Mortality	Two males, both from the 300 mg/kg/day group, died prior to the scheduled euthanasia day. One mouse was found dead on dosing day 62. This animal had no apparent clinical or macroscopic findings. Another mouse was moribund and euthanized on dosing day 33. This animal had decreased activity, was cold to the

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	touch, had irregular breathing, a distended abdomen, and partially closed eyelids. The animal's body weight had decreased and there were macroscopic findings observed in the GI tract that included distention, gas, and a yellow fluid. The causes of death were undetermined in these animals.																																																																										
Clinical signs	Unremarkable																																																																										
Body weights	Unremarkable																																																																										
Food consumption	Unremarkable																																																																										
Estrous cycle	Unremarkable																																																																										
Organ weights	Umbralisib-related reductions in testicular weight were noted. Significant and dose-dependent absolute right and left testis weight reductions were noted in all umbralisib treatment groups, and reductions in relative right and left testis weights were noted in the 300 mg/kg/day group. There were also notable weight reductions in the right and left epididymis in all umbralisib treatment groups. The historical control data for CD-1 mice from (b) (4) showed that the reductions in testes and epididymis weights were within normal ranges.																																																																										
Necropsy findings	Unremarkable																																																																										
Mating, fertility, and sperm analysis	There were 2 males in each of the 50 mg/kg/day and 150 mg/kg/day groups who did not successfully mate after 14 days of pairing. These were removed from the study pairings and replaced with males from within each group who had successfully mated. Umbralisib-associated changes included reduced sperm motility in the 300 mg/kg/day group and reduced sperm counts in the 150 and 300 mg/kg/day groups. <table><tr><th>Dose (mg/kg/day)</th><th>0</th><th>50</th><th>150</th><th>300</th></tr><tr><td>No evaluated:</td><td></td><td></td><td></td><td></td></tr><tr><td>Male</td><td>22</td><td>20</td><td>20</td><td>22</td></tr><tr><td>Female</td><td>22</td><td>22</td><td>22</td><td>22</td></tr><tr><td>Females confirmed pregnant</td><td>18</td><td>20</td><td>19</td><td>21</td></tr><tr><td>Fertility index (%):</td><td></td><td></td><td></td><td></td></tr><tr><td>Male</td><td>81.8*</td><td>90.0</td><td>85.0</td><td>95.5</td></tr><tr><td>Female</td><td>81.8**</td><td>90.9</td><td>86.4</td><td>95.5</td></tr><tr><td>Mean no of live conceptus</td><td>11.6</td><td>11.9</td><td>12.0</td><td>11.3</td></tr><tr><td>Resorptions (mean %)</td><td>0.4</td><td>0.3</td><td>1.1</td><td>0.3</td></tr><tr><td>Post-implantation loss (%)</td><td>3.5</td><td>2.4</td><td>10.2</td><td>2.9</td></tr><tr><td>Sperm motility (%)</td><td>98.0</td><td>98.3</td><td>98.8</td><td>94.6</td></tr><tr><td>Sperm count (millions/g)</td><td>372.0</td><td>388.8</td><td>352.3</td><td>316.3</td></tr><tr><td>Normal sperm morphology (%)</td><td>60.1</td><td>56.9</td><td>59.3</td><td>57.2</td></tr></table> *Value is below the mean value in the historical control (HC; (b) (4) (b) (4)). HC data shows a mean value of 92.5% (range of 76% to 100%). HC data from (b) (4) is not available. ** Value is below the mean value in the HC ((b) (4) (b) (4)). HC data shows a mean value of 91.3% (range of 76% to 100%)					Dose (mg/kg/day)	0	50	150	300	No evaluated:					Male	22	20	20	22	Female	22	22	22	22	Females confirmed pregnant	18	20	19	21	Fertility index (%):					Male	81.8*	90.0	85.0	95.5	Female	81.8**	90.9	86.4	95.5	Mean no of live conceptus	11.6	11.9	12.0	11.3	Resorptions (mean %)	0.4	0.3	1.1	0.3	Post-implantation loss (%)	3.5	2.4	10.2	2.9	Sperm motility (%)	98.0	98.3	98.8	94.6	Sperm count (millions/g)	372.0	388.8	352.3	316.3	Normal sperm morphology (%)	60.1	56.9	59.3	57.2
Dose (mg/kg/day)	0	50	150	300																																																																							
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Male	22	20	20	22																																																																							
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Toxicokinetics (Day 63)	<table><tr><th>Dose (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th>AUC₀₋₂₄ (ng.h/mL)</th></tr><tr><td>50</td><td>13351.39</td><td>102000 (0.7X*)</td></tr><tr><td>150</td><td>20774.27</td><td>184000 (1.3X*)</td></tr><tr><td>300</td><td>25368.70</td><td>262000 (1.86X*)</td></tr></table>	Dose (mg/kg/day)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng.h/mL)	50	13351.39	102000 (0.7X*)	150	20774.27	184000 (1.3X*)	300	25368.70	262000 (1.86X*)																																																														
Dose (mg/kg/day)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng.h/mL)																																																																									
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*Fold exposure compared to the recommended clinical dose of 800 mg/day
(mean steady-state AUC was 141 µg (141000ng)*h/mL)

Embryo-Fetal Development

Study title/ number: An Embryo Fetal Development Study in Mice via Oral Gavage/GD46XG

Key Study Findings

- Adverse findings were observed at all dose levels but were most evident at mid-dose and high-dose.
- Increased litter losses were observed at all dose levels.
- Increased skeletal abnormalities were noted in all umbralisib-dosed groups.
- Increased cleft palate rates were noted in 200 and 400 mg/kg/day groups.
- The 100, 200, and 400 mg/kg/day groups had exposures that were 0.9, 1.4, and 2.4 times the exposures at the recommended clinical dose of 800 mg/day.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing:

0, 100, 200, or 400 mg/kg/day from GD6 to GD15

Route of administration:

Oral gavage

Formulation/Vehicle:

Polysorbate 80 (PS80, 10% v/v) and methylcellulose (0.5% w/v) in deionized water

Species/Strain:

Mice/Crl:CD-1

Number/Sex/Group:

Main study: 22 females/group

Toxicology study: Control: 6 females/group

Umbralisib: 18 females/group

Satellite groups:

Four mated females were retained for possible replacement.

Study design:

Pregnant mice received umbralisib daily during GD 6 through 15. Euthanization/caesarean section/necropsy were performed on GD17.

Deviation from study protocol affecting interpretation of results:

No

Observations and Results

Parameters	Major findings																																													
Mortality	One HD female was found dead on GD12. Overall, the necropsy was unremarkable which led to the cause of death being undetermined and considered not test article related. The animal was bearing 13 fetuses that were all resorbed.																																													
Clinical Signs	No umbralisib-related clinical signs were noted.																																													
Body Weights (adjusted for uterine weight)	Changes in the body weights were not considered test article-related due to the lack of dose-dependency.																																													
Macroscopic observations	Unremarkable																																													
Necropsy findings Cesarean Section Data	Drug-related findings included non-viable fetuses, total resorptions, and post-implantation losses. <table><tr><th>Dose (mg/kg/day)</th><th>Control</th><th>100</th><th>200</th><th>400</th></tr><tr><th>Number tested</th><th>22</th><th>22</th><th>22</th><th>22</th></tr><tr><td>No of Pregnancy (%)</td><td>14 (63.6*)</td><td>15 (68.2)</td><td>15 (68.2)</td><td>20 (90.9)</td></tr><tr><td>No of pregnant animals with 100% non-viable fetuses</td><td>0</td><td>1</td><td>2</td><td>2</td></tr><tr><td>Mean total resorptions</td><td>1.1</td><td>0.4</td><td>1.8</td><td>2.1</td></tr><tr><td>Mean pre-implantation losses (%)</td><td>5.4</td><td>15.3</td><td>13.7</td><td>5.7</td></tr><tr><td>Mean post-implantation losses (%)</td><td>8.1</td><td>10.2</td><td>17.2</td><td>16.5</td></tr><tr><td>Total live pups/litter</td><td>11.8</td><td>11.7</td><td>10.9</td><td>12.3</td></tr><tr><td colspan="5">* Below the values for the historical control (HC; (b) (4)). HC has a mean value of 91.3% and a range of 76.0% to 100%. HC data from (b) (4) is not available.</td></tr></table>	Dose (mg/kg/day)	Control	100	200	400	Number tested	22	22	22	22	No of Pregnancy (%)	14 (63.6*)	15 (68.2)	15 (68.2)	20 (90.9)	No of pregnant animals with 100% non-viable fetuses	0	1	2	2	Mean total resorptions	1.1	0.4	1.8	2.1	Mean pre-implantation losses (%)	5.4	15.3	13.7	5.7	Mean post-implantation losses (%)	8.1	10.2	17.2	16.5	Total live pups/litter	11.8	11.7	10.9	12.3	* Below the values for the historical control (HC; (b) (4)). HC has a mean value of 91.3% and a range of 76.0% to 100%. HC data from (b) (4) is not available.				
Dose (mg/kg/day)	Control	100	200	400																																										
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* Below the values for the historical control (HC; (b) (4)). HC has a mean value of 91.3% and a range of 76.0% to 100%. HC data from (b) (4) is not available.																																														
Fetal observations	Treatment with umbralisib resulted in malformations. Increased folded retinas and/or skeletal abnormalities were noted in all umbralisib-dosed groups. Increased cleft palate rates were noted in the MD and HD groups. An incident of nasopharyngeal fistula formation was noted in the HD group. <table><tr><th></th><th colspan="4">Incidences (fetuses/litters)</th></tr><tr><th>No examined</th><th>81/14</th><th>81/14</th><th>69/13</th><th>110/18</th></tr><tr><th>Dose (mg/kg)</th><th>Control</th><th>100</th><th>200</th><th>400</th></tr><tr><td>Folded retina</td><td>1/1</td><td>4/2</td><td>0/0</td><td>2/2</td></tr><tr><td>Lung fusions/absent lobes</td><td>0/0</td><td>0/0</td><td>7/3</td><td>1/1</td></tr></table>		Incidences (fetuses/litters)				No examined	81/14	81/14	69/13	110/18	Dose (mg/kg)	Control	100	200	400	Folded retina	1/1	4/2	0/0	2/2	Lung fusions/absent lobes	0/0	0/0	7/3	1/1																				
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NDA Multi-disciplinary Review and Evaluation NDA 213176
UKONIQ (umbralisib)

	Kidney: dilated pelvis	4/3	1/1	8/6	5/5
	Rib and vertebra supernumerary	34/12	58/13	50/13	95/18
	Incomplete sternebrae	4/3	6/5	13/7	20/12
	Incomplete vertebrae	38/13	51/13	44/16	82/19
	Increased ossification	11/3	26/8	15/3	10/6
	Cleft palate	1/1	1/1	3/2	15/6
	Nasopharyngeal fistula	0/0	0/0	0/0	1/1
Toxicokinetics (GD15); mean values	Dose (mg/kg)	C_{max} (ng/mL)		AUC₀₋₂₄ (ng.h/mL)	
	100	10607		129000 (0.9X*)	
	200	14154		194000 (1.4X*)	
	400	361000		339000 (2.4X*)	

LD: low dose; MD: mid dose; HD: high dose

*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC was 141 µg (141000ng)*h/mL)

Study title/ number: An Oral (Gavage) Embryo-Fetal Development Study in Rabbits/TGR-1202

Key Study Findings

- Umbralisib administered at the highest dose of 300 mg/kg/day resulted in maternal toxicity characterized by a 50% reduction in food intake and an 8% reduction in body weight by the end of the dosing period. Both findings reversed by the end of the dosing-free period prior to euthanasia.
- Fetal weights at the high-dose were significantly lower than controls.
- Increased fetal skeletal abnormalities compared to the concurrent controls were noted principally in the 100 mg/kg/day (0.08 time the patient exposure) and 300 mg/kg/day dosing groups. These findings were considered within the common range for the strain of rabbits.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing: 0, 30, 100, or 300 mg/kg/day from GD6 to GD19
Route of administration: Oral gavage
Formulation/Vehicle: 10% (v/v) PS80 and 0.5% methylcellulose (w/v) in purified water.
Species/Strain: Rabbits/NZW
Number/Sex/Group: Main study: 22
Toxicokinetic study: 3

Satellite groups:	Four female mated rabbits were used for possible replacement prior to and including GD6.
Study design:	Pregnant rabbits were given daily oral doses of umbralisib from GD6 through GD19. Euthanization/cesarean section/necropsy was performed on GD29.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

Parameters	Major findings															
Mortality	There were 7 unscheduled deaths. Four HD animals were euthanized, one each on GD 21, 22, 23, and 28. They displayed red vaginal discharge, decreased fecal pellets, perigenital/perianal staining, and inappetence. At necropsy there were no notable macroscopic findings and all animals were pregnant. Their deaths were attributed to umbralisib. Three animals were found dead. A control group female was found dead on GD13 and 2 LD animals were found dead on GD6. All 3 animals presented with lung damage consistent with gavage errors.															
Clinical Signs	MD and HD groups showed decreased defecation.															
Body Weights/food consumption	HD animals had significantly reduced food consumption and body weights compared to the control group. These findings were reversible. <table><tr><th>Dose (mg/kg)</th><th>Control</th><th>30</th><th>100</th><th>300</th></tr><tr><td>Body weight (kg) on GD20 (% change from control)</td><td>3.49</td><td>3.44 (-1%)</td><td>3.50 (0%)</td><td>3.21 (-8%)</td></tr><tr><td>Food consumption (g) on GD18-19 (% change from control)</td><td>157</td><td>149 (-5%)</td><td>149 (-5%)</td><td>81 (-48%)</td></tr></table>	Dose (mg/kg)	Control	30	100	300	Body weight (kg) on GD20 (% change from control)	3.49	3.44 (-1%)	3.50 (0%)	3.21 (-8%)	Food consumption (g) on GD18-19 (% change from control)	157	149 (-5%)	149 (-5%)	81 (-48%)
Dose (mg/kg)	Control	30	100	300												
Body weight (kg) on GD20 (% change from control)	3.49	3.44 (-1%)	3.50 (0%)	3.21 (-8%)												
Food consumption (g) on GD18-19 (% change from control)	157	149 (-5%)	149 (-5%)	81 (-48%)												
Macroscopic observations	Unremarkable															
Necropsy findings Cesarean Section Data	Unremarkable															
Fetal observations	MD and HD fetal weights were notably lower than those in control animals.															

	Dose (mg/kg)	Control	30	100	300
	Fetal weight (g) (% change from control)	41.2	40.5 (-2%)	38.0 (-8%)	37.8 (-8%)
	Fetal abnormalities were noted in all umbralisib-dosed groups.				
		Incidences (fetuses/litters)			
	No examined	171/20	184/21	220/21	157/18
	Dose (mg/kg)	Control	30	100	300
	Lung: Absent lobe	7/4	8/3	18/11	9/6
	Rib: Interrupted ossification	6/5	11/9	11/6	8/6
	Sternebrae: Wide	0/0	0/0	1/1	2/2
	Ossification deficiency: Cranial	0/0	4/3	4/2	8/4
	Ossification deficiency: Appendicular skeleton	10/7	10/5	18/12	52/16
	Increased ossification: Cranial	0/0	0/0	3/1	11/2
Toxicokinetics (GD19); mean values	Dose (mg/kg)	C_{max} (ng/mL)		AUC₀₋₂₄ (ng.h/mL)	
	30	725		4220 (0.03X*)	
	100	1010		10500 (0.08X*)	
	300	406		3780 (0.03X*)	

LD: low dose; MD: mid dose; HD: high dose

*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC was 141 µg (141000ng)*h/mL)

5.5.5. Other Toxicology Studies

The Applicant's Position:

No other toxicology studies have been conducted.

The FDA's Assessment:

The FDA concurs with the Applicant.

X

X

Simon Williams, PhD
Primary Reviewer

Brenda Gehrke, PhD
Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Umbralisib is a small molecule inhibitor of phosphoinositide-3-kinase delta (PI3K δ) and casein kinase 1 epsilon (CK1 ϵ). The Applicant is seeking approval of umbralisib for the treatment of patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. The proposed dosing regimen is 800 mg QD taken orally with food.

The Clinical Pharmacology section of the NDA is supported by single and multiple dose pharmacokinetics (PK) characterization, population PK and exposure-response analyses, QT assessment, human mass balance, relative bioavailability, and in vivo food effect studies, in vitro metabolic and transport studies, and physiologically-based pharmacokinetic (PBPK) modeling.

The clinical pharmacology review focused on the appropriateness of the proposed dosing regimen and dose recommendations for patients with hepatic impairment, and drug-drug interactions.

Recommendations:

The Office of Clinical Pharmacology has reviewed the information submitted in NDA213176 (b) (4). This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized in the table below.

Table 2: Key Clinical Pharmacology Review Issues by FDA

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal study UTX-TGR-205. The proposed dosing regimen is supported by the overall efficacy of umbralisib with an objective response rate (ORR) of 49% (95% CI: 37.0, 61.6) in patients with relapsed or refractory marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimens.
General dosing instructions	The proposed umbralisib dosing regimen of 800 mg given orally with food is acceptable for approval from a clinical pharmacology perspective: Favorable anti-tumor activity: This dosing regimen demonstrated an ORR of 49% in patients with MZL. There was a flat exposure-response relationship for ORR; efficacy data at lower dose levels (< 800 mg QD) were limited.

Review Issue	Recommendations and Comments
	Positive exposure-response relationships for safety: Higher exposure resulted in higher incidence of adverse events, particularly for diarrhea and elevated ALT and AST levels.
Dosing in patient subgroups (intrinsic and extrinsic factors)	- No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin $\leq$ upper limit of normal [ULN] with AST $>$ ULN or total bilirubin >1 to $1.5 \times$ ULN with any AST). There is no data available for patients with moderate or severe hepatic impairment ($>1.5 \times$ ULN and any AST). - No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr 30-89 mL/min). There is no data available for patients with severe renal impairment (CLcr 15-29 mL/min). - Based on PopPK analyses, no dose adjustment is required based on age (18 to 87 years old), sex, race (White and Black), and body weight (44 to 165 kg).
Drug-drug interactions	- No clinically significant differences in umbralisib pharmacokinetics were observed when used concomitantly with omeprazole, a proton pump inhibitor. - The available data do not support the Applicant's claim that co-administration of umbralisib is not expected to significantly impact the PK of P-gp sensitive substrates. - The available data do not support the Applicant's claim that co-administration of umbralisib is not expected to significantly impact the PK of cytochrome (CYP) sensitive substrates. - The available data do not support the Applicant's claim that co-administration of strong CYP3A inhibitors is not expected to significantly impact the PK of umbralisib. - There is no data to evaluate the effect of CYP2C9 modulators on the PK of umbralisib.
Labeling	Overall, the proposed labeling recommendations are acceptable contingent upon the Applicant's agreement with the FDA revisions to the label. Clinical pharmacology labeling recommendations are detailed in Section 2.1, 8.6, 8.7, 12.2, and 12.3.

Postmarketing Requirements and Commitments

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Umbralisib dose in patients with moderate to severe hepatic impairment	Hepatic metabolism plays a major role in the elimination of umbralisib. The recommended dose of umbralisib in patients with moderate and severe hepatic impairment (based on NCI-ODWG criteria) has not been established. The clinical study will determine whether dose adjustment is needed in this specific population.	Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of umbralisib in patients with moderate to severe hepatic impairment (based on NCI criteria).
PMR	The effect of strong CYP3A and moderate CYP2C9 inhibitors on the exposure of umbralisib	CYP3A and CYP2C9 plays a role in the elimination of umbralisib. The recommended dose of umbralisib when used concomitantly with a strong CYP3A or moderate CYP2C9 inhibitor has not been established. The clinical study will determine whether dose adjustment is needed in these patients.	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP3A and CYP2C9 inhibitors on the single dose pharmacokinetics of umbralisib to determine appropriate dosing recommendations.
PMR	The effect of umbralisib on the exposure of CYP and P-gp substrates	In vitro, umbralisib has the potential to inhibit CYP2C8, CYP2C9, CYP2C19, and CYP3A4 and P-gp. However, repeated dosing of umbralisib on the PK of CYP and P-gp sensitive substrates in clinical trials is not fully characterized. The clinical study will evaluate the effect of repeated dosing of umbralisib on these CYP and P-gp sensitive substrates and address the potential for excessive drug toxicity.	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of umbralisib on the single dose pharmacokinetics of sensitive CYP2C8, CYP2C9, CYP2C19, and CYP3A and P-gp substrates to address the potential for excessive drug toxicity.

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	The effect of umbralisib on QT interval	The effect of umbralisib on the QT interval is not fully characterized as umbralisib exposure observed in TGR-1202-102 for QT assessment is 37% lower than the expected maximum therapeutic exposure (C _{max,ss}). Additional ECG data are needed to assess the risk of QTc prolongation with umbralisib.	The QT study can be conducted as a dedicated study or as a sub-study of ongoing trials to characterize QTc prolongation risk with umbralisib at steady-state maximal concentrations.
PMC	The effect of strong CYP3A ^{(b) (4)} inducers on the exposure of umbralisib	CYP3A ^{(b) (4)} plays a role in the elimination of umbralisib. The recommended dose of umbralisib when used concomitantly with a strong CYP3A ^{(b) (4)} inducer has not been established. The clinical study will determine whether dose adjustment is needed in these patients.	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP3A ^{(b) (4)} inducers on the single dose pharmacokinetics of umbralisib to determine appropriate dosing recommendations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of umbralisib has been well characterized. The data in the application to support the use of umbralisib 800 mg once daily (QD) in subjects with MZL comprise in vitro experiments using human biomaterials; clinical pharmacology studies with umbralisib in healthy subjects and subjects with cancer including single and repeat-dosing pharmacokinetic (PK) studies, biopharmaceutic studies (food effect), intrinsic factors (sex), extrinsic factors

(drug-drug interactions [DDIs]); and population PK analyses.

The FDA's Assessment:

The FDA does not agree that the clinical pharmacology of umbralisib has been well characterized. The PK of umbralisib in patients with moderate to severe hepatic impairment, potential drug interactions of umbralisib as a perpetrator of CYP enzymes (CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and P-gp and a victim (CYP3A and CYP2C9 inhibitors and inducers), and the effect of umbralisib on the QT interval are not well characterized. Additional studies are needed (see Postmarketing Requirements and Commitments, Section 13).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

During the course of the development of umbralisib, absorption, distribution, metabolism, excretion, and DDI properties were evaluated. The appropriateness of umbralisib for the MZL indication was evaluated in the exposure-response (E-R) analyses for efficacy and safety across five dose levels: 400, 600, 800, 1000, and 1200 mg. The pooled population pharmacokinetics (PPK)/E-R analyses evaluated biologically inter-dependent endpoints of efficacy and safety. Overall, the dose-response results demonstrate an acceptable balance between benefits and risk at the recommended dose of 800 mg and justify the use of this dose regimen in patients with MZL.

The FDA's Assessment:

The FDA agrees with the Applicant's position that the recommended dosing regimen of 800 mg QD with food for patients with MZL is reasonable based on the flat E-R relationship for efficacy and positive E-R relationships for safety.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors (age, sex, race, body weight), DDIs (use of acid-reducing agent [ARA], concomitant use of strong 3A4 inhibitor, P-glycoprotein [P-gp] substrates), or in special populations of mild hepatic impairment or mild and moderate renal impairment. The impact of umbralisib on moderate and severe hepatic impairment and severe renal impairment has not been investigated.

The FDA's Assessment:

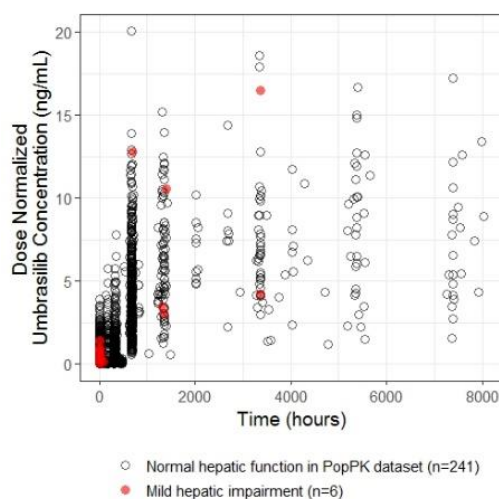
Based on the population PK (PPK) analysis, FDA agrees with the Applicant that no dose adjustment is needed for demographic factors (age, sex, race and body weight) and patients

with mild to moderate renal impairment. However, the FDA does not agree with the Applicant's position regarding the dose recommendations for concomitant use of strong CYP3A4 inhibitors based on the PPK analysis.

In the Applicant's evaluation of the impact of concomitant strong CYP3A4 inhibitors, the frequency and dosing time of the co-administered strong CYP3A4 inhibitors were not available. In addition, in a pooled PK analysis (Study TGR-1202-101 and Study UTX-TGR-205) of 10 patients who were co-administered strong CYP3A4 inhibitors, only 4 patients had intense PK data available, while 6 patients had sparse PK of 1-3 PK samples. Based on the limited PK data and information on the administration time of concomitant strong CYP3A4 inhibitors, the Applicant's current conclusion that no dose adjustment would be needed for concomitant administration of strong CYP3A4 inhibitors is not acceptable.

The FDA agrees with the Applicant that no dose adjustment is needed for patients with mild hepatic impairment. In the Applicant's PPK evaluation of the impact of mild hepatic impairment, PK data were only available for 6 patients with mild hepatic impairment (classified by NCI-ODWG criteria). Out of the 6 patients, 4 patients had only one PK datapoint. The available data were insufficient to use the PPK approach to assess the effect of mild hepatic impairment on the PK of umbralisib; however, the observed dose-normalized umbralisib concentrations from patients with mild hepatic impairment were within the range of those from patients with normal hepatic function (Figure 1), supporting no dose adjustment in patients with mild hepatic impairment. There are no data for patients with moderate or severe hepatic impairment.

Figure 1: Comparison of umbralisib observed concentrations between patients with normal hepatic function and mild hepatic impairment



Source: Reviewer's analysis

6.2.2.3. Outstanding Issues

The Applicant's Position:

None

The FDA's Assessment:

The FDA disagrees with the Applicant's position that there are no outstanding issues. The PK characterization of umbralisib in patients with hepatic impairment, potential drug interactions of umbralisib as a perpetrator of CYP enzymes (CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and P-gp and a victim (CYP3A and CYP2C9 inhibitors and inducers), and the effect of umbralisib on the QT interval are not well characterized. Refer to the Postmarketing Requirements and Commitments, Section 13.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Based on comprehensive clinical pharmacology evaluations of umbralisib, the following characteristics of umbralisib were observed.

Absorption and Pharmacokinetics:

- From Study TGR-1202-101, the observed median T_{max} at 800 mg was 2.1 and 3.9 hours on Days 1 and 29 of dosing, respectively.
- Linear PK was observed over a dose range of 200 to 1000 mg by non-compartmental analysis and 200 to 1800 mg by PPK analysis, although the number of subjects at 1800 mg was limited (n=2).
- Following repeat dosing at 800 mg, the observed accumulation ratio for area under the plasma/serum concentration-time curve (AUC) and maximum concentration (C_{max}) were 5.2- and 2.8-fold, respectively; the PPK model-estimated median steady state accumulation ratio for AUC was 6.4-fold (95% confidence interval [CI]: 3.7, 10.9). Ninety percent of the AUC at steady state was achieved after 35.5 doses (95% CI: 20, 70) of 800 mg QD.
- The PPK model-estimated relative oral bioavailability of drug product (DP)

containing (b) (4) drug substance (DS) was 193% compared to DP containing (b) (4) DS.

Distribution:

- The geometric mean (percentage coefficient of variation [CV%]) apparent volume of distribution at steady state in healthy subjects was 1900 L/h (38%). This value is approximately 30 times greater than the volume of total body water in humans (Davies and Morris 1993), suggesting wide tissue distribution of umbralisib. This observation is expected for a Biopharmaceutics Classification System Class 2 compound, such as umbralisib.
- Umbralisib plasma protein binding was high in humans at concentrations of 2 (99.7%) and 5 (99.8%) $\mu\text{mol/L}$. The PPK model-estimated C_{max} at steady state and minimum plasma concentration at steady state ($C_{\text{min,ss}}$) were 11 and 8 $\mu\text{mol/L}$ (6.3 and 4.7 $\mu\text{g/mL}$), respectively.

Elimination:

Metabolism:

- In plasma, umbralisib was minimally metabolized. In a radiolabeled mass balance study, unchanged umbralisib was the predominant radioactive component found in plasma (79.2% of total radioactivity area under the plasma concentration-time curve from time zero to 48 hours post-dose [AUC_{0-48}]) with 2 minor metabolites identified. Each plasma metabolite represented <5% of total radioactive AUC_{0-48} .
- The proposed metabolites were formed by O-de-alkylation, mono-oxidation, methylation, oxidative defluorination, hydrogenation, glucuronidation, or combinations thereof.

Excretion:

- Hepatobiliary elimination was the major excretion pathway for umbralisib, with fecal excretion accounting for 81% and urine excretion accounting for 3% of the total radioactive dose administered orally.
- In Study TGR-1202-904, the geometric mean (CV%) umbralisib apparent clearance was 8.72 (31%) L, with an apparent terminal phase half-life of 151 (33%) hours.

The FDA's Assessment:

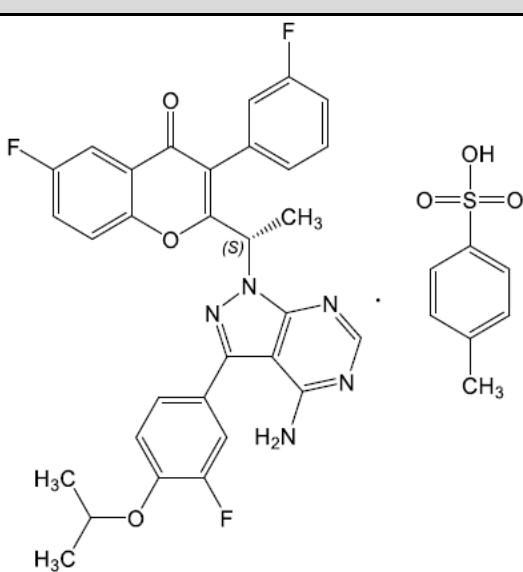
The FDA generally agrees with the Applicant's assessment on general pharmacology and pharmacokinetic characteristics of umbralisib.

The FDA disagrees with the Applicant's position that umbralisib is minimally metabolized. Based on data from the human mass balance study (TGR-1202-902), the majority of radioactivities in feces and urine were observed to be metabolites. Thus, umbralisib is mainly eliminated through metabolic pathways.

Differences in PK exposure was observed between healthy subjects and patients. Based on the PPK analysis, healthy subjects (n = 24) appeared to have 30% lower relative bioavailability (F) in Study 1102 compared to subjects with hematological malignancies in Study 101 (n=83). Central volume of distribution (Vc/F) in healthy subjects (n=24) appeared to be 79.5% lower than those in patients (n = 223) with hematological malignancies. The impact of food effect and formulations (b) (4) on relative bioavailability was taken into account in the PPK analysis and could not fully explain the exposure difference observed between Study 101 and Study 205. The rationale for the difference is currently unknown.

The general overview of umbralisib ADME and clinical PK information as assessed by FDA are presented in the table below.

Table 3: Highlights of Clinical Pharmacology for umbralisib

Physiochemical properties			
Chemical structure and molecular weight	 Chemical Structure of umbralisib (Source: NDA213176, Module 3.2.S.1.2. Figure 1) Molecular weight of umbralisib tosylate: 743.75 g/mol (571.56 g/mol salt form) Log P: 4.84 Log D: 4.79 at pH 7.4 Umbralisib is a weak base with pKa of 2.71 and exhibits pH dependent solubility characteristics (Table 4). Table 4: Aqueous Solubility of umbralisib tosylate at 25°C. <table border="1"> <tr> <td>Solubility - Aqueous (25°C)</td><td> 0.032 mg/ml @ pH 1.2 0.018 mg/ml @ pH 2.2 0.002 mg/ml @ pH 4.5 0.003 mg/ml @ pH 7.4 0.003 mg/ml @ pH 10.2 </td></tr> </table> (Source: NDA213176, Module 3.2.S.1.3. General Properties, Table 1)	Solubility - Aqueous (25°C)	0.032 mg/ml @ pH 1.2 0.018 mg/ml @ pH 2.2 0.002 mg/ml @ pH 4.5 0.003 mg/ml @ pH 7.4 0.003 mg/ml @ pH 10.2
Solubility - Aqueous (25°C)	0.032 mg/ml @ pH 1.2 0.018 mg/ml @ pH 2.2 0.002 mg/ml @ pH 4.5 0.003 mg/ml @ pH 7.4 0.003 mg/ml @ pH 10.2		

Pharmacology	
Mechanism of Action	Umbralisib is a small molecule inhibitor of phosphoinositide-3-kinase delta (PI3K δ) and casein kinase 1 epsilon (CK1 ϵ). The mechanism of action (MOA) involves competitive binding of umbralisib to PI3K δ and CK1 ϵ , inhibiting cell proliferation and inducing apoptosis of lymphoma and leukemic cell lines and primary tumor cells.
Active Moieties	Umbralisib was observed to be the major active species in plasma (79.2%).
QT/QTc Prolongation	Umbralisib exhibits no large mean increases in the QTc interval (i.e., >20 msec). However, the effect of umbralisib on the QT interval is not fully characterized as umbralisib exposure observed in TGR-1202-102 for QTc assessment is 37% lower than that reported by the PPK model. The effect of food and formulation differences in clinical trials and bioanalytical assays were not considered factors for this PK differences.
General Information	
Bioanalysis	Two validated PK assays were used to measure umbralisib concentrations in human plasma (MET126) and serum (MET193). A cross-validation study of plasma and serum (MET126 Addendum 1) indicated 12.5% bias between the methods, which is not a significant factor. The majority of PK data were obtained from plasma PK samples (91.6%). A summary of the method validation reports is included in Appendix 19.4.1.
Healthy Volunteers vs. Patients	Based on population PK analysis, F and Vc/F in healthy subjects were 30% and 79.5% lower when compared to those in patients with hematological malignancies. The reason for this difference is currently unknown.
Drug exposure at steady state following the therapeutic dosing regimen	In adult patients with hematological malignancies who received umbralisib 800 mg QD with food, geometric steady-state (CV%) C _{max} and AUC _{tau} of umbralisib were 7.3 (39%) μ g/mL and 141 (46%) μ g*h/mL, respectively, based on the PPK model. Noncompartmental pooled PK analysis was not conducted as there were a limited number of patients (n=3) with intense PK sampling available in Phase 1 portion of Study TGR-1202-101.
Minimal effective dose or exposure	Not determined.

Maximal tolerated dose or exposure	In Study TGR-1202-101, the MTD of umbralisib as a single-agent treatment in patients with hematological malignancies was not reached at doses up to 1800 mg due to PK saturation in absorption.
Dose Proportionality	Umbralisib (b) (4) appears to show dose-proportionality for both C_{max} and AUC in the dose range of 200 to 1000 mg following a single dose and at steady state.
Accumulation	The median accumulation ratios (R_{acc}) following umbralisib 800 mg QD with food was approximately 6.4-fold for AUC_{tau} and 3.8-fold for C_{max} based on PPK analysis.
Variability	Based on PPK analysis, the inter-subject variability (CV%) of apparent clearance (CL/F) and central volume of distribution (V_c/F) were 51.9% and 185%, respectively.
Absorption	
Bioavailability	Absolute bioavailability study was not conducted.
T_{max}	The median time to reach peak plasma concentration (T_{max}) of umbralisib following 800 mg QD with food was about 3.9 hours.

Relative Bioavailability	Study TGR-1202-PK102 was an open-label, randomized, 2-way crossover study in 26 healthy subjects to evaluate the PK of umbralisib with (b) (4) tablets. The results showed that the exposure of umbralisib was increased 60% and 2.2-fold for AUC and C_{max}, respectively, following a single dose of 200 mg (b) (4) tablet and a single dose of 200 mg (b) (4) tablet in healthy subjects under fasting condition (Table 5).		
(b) (4)	Table 5: Statistical analysis (test/reference) of umbralisib PK parameters between (b) (4) (reference) and (b) (4) (test) tablets		
	AUC_{0-inf} (GMR, 90% CI)	C_{max} (GMR, 90% CI)	T_{max} (hours) (range)
	1.60 (1.47-1.76)	2.24 (2.02-2.47)	(b) (4) 3.0 (2.0-6.0) (b) (4) 3.0 (2.0-4.0)

Food effect (Fed/fasted)	There were two studies (TGR-1202-PK101 and TGR-1202-908) evaluating the effect of food on the PK of umbralisib with two different formulations (b) (4).		
	Study TGR-1202-PK101 was an open-label, single-dose, randomized, crossover study to determine whether high-fat, high calorie food has an effect on the PK of umbralisib in 24 healthy subjects who received a single dose of 200 mg (b) (4) tablet. Results showed that the exposure of umbralisib was increased 67% and 2.7-fold for AUC and C _{max} , respectively, with food following a single dose of 200 mg (b) (4) tablet in healthy subjects (Table 6).		
	Table 6: Statistical analysis (test/reference) of umbralisib PK parameters (umbralisib (b) (4) tablets) under fasted (reference) and fed (test) condition		
	AUC _{0-inf} (GMR, 90% CI)	C _{max} (GMR, 90% CI)	T _{max} (hours) (range)
	1.67 (1.42-1.98)	2.73 (1.77-4.83)	Fasted 3.0 (2.0-4.0) Fed 4.0 (2.0-8.0)
	Study TGR-1202-908 was an open-label, single-dose, randomized, crossover study to determine whether high-fat, high calorie food (approximately 917 calories with 171 calories from protein, 232 calories from carbohydrate, and 502 calories from fat) has an effect on the PK of umbralisib in 24 healthy subjects who received a single dose of 200 mg (b) (4) tablet. Results showed that the exposure of umbralisib was increased 40% and 2.2-fold for AUC and C _{max} , respectively, with food following a single dose of 200 mg (b) (4) tablet in healthy subjects (Table 7).		
	Table 7: Statistical analysis (test/reference) of umbralisib PK parameters (umbralisib (b) (4) tablets) under fasted (reference) and fed (test) condition		
	AUC _{0-inf} (GMR, 90% CI)	C _{max} (GMR, 90% CI)	T _{max} (hours) (range)
	1.40 (1.21-1.62)	2.15 (1.84-2.51)	Fasted 3.0 (1.5-6.0) Fed 4.0 (3.0-5.0)

Proton Pump Inhibitor (PPI) effect (omeprazole)	Study TGR-1202-904 was an open-label, single-dose, crossover study to determine whether repeated doses of omeprazole (40 mg QD for 4 consecutive days), a proton pump inhibitor (PPI), has an effect on the PK of umbralisib in 18 healthy subjects who received a single dose of 800 mg (b) (4) tablet under fed conditions. Results showed that there was no clinically meaningful PK changes on the exposure of umbralisib, following a single dose of 800 mg (b) (4) tablet in healthy subjects with food (Table 8).		
	Table 8: Statistical analysis (test/reference) of umbralisib PK parameters (umbralisib (b) (4) tablets) with (test) and without PPI (reference)		
	AUC _{0-inf} (GMR, 90% CI)	C _{max} (GMR, 90% CI)	T _{max} (hours) (range)
	1.20 (1.10-1.31)	0.92 (0.83-1.01)	Fast 4.0 (2.0-6.0) Fed 4.0 (2.0-6.0)
Distribution			
Volume of distribution	Based on the PPK analysis, the geometric mean apparent volume of distribution of the central compartment (V _c /F) of umbralisib was estimated to be 312 L in patients with hematological malignancies.		
Plasma protein binding	In vitro, protein binding of umbralisib was 99.7-99.8%.		
Blood to plasma ratio	The mean blood-to-plasma ratio was 0.61-0.64 for umbralisib.		
Elimination			
Half-life	Following a single 800 mg dose in healthy subjects, the mean apparent elimination half-life (t _{1/2}) of umbralisib was approximately 110 hours based on noncompartmental analysis. In patients with hematological malignancies who received 800 mg QD, the geometric mean effective t _{1/2} of umbralisib was approximately 91 hours (42% CV) based on PPK analysis.		

Clearance	Based on the PPK analysis, the geometric mean apparent clearance of umbralisib was estimated to be 15.5 L/h in patients with hematological malignancies.
Metabolism	
Primary metabolic pathway(s)	In vitro, umbralisib appears to be metabolized by CYP3A4 and CYP2C9 and to a lesser extent CYP1A2. The metabolic assay [low incubation time (1 hr) of umbralisib with human recombinant P450 enzymes] was not adequate to determine the exact enzyme contribution due to low hepatic extraction of umbralisib.
Inhibitor/Inducer	In vitro, • Umbralisib inhibits CYP2C8 (IC₅₀ value of 10.6 µmol/L), CYP2C9 (IC₅₀ value of 3.4 µmol/L), CYP2C19 (IC₅₀ value of 13.5 µmol/L), and CYP3A4 (IC₅₀ value of 3.9 to 4.6 µmol/L), but does not inhibit CYP1A2, CYP2B6, and CYP2D6. • Umbralisib induces CYP3A4. • Umbralisib is not a substrate to P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K. • Umbralisib inhibits P-gp (IC₅₀ value of 0.0653 µmol/L).
Excretion	
Primary excretion pathways (% dose) ±SD	In the human mass balance Study TGR-1202-902 with mean total radioactivity recovery of 57.0-86.8% over 600 hours period, the mean radioactivity recovery in feces and urine in 6 healthy subjects were 81.0% (16.9% unchanged umbralisib) and 3.2%, respectively.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes, at 800 mg QD, a 61% objective response rate (ORR) was observed among subjects with MZL for whom PK data was available for E-R analysis, and 59% of subjects with MZL achieved >50% decrease in target lesion dimensions. The E-R model predicted ORR rate was 56.9 (90% CI: 43.2, 69.8) at 800 mg. The model predicted percent change from baseline (%CfB) (90% CI) in target lesion dimensions was -52.3% (-60.1, -44.3). There were no significant (p>0.05) exposure-efficacy relationships for ORR, duration of response (DOR), PFS, time to response (TTR), and %CfB in subjects with MZL. The PPK model-predicted C_{min,ss} (bound and unbound

umbralisib) after 800 mg QD was at least 7-fold higher than the concentration achieving 90% of maximal inhibition of PI3K δ inhibition for the MZL population.

The FDA's Assessment:

The FDA agrees with the Applicant's position that flat exposure-response relationships for efficacy were observed for ORR, DOR, PFS, TTR and %CfB of target lesion dimensions in patients with MZL.

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

The Applicant's Position:

Yes, the proposed dose of 800 mg QD is effective and generally well tolerated with no dosing difference observed in PK for age, sex, race, body weight, use of ARA, concomitant use of strong 3A4 inhibitor, mild hepatic impairment, or mild and moderate renal impairment.

During umbralisib development, 800 mg under fed conditions was implemented as the clinical dose for Phase II and later studies. The appropriateness of umbralisib for the MZL indication was evaluated in the PK-efficacy relationships across several dose/exposure levels, including the clinical dose of 800 mg. This assessment used the final population PK model for all efficacy and safety endpoints. The integrated view of absorption, distribution, metabolism, excretion, and DDI properties of umbralisib and the dose-exposure-response relationships showed consistent trends that support the proposed clinical dose of 800 mg for patients with MZL.

Exposure-response analysis indicated no positive exposure-response relationship between average steady-state concentration and adverse events of special interest (AESIs), with the exception of diarrhea (any grade) and elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) (any grade and Grade ≥ 3). Exposure-corrected QT interval (QTc) analyses indicated no cardiac safety-related risk at the recommended umbralisib dose of 800 mg or at a supratherapeutic dose of 1200 mg. Other additional covariate analyses supported no dose adjustment for subjects with hepatic or renal impairment.

The FDA's Assessment:

The FDA agrees with the Applicant's proposed dosing regimen for the general patient population. However, the FDA disagrees with the Applicant's position that there is no risk of QTc prolongation with umbralisib. The Applicant's exposure-corrected QT interval (QTc) analyses were conducted using steady state exposure ($C_{max,ss}$) data in Study TGR-1202-102. The geometric mean C_{max} on Cycle 2 Day 1 was 4012 ng/mL (n=20), which was lower than the therapeutic exposure (7266 ng/mL) obtained from PPK analysis. The 1200 mg QD dose group in Study TGR-1202-102 did not provide higher exposure (4172 ng/mL) as compared to the 800 mg QD dose group. Thus, the Applicant's QT assessment was not adequate to extrapolate the risk of QTc prolongation to the higher exposure range. The FDA agrees that there were no large

mean increases (i.e., 20 msec) with umbralisib treatment.

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

The Applicant's Position:

No. Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in special populations.

Specific Populations: No clinically significant differences in the PK of umbralisib were observed based on age (<65 or ≥65 years old), sex, race (White or non-White), body weight (<78.5 or ≥78.5 kg), or mild and moderate renal impairment (estimated glomerular filtration rate [eGFR] 60 to <90 or 30 to <60 mL/min, respectively, estimated by Modification of Diet in Renal Disease equation). The effect of severe renal impairment (eGFR <30 mL/min) and dialysis on umbralisib PK is unknown.

Hepatic Impairment: Umbralisib is minimally metabolized in the liver. No significant difference in the PK of umbralisib was observed in patients with mild hepatic impairment (total bilirubin >1 to 1.5 × upper limit of normal and any AST/ALT, by National Cancer Institute - Organ Dysfunction Working Group criteria). The effect of moderate and severe hepatic impairment on umbralisib PK is unknown.

The FDA's Assessment:

The FDA agrees with the Applicant that no dose adjustment is required based on age (18 to 87 years old), sex, race [83.8% (n=207) White and 5.7% (n=14) Black], body weight (44 to 165 kg) or mild to moderate renal impairment (CLcr 30 to 89 mL/min, estimated by the Cockcroft-Gault equation). In the Applicant's PPK evaluation of the impact of mild hepatic impairment, only 6 patients with mild hepatic impairment were included. Of the 6 patients, 4 patients had only 1 available PK sample for analysis. The available data were insufficient to use the PPK approach to assess the effect of mild hepatic impairment on the PK of umbralisib; however, the observed dose-normalized umbralisib concentrations from patients with mild hepatic impairment were within the range of those with normal hepatic function (Figure 1), supporting no adjustment in patients with mild hepatic impairment.

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

The Applicant's Position:

The clinically relevant food-drug interactions and DDIs with concomitant medications are described in further detail below with their respective recommendation for management.

Food: Umbralisib is recommended to be taken with food as administration of a single dose with a high-fat meal in healthy subjects increased AUC and C_{max} of umbralisib by 61% and 115%, respectively, relative to fasting condition.

Effect of Other Drugs on Umbralisib:

ARAs: Repeat dosing of omeprazole, an ARA, had no apparent impact on the exposure of a single dose of umbralisib. The area under the plasma/serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-t}) and area under the plasma concentration-time curve from time zero to infinity (AUC_{0-inf}) were both increased by 20% and the C_{max} decreased by 8% in the coadministration group, relative to the umbralisib alone group.

Cytochrome P450 (CYP)3A4 Inhibitors or Inducers: PPK analysis revealed that concomitant use of CYP3A4 inhibitors with umbralisib did not impact the PK of umbralisib. Use of strong CYP3A4 inducers (n=9) on the PK of umbralisib is unknown.

Transporter Systems: Umbralisib was not a substrate of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transport protein (OATP)1B1, OATP1B3, multidrug and toxic compound extrusion transporter (MATE)1, MATE2 K, P-gp, and breast cancer resistance protein. Thus, no impact on the PK of umbralisib is expected with concomitant use of these transporter substrates.

Effect of Umbralisib on Other Drugs:

P-gp Substrates: Umbralisib increased the absorption rate of fexofenadine (a sensitive P-gp substrate) producing a 42% higher C_{max} and a 1 hour decrease of T_{max} in the coadministration group relative to the fexofenadine alone group. However, the overall extent of fexofenadine exposure was unaffected, with the AUC_{0-t} and AUC_{0-inf} increased by 9% to 10%, respectively, in the coadministration group relative to the fexofenadine alone group. Therefore, co-administration of umbralisib is not expected to significantly impact the PK of P-gp substrates.

CYP3A4 Substrates: Simultaneous simulation using a physiologically-based PK (PBPK) model suggested umbralisib was a weak (≥ 1.25 - to ≤ 2 -fold changes in C_{max} and AUC ratios, respectively) inhibitor. Specifically, multiple doses of umbralisib increased AUC and C_{max} of single dose midazolam 1.56- and 1.52-fold, respectively. These simulated exposure increases of midazolam suggested that umbralisib did not induce CYP3A4.

CYP2C8, CYP2C9 and CYP2C19 Substrates: Simulation using PBPK modeling suggested that multiple doses of umbralisib did not impact the exposures of single doses of repaglinide (CYP2C8 substrate), tolbutamide (CYP2C9 substrate), or S-mephenytoin (CYP2C19 substrate). Specifically, the predicted C_{max} and AUC ratios with and without simulated coadministration of the probe substrate for each CYP isozyme were < 1.25 -fold under simulated steady state conditions of umbralisib.

The FDA's Assessment:

The FDA agrees with the Applicant that umbralisib should be taken with food.

Effect of omeprazole on PK of umbralisib:

The FDA agrees with the Applicant that no dose adjustment is required for the use of omeprazole.

Effect of umbralisib on PK of P-gp substrates:

The FDA disagrees with the Applicant's position that co-administration of umbralisib is not expected to significantly impact the PK of P-gp substrates. In Study TGR-1202-901, the study design is only sufficient to examine the effect of intestinal P-gp inhibition as only a single oral dose of umbralisib (800 mg with food) and fexofenadine (180 mg) were administered to healthy subjects. However, in vitro data suggest that umbralisib inhibits P-gp with an IC_{50} value of 0.064 $\mu\text{mol/L}$. Umbralisib has a high accumulation ratio (6.4-fold), a long half-life (effective half-life of 91 hours), and a small fluctuation between C_{max} and C_{min} (0.008 to 0.011 $\mu\text{mol/mL}$) at steady state. Under a worst case scenario when steady state of umbralisib is reached, there is a high potential that systemic inhibition of P-gp (liver and kidney) may affect the PK of P-gp sensitive substrates. Thus, the current data do not support the claim that umbralisib does not affect the PK of P-gp sensitive substrates.

Effect of strong CYP3A inhibitors on PK of umbralisib:

The FDA disagrees with Applicant's position that co-administration of strong CYP3A inhibitors is not expected to significantly impact the PK of umbralisib. In the Applicant's evaluation of the impact of concomitant strong CYP3A4 inhibitors, the frequency and dosing time of the co-administered strong CYP3A4 inhibitors were not available. In addition, of the 10 patients who were co-administered strong CYP3A4 inhibitors, only 4 patients had intense PK, while 6 patients only had sparse PK data of 1-3 PK samples. Based on the limited PK data and information on the administration time of concomitant strong CYP3A4 inhibitors, the Applicant's current conclusion that no dose adjustment would be needed for concomitant administration of strong CYP3A4 inhibitors is not acceptable.

Effect of umbralisib on PK of CYP substrates:

The FDA disagrees with Applicant's position that co-administration of umbralisib is not expected to significantly impact CYP substrates. The effect of umbralisib on CYP3A, CYP2C8, CYP2C9 and CYP2C19 substrates could not be confidently predicted using the PBPK modeling approach due to uncertainties about the in vitro to in vivo extrapolation. The potential of drug-drug interactions of umbralisib with substrates of these enzymes cannot be ruled out.

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and safety are summarized in Table 9.

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Table 9: Listing of Clinical Trials Relevant to this NDA

Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
UTX-TGR-205/ Phase IIb/ NCT02793583	Open-label, randomized Phase IIb study of single agent umbralisib and in combination with ublituximab with or without bendamustine in subjects with previously treated iNHL, MCL, or DLBCL	FL and SLL cohorts: <u>Stage 1:</u> Single agent umbralisib <u>Stage 2:</u> Arm A: U2 Arm B: single agent umbralisib Arm D: single agent ublituximab MZL cohort: <u>Stage 1:</u> Single agent umbralisib <u>Stage 2:</u> U2 MCL cohort: <u>Stage 1:</u> Single agent umbralisib <u>Stage 2:</u> U2 DLBCL cohort: <u>Stage 1:</u> Arm A: U2 Arm B: umbralisib Following futility analysis: <u>Stage 2:</u> Arm A: U2 Arm C: U2+bendamustine	Primary efficacy: ORR based on the IRC and Investigator assessments Secondary efficacy: CR, PFS, DOR and TTR Safety endpoints: TEAEs, laboratory parameters, vital signs, ECOG performance status	Median duration of exposure = 9.43 months (range: 0.2 to 23.0 months) for subjects with MZL. Median time of follow- up for all subjects with MZL from study treatment to data cutoff: 20.3 months (range: 15.0 to 28.7 months) Median duration of exposure = 7.33 months (range: 1.0 to 22.5 months) for subjects with FL. Median time of follow- up for all subjects with FL from study treatment to data cutoff: 20.1 months (range: 13.5 to 29.6 months).	Umbralisib: Total: 275 MZL: 69 FL: 131 MCL: 23 DLBCL: 30 SLL: 22 U2: Total: 147 MZL: 17 FL: 41 MCL: 23 DLBCL: 66	Subjects with previously treated NHL with histological subtypes: FL (Grades 1, 2, and 3A), SLL, MZL, MCL, or DLBCL	US (82) Poland (10) UK (6) South Korea (5) Spain (5) Italy (4) Israel (4) Australia (3) Slovakia (1)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
		<u>Ublituximab:</u> 900 mg on Days 1, 8, and 15 of Cycle 1, then on Day 1 of Cycles 2 through 6, and thereafter on Day 1 every 3 cycles from Cycle 9 through Cycle 24; IV <u>Umbralisib:</u> 800 mg QD with food during all cycles in the study, starting on Day 1 of Cycle 1; PO <u>Bendamustine:</u> 90 mg/m² on Days 1 and 2 of Cycles 1 through 6; IV					
TGR-1202-101 (HEMREF 31)/ Phase I/ NCT01767766	First-in-human, open-label, Phase I study of umbralisib administered as a single agent in subjects with relapsed or refractory hematologic malignancies	<u>Umbralisib</u> (b) (4): 50 mg QD increased to 100, 200, 400, 800, 1200, and 1800 mg QD until the MTD was identified; PO <u>Umbralisib</u> (b) (4): 200 mg QD with food increased to 400, 800, 1200, and 1800 mg QD with food until the MTD was identified; PO Dose expansion phase: <u>Umbralisib</u> 800, 1000, and 1200 mg QD with food; PO	Primary safety: MTD and PK Primary efficacy: ORR (PR, CR, or CR with incomplete marrow recovery [Cri] for CLL per Hallek definition) Secondary efficacy: DCR, DOR Exploratory: PD biomarker assessment	Overall mean (median) duration of exposure - 10.3 (4.4) months Mean exposure: CLL: 15.4 months DLBCL: 6.0 months FL: 14.1 months HL: 3.6 months MZL: 15.2 months Other: 4.6 months	Total: 90 CLL: 25 DLBCL: 16 FL: 19 HL: 11 MZL: 5 Other: 14	Subjects with histologically confirmed HL, B-cell NHL, PTCL, CLL, SLL, or other B-cell lymphoproliferative disorders whose disease had relapsed after, or was refractory to, at least 1 previous treatment regimen	US (7)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
TGR-1202-102 (REFMAL404)/ Phase I/ NCT02574663	Open-label, Phase I study of umbralisib administered as a single agent and in combination either with nab-paclitaxel plus gemcitabine, with FOLFOX (±bevacizumab) , or nivolumab in subjects with solid tumor malignancies	<u>Umbralisib</u> : 800 and 1200 mg QD; PO <u>Umbralisib+nab-paclitaxel+ gemcitabine (Cohort 1)</u> : Umbralisib (800 mg QD; PO) +nab-paclitaxel (125 mg/m ² Days 1, 8, and 15 of each cycle; IV) +gemcitabine (1000 mg/m ² Days 1, 8, and 15 of each cycle; IV) <u>Umbralisib+FOLFOX+ bevacizumab (Cohort C)</u> : Umbralisib (800 mg QD; PO) +FOLFOX (Days 1 and 15 of each cycle; IV) +bevacizumab (5 mg/kg prior to FOLFOX Days 1 and 15 of each cycle; IV) <u>Umbralisib+nivolumab (Cohort N)</u> : Umbralisib (800 mg QD; PO) +nivolumab (240 mg every 2 weeks; IV)	Primary safety : TEAEs, laboratory parameters, vital signs, ECGs, ECOG performance status Primary efficacy : ORR, DOR, and PFS Exploratory : PK parameters	Median duration of exposure to umbralisib monotherapy = 1.6 months (range: 0 to 9.5 months) Median duration of exposure to umbralisib/ other agents: umbralisib+ nab-paclitaxel+ gemcitabine = 2.8/3.0 months Umbralisib+FOLFOX+ bevacizumab = 2.0/2.5 months Umbralisib+nivolumab = 3.4/2.2 months	Total: 66 Single agent umbralisib: 32 Umbralisib in combination with other agents: 34	Subjects with histologically or cytologically confirmed solid tumor that was locally advanced, recurrent, or metastatic, for which curative resection was not currently possible and for which systemic treatment with one of the selected anticancer agents was a reasonable therapeutic option	US (5)
UTX-TGR-501/ Ongoing Safety and Efficacy Long-term Extension/ NCT03207256	Open-label, long-term safety and efficacy extension study for subjects who completed treatment in	<u>Umbralisib</u> : Parent Studies TGR-1202- 101 and UTX-TGR-103: 200, 400, 600, 800, or 1200 mg with food QD ; PO Parent Studies TGR-1202- 102 and TGR-GA-106: 200, 400, 600, or 800 mg with food QD; PO	Safety endpoints : TEAEs, laboratory parameters Efficacy endpoints : PFS and DOR	Of the 7 subjects who rolled over from Study TGR-1202-101, mean duration of exposure to umbralisib in this study = 11.7 months (range: 0.9 to 20.1 months) as of the cutoff date.	Total: 10 TGR-1202- 101: 7 TGR-1202- 102: 0 UTX-TGR-	Subjects must have completed at least 6 cycles of therapy on their current parent protocol and have at least stable disease at the time of entry	US (5)

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UKONIQ (umbralisib)

Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
	parent studies TGR-1202-101 (single agent umbralisib), TGR-1202-102 (single agent umbralisib), TGR-GA-106 (on single agent umbralisib and have completed or discontinued obinutuzumab and chlorambucil therapy), or UTX-TGR-103 (on umbralisib and/or ublituximab only and have completed or discontinued concomitant ibrutinib or bendamustine therapy)	<u>Ublituximab</u> : Study UTX-TGR-103: 900 mg at the next planned dose, >12 weeks from the immediate prior dose in the previous study, then every 12 weeks; IV		Of the 3 subjects who rolled over from Study UTX-TGR-103, mean duration of exposure to umbralisib in this study = 10.9 months (range: 2.5 to 19.7 months) as of the cutoff date.	103: 3 TGR-GA- 106: 0		
TGR-1202-202/ Phase II/ NCT03364231	Open-label, Phase II study of single agent umbralisib in subjects with non-follicular	Umbralisib 800 mg with food QD; PO	Primary efficacy: ORR (CR+PR+VGPR+MR) and DOR Secondary: PFS, time to treatment failure,	Mean duration of exposure = 8.0 months for subjects with MZL and 4.5 months for subjects with WM.	Total: 18 MZL: 8 WM: 10	Subjects with non- follicular iNHL (MZL and WM) who either relapsed or were refractory	US (4)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
	iNHL that is relapsed or refractory following at least 1 prior standard therapy regimen		safety (TEAEs)			following at least 1 prior regimen of standard therapy.	
UTX-TGR-103/ Phase I/Ib/ NCT02006485	Open-label, Phase I/Ib study of U2, U2+ibrutinib, and U2+bendamustine in subjects with B-cell malignancies	Dose escalation in the 2 disease groups (NHL or CLL/SLL) was carried out separately. U2: 3-6 subjects were enrolled in each cohort (Cohorts 1, 2, 3, 3a, 4, 7, and 9) of each disease group U2+ibrutinib: Once a dose level in the U2 cohort was determined safe, the triplet cohort was initiated (Cohorts 5, 5a, 6, and 8) U2+bendamustine: 2 dose cohorts were planned with the triplet combination (Cohorts 11 and 11a), with 3-6 subjects per cohort. Only subjects with DLBCL or FL were included. Following confirmation of MTD in either NHL or CLL/SLL groups, additional subjects were enrolled	Efficacy endpoints: Lymphoma response (CR, PR, or stable disease) and disease progression according to the Revised Response Criteria for Malignant Lymphoma for NHL subjects and the International Workshop on Chronic Lymphocytic Leukemia Working Guidelines for CLL/SLL subjects. Safety endpoints: TEAEs, laboratory parameters, vital signs	Median duration of exposure to umbralisib = 3.0 months (17.3 months for subjects with MZL, 6.4 months for subjects with FL, and 1.7 months for subjects with DLBCL). Median duration of exposure to ublituximab = 2.5 months (10.3 months for subjects with MZL, 5.0 months for subjects with FL, and 1.1 months for subjects with DLBCL).	U2: Total: 46 MZL: 5 FL: 14 MCL: 2 DLBCL: 25	The NHL cohort included subject's refractory to or relapsed after at least 1 prior treatment regimen. The CLL/SLL cohort included subjects previously untreated or with relapsed or refractory disease. The U2+bendamustine cohorts were restricted to subjects with DLBCL or FL refractory to or relapsed after at least 1 prior	US (6)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
		(Cohorts 7E, 9E, and 10E) <u>Ublituximab:</u> Protocol Version 4.1 or earlier: 600 or 900 mg IV infusion on Days 1, 8, and 15 of Cycles 1 and 2, then on Day 1 of Cycles 4, 6, 9, and 12, and every 3 to 6 months thereafter based on Investigator's discretion <u>Protocol Version 5.0 or later:</u> 600 or 900 mg IV infusion on Days 1, 8, and 15 of Cycle 1, then on Day 1 of Cycles 2 to 6, 9, and 12, and every 3 to 6 months thereafter based on Investigator's discretion <u>Umbralisib</u> (b) (4): 800 or 1200 mg QD; PO <u>Umbralisib</u> (b) (4): 400, 600 (NHL only), 800, or 1200 mg QD with food; PO <u>Ibrutinib:</u> 420 mg (CLL) or 560 mg (NHL) QD; PO <u>Bendamustine:</u> 90 mg/m² on Days 1 and 2 of Cycles 1-6; IV				treatment.	

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Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; DCR, disease control rate; DLBCL, diffuse large B-cell lymphoma; DLT, dose-limiting toxicity; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; HL, Hodgkin lymphoma; iNHL, indolent NHL; IRC, Independent Review Committee; IV, intravenous; MCL, mantle cell lymphoma; MR, minor response; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NCT, National Clinical Trial; NHL, non-Hodgkin lymphoma; No., number; ORR, overall response rate; PFS, progression-free survival; PD, progressive disease; P-gp, P-glycoprotein; PI3K, phosphoinositide 3-kinase; PK, pharmacokinetic(s); PO, oral; PR, partial response; PTCL, peripheral T-cell lymphoma; QD, once daily; SLL, small lymphocytic lymphoma; TEAE, treatment-emergent adverse event; TTR, time to response; U2, ublituximab+umbralisib; UK, United Kingdom; US, United States; VGPR, very good partial response; WM, Waldenstrom's macroglobulinemia.

The FDA's Assessment:

The clinical review of efficacy was primarily based on an analysis of the single-arm cohort of study UTX-TGR-205, an open-label, multi-center, multi-cohort trial (NCT02793583) that included 69 patients with relapsed or refractory MZL.

The review of safety is primarily based on the pooled data from 371 patients with hematologic malignancies in three single-arm, open-label trials (Study TGR-1202-101, TGR-1202-202, and UTX-TGR-205) and one open-label extension trial (Study UTX-TGR-501). Of note, data from UTX-TGR-103, described in the table above, was not included in the NDA submission.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 13.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.8 (Enterprise Performance and Lifecycle System Design).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy of umbralisib in subjects with MZL was evaluated in a Phase I study, TGR-1202-101, and 2 Phase II single-arm studies, UTX-TGR-205 and TGR-1202-202. The pivotal study to characterize the efficacy of umbralisib in MZL is the ongoing Phase IIb Study UTX-TGR-205; efficacy data of subjects with MZL are summarized as of the cutoff date of 30 November 2019. Efficacy data from Study TGR-1202-101 and Study TGR-1202-202 are used as supportive information.

8.1.1. Study UTX-TGR-205

Trial Design

The Applicant's Description:

Basic Study Design

Study UTX-TGR-205 is an ongoing, Phase IIb, randomized study to evaluate the efficacy and safety of single agent umbralisib and umbralisib in combination with ublituximab with or without bendamustine in subjects with previously treated iNHL, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL). Subjects were enrolled into 1 of 4 cohorts (MZL, follicular lymphoma [FL] and small lymphocytic lymphoma [SLL], MCL, or DLBCL) based on tumor type.

Trial Location

This study is being conducted at 83 sites in the US and 38 sites outside of the US (10 sites in Poland, 6 sites in the United Kingdom, 5 sites each in Spain and South Korea, 4 sites each in Israel and Italy, 3 sites in Australia, and 1 site in Slovakia).

Choice of Control Group

On the basis of the disease types and settings being studied, an open-label Phase II design without an active controlled standard of care arm was selected.

Diagnostic Criteria

Subjects were enrolled with histologically confirmed diagnosis of B-cell NHL with histological subtype MZL (splenic, nodal, or extranodal) based on criteria established by

the World Health Organization 2008 classification of tumors of hematopoietic and lymphoid tissues.

Key Inclusion/Exclusion Criteria

Male or female subjects ≥ 18 years of age with MZL were required to have prior treatment with 1 or more lines of therapy, including at least 1 anti-CD20-based regimen (either as monotherapy or chemoimmunotherapy). Additional requirements included documented failure to achieve at least partial response (PR) or documented progressive disease (PD) after the most recent systemic treatment regimen and must have documented evidence for requiring treatment (1 or more of the following: bulky disease [>5 cm], high lactate dehydrogenase level, B symptoms, threatened organ function, splenomegaly, cytopenias due to lymphoma, or effusions).

Subjects with MZL also had to have measurable disease, defined as at least 1 measurable disease lesion >1.5 cm in at least 1 diameter by computed tomography (CT), positron emission tomography (PET)-CT, or magnetic resonance imaging (MRI) in an area of no prior radiation therapy, or in an area that was previously irradiated that has documented progression.

Subjects were excluded if they were receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery, and/or tumor embolization) or any investigational drug within 21 days of Day 1 of Cycle 1 or had prior exposure to drugs that specifically inhibit PI3K.

Dose Selection

Based on the results from a Phase I dose-escalation study of umbralisib (TGR-1202-101) and 2 Phase I PK studies in healthy volunteers (TGR-1202-PK101 and TGR 1202-PK102), a dose of 800 mg QD of umbralisib under fed condition was selected.

Study Treatments

Umbralisib 800 mg QD was taken orally with food during all cycles in the study. Umbralisib was to be continued daily until disease progression, unacceptable toxicity, or withdrawal from the study for other reasons.

Assignment to Study Treatment

In Stage 1, eligible MZL subjects received single agent umbralisib.

Blinding

This was an open-label study.

Dose Modification

For adverse events (AEs) suspected to be related to umbralisib, management guidance and dose delays and/or modifications were provided in the protocol. Supportive care was to be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If a subject experienced a treatment-related AE requiring dose modification during the course of therapy, then study drug administration was to be held, as necessary, until the AE resolves or stabilizes to an acceptable degree.

Administrative Structure

The best clinical response as well as disease progression was determined by an Independent Central Radiology Group, also referred to as an Independent Review Committee (IRC).

An independent Data Safety Monitoring Board was established to advise the Sponsor on safety for subjects enrolled in the study. Given that this was an open-label, non-comparator Phase II trial, the Sponsor evaluated preliminary efficacy and safety data periodically to guide continued development of ublituximab and umbralisib.

Procedures and Schedule

During the study period, all subjects were evaluated for response by CT, PET-CT, and/or MRI at the end of Cycle 3 and then within 14 days prior to Day 1 of Cycles 6, 9, and 12. After Cycle 12, response assessments occurred every 6 cycles or more frequently. Subjects remained on study drug until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to Investigator decision or other reasons. Subjects who discontinued from study drug for reasons other than disease progression were followed for progression.

Treatment Compliance

Study drug compliance was reviewed with the subject at the beginning of each new treatment cycle and as needed.

Subject Completion

Subjects continued on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to Investigator

decision or other reasons. Subjects who discontinued from study treatment (either for toxicity or physician choice) and have not progressed were followed for progression.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Study Endpoints

The Applicant's Description:

The study endpoints ORR and PFS are all accepted and well-recognized for oncology trials. The primary efficacy outcome, ORR, was defined as the percentage of subjects who achieved CR or PR, according to the Revised Criteria for Malignant Lymphoma (Cheson 2007). The primary analysis for ORR was based on the IRC assessments.

The FDA's Assessment:

The FDA agrees with the Applicant's position and has the following comment. In the absence of a control arm and due to the open-label single arm design of the trial, it is difficult to interpret and is unlikely to provide evidence to support the time-to-event endpoints, PFS and OS. The major limitation is that the measurements in isolation are out of context and comparing them to historical controls is prone to biases. The durability of the ORR will be assessed by using the duration of response.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Statistical Analysis Plan (SAP) was agreed upon and finalized prior to the conduct of any efficacy analysis.

Analysis Populations

The intent-to-treat (ITT) Population included all subjects who were enrolled in the MZL cohort (Stage 1) and who received at least 1 dose of single agent umbralisib. The ITT Population was used for the efficacy analyses of ORR, DOR, PFS, CR, and TTR. To be included in the ITT population, an MZL subject must have:

- been enrolled in the MZL cohort Stage 1 (last enrollment 31 Aug 2019) to receive single agent umbralisib, and indicated as MZL at Screening
- received at least 1 dose of study drug
- had 1 or more prior lines of systemic therapy including an anti-CD20 regimen.

The Per Protocol (PP) Population included all ITT subjects without major protocol

deviations related to efficacy parameters and who had at least 1 post-baseline response assessment.

Interim Analysis

This was an interim analysis based on Amendment 7, Version 5.1 of the study protocol as of the data cutoff date of 30 November 2019. Results from the following analyses were presented in the interim clinical study report (CSR):

- Efficacy assessments of single agent umbralisib in MZL cohort (Stage 1)
- Safety assessments for single agent umbralisib and by disease type, if appropriate

Efficacy Analysis

The primary efficacy outcome was ORR defined as the percent of subjects who achieved CR or PR, according to the Revised Criteria for Malignant Lymphoma (Cheson 2007). The primary analysis for ORR was conducted in the ITT population based on the IRC assessments. The estimated response rate and the exact 2-sided 95% CI (Clopper-Pearson method) were presented. Waterfall plots of maximum percentage decrease in sum of the products of longest diameters (SPD) by IRC assessment was presented, also showing MZL subtypes. Additionally, the Investigator assessments were summarized in supportive analyses, and agreement in best overall response between IRC and Investigator assessments was also summarized.

Subject follow-up time (months) was calculated as follows: (date of efficacy data cutoff - date of first dosing +1)/30.4375.

The DOR was defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause. The DOR was calculated based on subjects who achieved a response. For subjects who responded but never progressed in the study, the DOR was censored at the time of last tumor assessment using the same censoring algorithm as for PFS. The DOR was summarized by Kaplan-Meier method.

The TTR was defined as the interval from enrollment to the first documentation of CR or PR. The Kaplan-Meier estimate for TTR was presented for the ITT population only in subjects who achieved CR or PR.

PFS was defined as the time from the date of enrollment until the date of first documentation of definitive disease progression or date of death from any cause, whichever occurred first. The median duration of PFS and the proportion of subjects who were progression-free at 6, 12, and 18 months were estimated using the Kaplan-

Meier method. For each estimate, a 95% CI was reported. Additional sensitivity analyses were also performed for PFS.

Efficacy endpoints were examined for subgroups of the ITT population. The same methodology as for the primary analysis of ORR, PFS, CR, and DOR was used. Forest plots were produced for ORR.

Safety Analysis

Study treatment exposure was summarized for the ITT and Safety populations. The number and percentage of subjects with treatment-emergent adverse events (TEAEs), Grade ≥ 3 TEAEs, drug-related (to umbralisib and to ublituximab) TEAEs, drug-related Grade ≥ 3 TEAEs, serious TEAEs, Grade ≥ 3 serious TEAEs, drug-related serious TEAEs, TEAEs resulting in discontinuation of study treatment (umbralisib or ublituximab), and TEAEs with fatal outcome were summarized by tumor type, system organ class (SOC), and preferred term (PT). The number and percentage of subjects with AESIs was also summarized by AESI category and PT. Laboratory data for hematology and serum chemistry tests, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status were also summarized with shift tables from baseline.

Planned Subgroup Analyses

Analyses using following subgroups were performed for efficacy endpoints ORR, CR, PFS, and DOR:

- Gender
- Age group (<65, ≥ 65 years)
- Race (Caucasian, Non-Caucasian)
- Geographical region (US, Non-US)
- Baseline ECOG Performance status score (0, ≥ 1)
- MZL disease subcategory (Splenic, Nodal, Extranodal)
- Relapse or refractory to last therapy (Relapse, Refractory)
- Bulky disease (>5 cm)
- Splenomegaly
- Number of prior lines of therapy (<2, ≥ 2 for subjects)
- Previously treated with a Bruton's tyrosine kinase (BTK) inhibitor (Yes, No)

- Previously treated with lenalidomide (Yes, No)
- Previously treated with lenalidomide in combination with anti-CD20 antibody (Yes, No)
- Previously treated with lenalidomide in combination with rituximab (Yes, No)
- Previously treated with Alkylating agent (Yes, No)

Changes to the Planned Analyses

The following changes to the planned subgroup analyses were revised from Version 1.0 of the SAP:

- Previously treated with a BTK inhibitor (Yes, No) for subjects with MZL
- Previously treated with alkylating agent (Yes, No) for subjects with MZL
- Previously treated with lenalidomide in combination with rituximab (Yes, No) was added as a new subgroup.

The FDA's Assessment:

The FDA agrees, in general, with the Applicant's position and has the following comments.

According to the SAP, the planned sample size was 60 patients. When using a test having one-sided 2.5% false positive error rate to assess the null hypothesis that the IRC-reviewed ORR is 25%, the trial would have 90% power (respectively, 97.5% power) against the alternative hypothesis that ORR is 45% (respectively, 49%). Using a confidence interval of the ORR derived using the Clopper-Pearson exact method, an estimated ORR of 38% (i.e., 23 subjects responding of 60 MZL subjects evaluated) would achieve a 1-sided 97.5% lower bound of 25.0%.

Although there were no planned interim analysis, updated efficacy data was submitted on 9/15/2020 during the review of this application. The updated efficacy results will be presented in the FDA's assessment section.

Protocol Amendments

The Applicant's Description:

The study protocol was amended 7 times during the study. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. Important modifications/amendments to the study protocol included the following:

- Amendment 3 (Version 2.0, 12 April 2017 and Version 2.0 UK 12 April 2017):
 - Live virus vaccines were prohibited within 4 weeks prior to enrollment, during therapy, or for 6 weeks post-treatment.
- Amendment 4 (Version 3.0, 01 October 2017):
 - Inclusion criterion was modified to require subjects with FL or SLL to be relapsed or refractory after ≥ 2 prior lines of therapy, and all subjects must have received an anti-CD20 monoclonal antibody and an alkylating agent.
 - Inclusion criterion was modified to require creatinine clearance ≥ 30 mL/min for subjects with FL, SLL, or MZL and ≥ 40 mL/min for subjects with DLBCL.
 - Exclusion criterion was modified to allow use of concomitant medications known to cause QT prolongation or torsades de pointes with caution and at the Investigator's discretion.
 - The FL/SLL cohort was modified to include a Stage 1 to evaluate single agent umbralisib in up to 150 subjects prior to proceeding to Stage 2, which randomized subjects to either umbralisib alone or in combination with ublituximab.
 - More specific instructions were given around dose modifications in the event of diarrhea and/or colitis.
 - Futility stopping rules were added for the MZL cohort and the FL/SLL cohort based on Simon's 2-stage design.
- Amendment 5 (Version 4.0, 15 February 2018):
 - Mention of copanlisib was added as an excluded prior therapy.
- Amendment 6 (Version 5.0, 20 August 2018)
 - The primary objectives of the study were revised to reflect ORR as the primary endpoint for all cohorts.
 - The key secondary objectives of CR rate for subjects with FL or SLL and PFS for subjects with DLBCL were revised to be secondary objectives.
 - Inclusion criterion was amended to require subjects with FL, SLL, or MZL to have documented evidence for requiring treatment.
 - Statistical assumptions for the MZL, FL/SLL, and DLBCL cohorts were revised in accordance with recent SAPs.
- Amendment 7 (Version 5.1, 20 September 2018)
 - Updated to include cytomegalovirus surveillance for all subjects

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- Revised to allow dose delays of any study medication for durations longer than 28 days to recover from toxicity
- Updated to provide clarification on the liver toxicity dose modification guidelines

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.1.2. Study Results - Study UTX-TGR-205

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and Code of Federal Regulations Title 21 Part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s). Written informed consent was obtained from each subject prior to performing any study assessments.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Financial Disclosure

The Applicant's Position:

Details of financial disclosure are presented in Section 19.2.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Patient Disposition

The Applicant's Position:

In Study UTX-TGR-205, a total of 69 subjects with MZL received at least 1 dose of umbralisib, with all 69 subjects included in the ITT Population.

In the ITT Population of 69 subjects with MZL, umbralisib was discontinued in 43 subjects (62.3%) with MZL (Table 10). The most common reason for treatment discontinuation was PD (27.5%). AEs contributed to discontinuation in 16 subjects (23.2%) with MZL.

Table 10: Summary of Disposition – End of Treatment and Reason of Discontinuation - Study UTX-TGR-205 (ITT Population)

	MZL (N=69) n (%)
Discontinued	43 (62.3)
Reason for treatment discontinuation	
Completion of protocol-specified regimen	0

	MZL (N=69) n (%)
Adverse event	16 (23.2)
Death	0
Lack of efficacy	1 (1.4)
Non-compliance with study	0
Investigator decision	4 (5.8)
Progressive disease	19 (27.5)
Withdrawal of consent	3 (4.3)
Other	0

Source: CSR UTX-TGR-205, Table 14.1.2.2 and Listing 16.2.1.2.1

Abbreviations: BM, bone marrow; CSR, clinical study report; ITT, intent-to-treat; MZL, marginal zone lymphoma.

Note: "Other" reasons included subject refused drug/further treatment, subject and family decided to stop study treatment due to mental and functional decline, subject was found to have multiple myeloma of the BM and was thus ineligible for the study, and subject decision.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Protocol Violations/Deviations

The Applicant's Position:

In the ITT Population, major protocol deviations were reported in 22 MZL subjects (31.9%). The most frequently reported deviations were those related to laboratory assessments (11 MZL subjects [15.9%]).

The FDA's Assessment:

The FDA agrees with the Applicant's position, though there is additional pertinent information. Per review of the protocol deviation database (ADDV), there were 41 major protocol violations in 22 patients. Major protocol deviations in the MZL patient population included deviations in five patients who experienced at least one SAE which was reported late, in some cases years after the event. The most significant event occurred in a patient with exfoliative dermatitis who developed staphylococcus epidermidis sepsis, leading to fatal organ failure and death. Following an information request, the Applicant noted delayed reporting from the individual clinical sites for the noted serious adverse events. Once the safety data was communicated to the Applicant from the clinical sites, the Applicant informed the relevant regulatory authorities

appropriately.

There were 13 major protocol deviations that related to efficacy assessments in seven patients. The majority of these were missing CTs at various follow-up points. Following review, the missing CT assessments were not likely to impact the overall efficacy results for patients with MZL.

Events that could potentially affect patient safety occurred in multiple patients;

- Five patients did not have CMV serology assessed at the specified timepoints.
- HBV serologies were missing for one patient at enrollment, and ECG for another.
- There were two major violations related to concomitant medications, including inadequate antiviral prophylaxis and > 10 mg of prednisone daily for approximately 1 month.
- One patient had inadvertently taken 1,200 mg of umbralisib for two consecutive days.

In general, the protocol deviations related to safety were not likely to substantially impact the safety evaluation for umbralisib.

Table of Demographic Characteristics

Data:

A summary of the demographic and baseline characteristics for the ITT Population is shown in Table 11.

Table 11: Summary of Demographics and Pre-treatment Disease Characteristics - Study UTX-TGR-205 (ITT Population)

Parameter	MZL (N=69)
Age (years)	
Mean (SD)	66 (10.0)
Median (minimum, maximum)	67 (34, 88)
Age categories, n (%)	
<65 years	27 (39.1)
≥65 years	42 (60.9)
Sex, n (%)	

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Parameter	MZL (N=69)
Male	33 (47.8)
Female	36 (52.2)
Race, n (%)	
White	57 (82.6)
Non-White	12 (17.4)
Region, n (%)	
US	39 (56.5)
Non-US	30 (43.5)
Weight (kg)	
Mean (SD)	81.2 (20.97)
Median (minimum, maximum)	80.0 (46.3, 165.0)
ECOG performance status, n (%)	
0	38 (55.1)
1	29 (42.0)
2	2 (2.9)
MZL type, n (%)	
Extranodal	38 (55.1)
Nodal	20 (29.0)
Splenic	11 (15.9)
Stage of disease at Screening, n (%)	
I	4 (5.8)
II	7 (10.1)
III	12 (17.4)
IV	44 (63.8)
Unknown	2 (2.9)
Prior systemic therapy	
Median (minimum, maximum)	2.0 (1, 6)
1	34 (49.3)
2	17 (24.6)

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Parameter	MZL (N=69)
3	8 (1.6)
>3	10 (14.5)
Anti-CD20 therapies, n (%)	69 (100.0)
Anti-CD20 monotherapy only	15 (21.7)
Anti-CD20 based chemoimmunotherapy	52 (75.4)
Lenalidomide (mono or combo)	4 (5.8)
Lenalidomide and anti-CD20 antibody	3 (4.3)
Lenalidomide and rituximab	3 (4.3)
BTK inhibitor	2 (2.9)
Alkylating agent	48 (69.6)

Source: CSR Study UTX-TGR-205, Table 14.1.3.1, Table 14.1.4.1, Table 14.1.6.4, and Table 14.1.6.7

Abbreviations: BTK, Bruton's tyrosine kinase; CD20, cluster of differentiation 20; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; ITT, intent-to-treat; MZL, marginal zone lymphoma; SD, standard deviation; US, United States.

The Applicant's Position:

For the 69 subjects with MZL the median age was 67 years (range: 34 to 88 years); 52.2% of subjects were females, 82.6% of subjects were White, and 56.5% of subjects were enrolled at US sites (Table 11). The ECOG performance status was 0 or 1 for 97.1% of the subjects.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment, with some additional pertinent population characteristics. There were 14 patients (20%) who were ≥75 years of age. The racial representation was 83% White, 7% Black, 3% Asian, and 7% Other. There were 2 (3%) patients who reported Hispanic ethnicity. The racial and ethnic distribution is a limitation of the data.

Patients were enrolled in six other countries besides the United States, 1 (1%) Australia, 1 (1%) Spain, 4 (6%) Great Britain, 9 (13%) Italy, 1 (1%) South Korea, 14 (20%) Poland.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

The MZL subtypes were extranodal (38 subjects [55.1%]), nodal (20 subjects [29.0%]), and splenic (11 subjects [15.9%]) (Table 11). Most of the subjects were Stage IV (63.8% of subjects). Three subjects (4.3%) previously received lenalidomide and anti-CD20 antibody, all of whom received R².

The FDA's Assessment:

The FDA agrees with the Applicant's position. In the 69 patients with MZL, the median number of prior lines of therapy was 2 (range: 1 to 6), with 26% being refractory to their last therapy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant's Position:

Treatment Compliance

No subjects with MZL discontinued due to non-compliance with study.

Concomitant Medications

All 69 subjects with MZL received at least 1 concomitant medication. Concomitant medications were categorized according to their potential for inhibition/induction of P450 isozymes and inhibition of transporters. In the category of P450 inhibition, the most frequently used drugs (at least 10% of subjects overall) were acyclovir (66.7% of subjects), allopurinol (34.8% of subjects), and omeprazole (23.2% of subjects), all of which are classified as weak inhibitors based on FDA guidance (FDA: Drug development and drug interactions). Overall, P450 inducers were used infrequently ($\leq 1.1\%$). The most frequently used clinical OATP1B1/OATP1B3 inhibitor was clarithromycin (11.6% of subjects), which is also an inhibitor of P-gp. Other frequently used clinical P-gp inhibitors included carvedilol (2.9%).

Rescue Medication Use

Not applicable

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

In Study UTX-TGR-205, umbralisib 800 mg QD was administered to patients with MZL who received at least 1 prior therapy including an anti-CD20 containing regimen. The

efficacy analysis included 69 patients with 3 sub-types of MZL: extranodal (N=38), nodal (N=20), and splenic (N=11). Primary efficacy results of ORR (defined as the percentage of subjects who achieved CR or PR) for subjects with MZL in the ITT population (N=69) are summarized in the table below.

Table 12: Summary of Overall Response for Subjects With MZL – Study UTX TGR 205 (ITT Population)

Parameter		IRC Assessment ^a MZL (N=69)	Investigator Assessment MZL (N=69)
ORR (CR+PR)	n (%)	34 (49.3)	37 (53.6)
	95% CI	37.0, 61.6	41.2, 65.7
CR	n (%)	11 (15.9)	5 (7.2)
	95% CI	8.2, 26.7	2.4, 16.1
PR	n (%)	23 (33.3)	32 (46.4)
	95% CI	22.4, 45.7	34.3, 58.8
DCR (CR+PR+stable disease)	n (%)	57 (82.6)	59 (85.5)
	95% CI	71.6, 90.7	75.0, 92.8
Stable disease	n (%)	23 (33.3)	22 (31.9)
	95% CI	22.4, 45.7	21.2, 44.2
Progressive disease	n (%)	7 (10.1)	6 (8.7)
	95% CI	4.2, 19.8	3.3, 18.0
Not evaluable	n (%)	5 (7.2)	4 (5.8)
	95% CI	2.4, 16.1	1.6, 14.2

Source: CSR UTX-TGR-205, Table 14.2.1.1

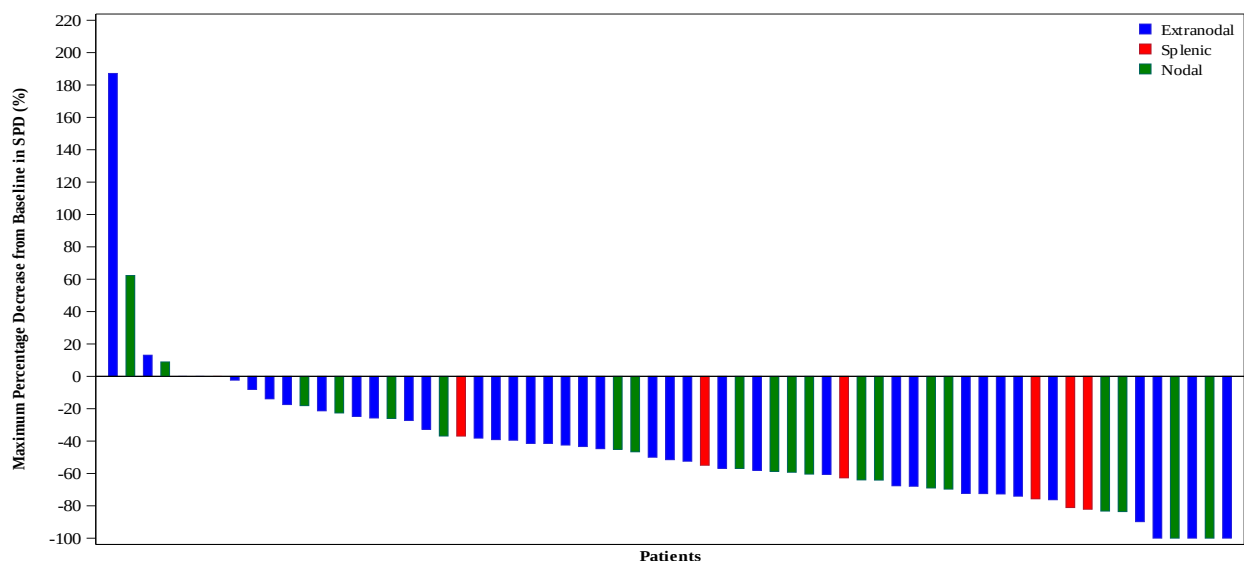
Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; DCR, disease control rate; IRC, Independent Review Committee; MZL, marginal zone lymphoma; ORR, overall response rate; NE, not evaluable; NR, not reached; PR, partial response

^a Per IRC according to Revised International Working Group Criteria

^b Denotes censored observation

The maximum percentage decrease in SPD by IRC assessment is presented in Figure 2. The majority of subjects showed a benefit with 59/65 (91%) of subjects with some reduction in tumor burden from baseline.

Figure 2: Waterfall Plot of Maximum Percentage Decrease in SPD for Subjects With MZL by IRC Assessment – Study UTX-TGR-205 (ITT Population)



Source : CSR UTX-TGR-205, Figure 14.2.1.4

Abbreviations: CSR, clinical study report; IRC, Independent Review Committee; ITT, intent-to-treat; MZL, marginal zone lymphoma; SPD, sum of the products of longest diameters.

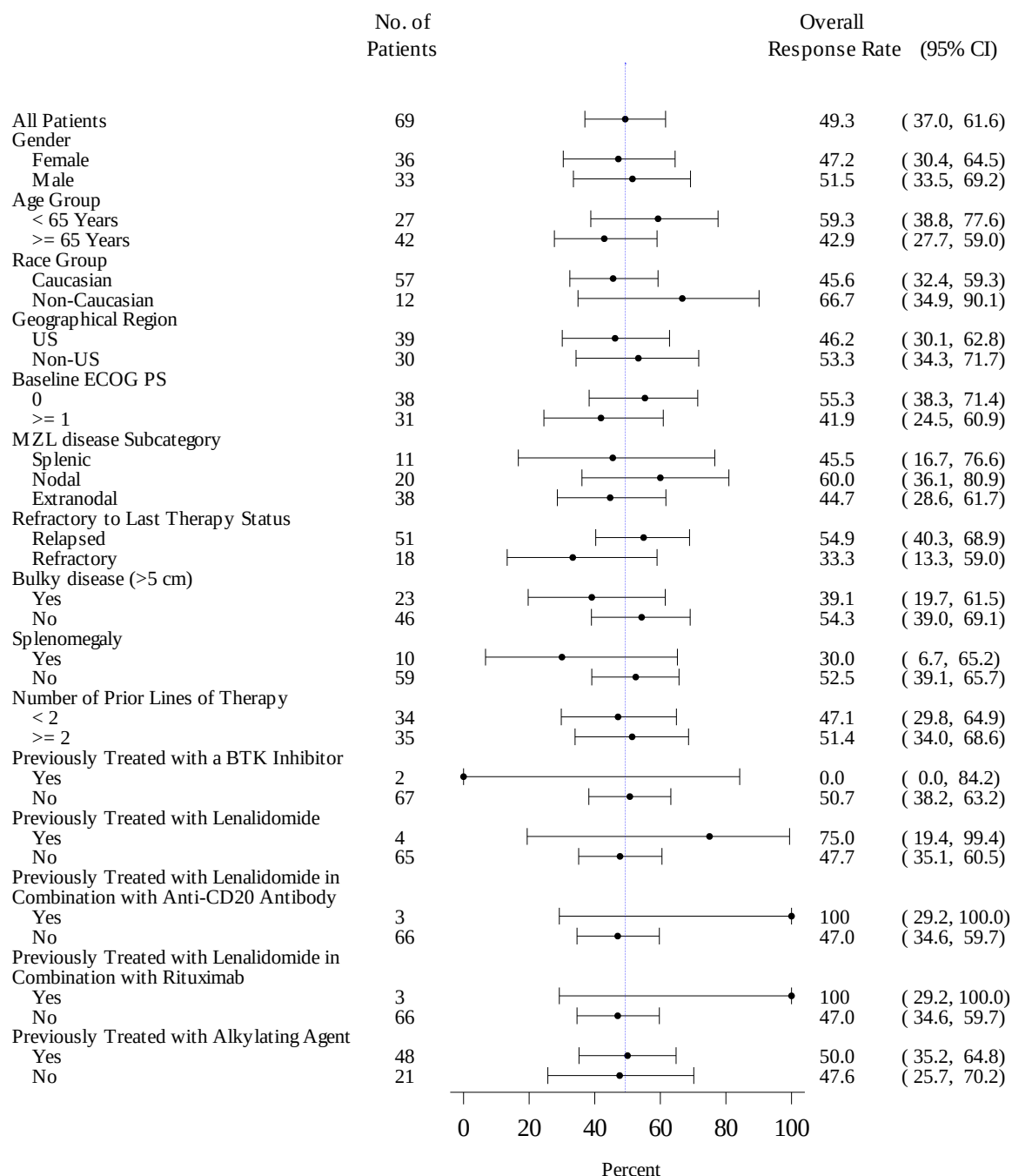
The median follow-up time on study to data cutoff was 20.3 months (range: 15.0 to 28.7 months), and the median time to response was 2.8 months (range: 1.8, 21.2 months).

For the PP Population, the ORR was 54.4%, with CR in 9 subjects (15.8%) and PR in 22 subjects (38.6%) based on IRC assessment and 54.4%, with CR in 4 subjects (7.0%) and PR in 27 subjects (47.4%) based on Investigator assessment.

Subgroup Analyses

Subgroup analyses of ORR based on IRC assessments for the ITT population are presented in Figure 3. With respect to MZL subtype (nodal, splenic, and extranodal), the ORR was 60.0%, 45.5%, and 44.7%, respectively. The ORR for subjects with <2 prior lines of therapy was 47.1% compared to 51.4% for subjects with ≥ 2 prior lines. For the 4 subjects previously treated with a lenalidomide containing regimen, 3 subjects (75%) achieved a response, of which all 3 had prior R² treatment. ORR was also consistent among patients with or without prior treatment with an alkylating agent (50% versus 47.6%).

Figure 3: Forest Plot of ORR for Subjects With MZL Based on IRC Assessment – Study UTX-TGR-205 (ITT Population)



Source : CSR UTX-TGR-205, Figure 14.2.1.1

Abbreviations: BTK, Bruton's tyrosine kinase; CI, confidence interval; CD20, cluster of differentiation 20; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; IRC, Independent Review Committee; ITT, intent-to treat; MZL, marginal zone lymphoma; No., number; ORR, overall response rate; PS, performance status; US, United States.

The FDA's Assessment:

The FDA agrees with Applicant's presentation of ORR results and the subgroup analyses results. Some of the subgroups had insufficient number of patients needed to draw meaningful conclusions, e.g., the previously treated with lenalidomide and BTK inhibitor categories have insufficient number of patients in the "Yes" subgroups to draw reasonable conclusions. In addition, these analyses are exploratory with no multiplicity adjustment and no pre-specified hypotheses. The outlier subgroups with wide confidence intervals can be attributed to the small number of patients and responders in that subgroup.

For the completeness of the demographic subgroups, the ORR results by ethnicity are as follows:

There were 2 responders out of 2 Hispanic or Latino patients, 28 responders out of 58 non-Hispanic or -Latino patients and 3 responders in the 8 patients who had not reported or had missing ethnicity.

For race, some of the subgroups had insufficient numbers, limiting the conclusions in this study to a broad patient population.

Based on the efficacy update provided on 9/11/2020 using the data cutoff of 15 July 2020, the ORR remained unchanged at 49.3% (95% CI: 37.0, 61.6).

Data Quality and Integrity

The Applicant's Position:

No data integrity concerns were reported following completion of site inspections.

The FDA's Assessment:

No issues were identified with the data quality from the pivotal study which could affect the efficacy results. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Duration of Response

The median DOR for subjects with MZL was not reached based on either IRC assessment

or Investigator assessment (Table 13). Based on IRC assessment, the DOR rates at 6 and 12 months were 82.2% and 65.9%, respectively.

Table 13: Summary of DOR for Subjects With MZL - Study UTX-TGR-205 (ITT Population – MZL Responders)

Subgroup	IRC Assessment MZL (N=34)	Investigator Assessment MZL (N=37)
Number of events, n (%)		
PD	9 (26.5)	11 (29.7)
Death (without PD)	0	0
Number of censored, n (%)	25 (73.5)	26 (70.3)
DOR (months)		
Median (95% CI) ^a	NR (9.3, NE)	NR (10.9, NE)
Minimum, maximum	0.03 ⁺ , 21.8 ⁺	0.03 ⁺ , 21.8 ⁺
DOR rate(%)		
At 3 months (95% CI) ^a	89.6 (71.2, 96.5)	88.2 (71.6, 95.4)
At 6 months (95% CI) ^a	82.2 (62.2, 92.2)	78.8 (60.5, 89.3)
At 12 months (95% CI) ^a	65.9 (44.3, 80.7)	67.5 (47.5, 81.2)

Source: CSR UTX-TGR-205, Table 14.2.2.1

Abbreviations: CI, confidence interval; DOR, duration of response; IRC, Independent Review Committee; ITT, intent-to-treat; NE, not evaluated; NR, not reached; PD, progressive disease; MZL, marginal zone lymphoma.

⁺ Denotes censored observation; ^a Based on Kaplan-Meier estimation.

Progression-free Survival

Based on IRC assessment, the median PFS was 21.2 months (range: 0.0+ to 24.4+ months). The PFS rates were 66.1% at 12 months and 48.7% at 24 months (Table 14). Based on Investigator assessment, the median PFS was 18.4 months (range: 0.0+ to 24.4+ months), and the PFS rates were 64.8% at 12 months and 49.4% at 24 months.

Table 14: Summary of PFS for Subjects With MZL - Study UTX-TGR-205 (ITT Population)

	IRC Assessment MZL (N=69)	Investigator Assessment MZL (N=69)
Number of events, n (%)		
PD	24 (34.8)	26 (37.7)
Death (without PD)	1 (1.4)	2 (2.9)

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	IRC Assessment MZL (N=69)	Investigator Assessment MZL (N=69)
Number of censored, n (%)		
No baseline disease assessments	1 (1.4)	0
No post-baseline disease assessments and no death	4 (5.8)	3 (4.3)
No PD and no death	35 (50.7)	32 (46.4)
Lost to follow-up without PD	0	0
Death or PD after ≥2 missed assessments	0	0
Withdrawal without further disease assessments	4 (5.8)	5 (7.2)
Use of new anticancer therapy	0	1 (1.4)
PFS (months)		
Median (95% CI)	21.2 (12.1, NE)	18.4 (12.1, NE)
Minimum, maximum	0.0 ⁺ , 24.4 ⁺	0.0 ⁺ , 24.4 ⁺
PFS rate (%) with 95% CI^a		
6 months	81.6 (69.1, 89.4)	77.2 (64.5, 85.8)
12 months	66.1 (52.0, 77.0)	64.8 (51.2, 75.5)
18 months	55.6 (41.1, 67.9)	52.7 (38.7, 64.9)
24 months	48.7 (30.6, 64.5)	49.4 (34.9, 62.3)

Source: CSR UTX-TGR-205, Table 14.2.4.1

Abbreviations: CI, confidence interval; CSR, clinical study report; IRC, Independent Review Committee; ITT, intent-to-treat; MZL, marginal zone lymphoma; NE, not evaluable; PD, progressive disease; PFS, progression-free survival.

Note: Median PFS with 95% CIs and PFS rates were estimated using Kaplan-Meier method. The 95% CIs of PFS rates were estimated using a normal approximation.

⁺ Denotes censored observation; ^a Based on Kaplan-Meier estimation.

The FDA's Assessment:

The FDA agrees with the estimates provided for the duration of response.

Based on the efficacy update provided on 9/11/2020 using the data cutoff of 15 July 2020, the ORR remained the same at 49.3% (95% CI: 37.0, 61.6). The point estimates of the IRC assessed median duration of response remained the same at NR (95%CI: 10.3, NR) months (the confidence interval changed).

As discussed in Section 8.1.1 under study endpoint, time-to event endpoints in single-arm studies have limited interpretability. Therefore, the PFS results are considered descriptive and exploratory.

Dose/Dose Response

The Applicant's Position:

PPK and E-R relationship after umbralisib administration was performed using data from Studies TGR-1202-101 and UTX-TGR-205. The exposure-efficacy analyses included 37 subjects with MZL. The pooled PPK/E-R analyses robustly evaluated biologically inter-dependent endpoints of efficacy and safety. Overall, the dose response results demonstrate an acceptable balance between benefits and risk at the recommended dose of umbralisib 800 mg and justify the use of this dose regimen in subjects with MZL.

The FDA's Assessment:

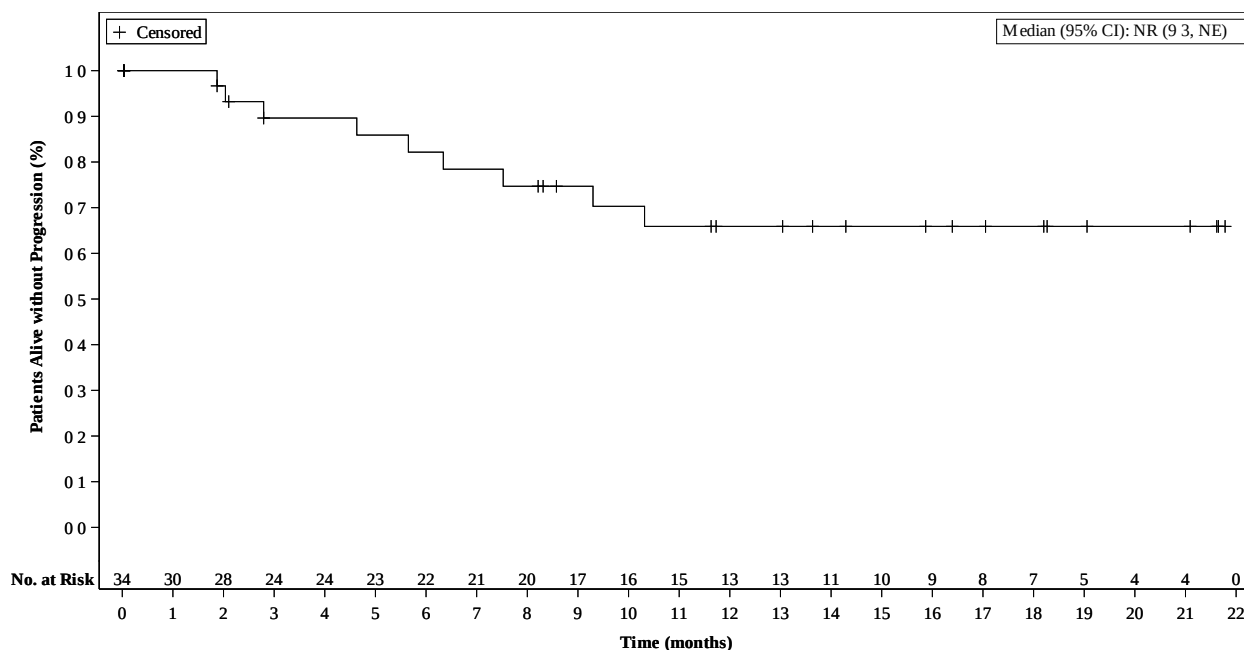
The FDA agrees with the Applicant's position.

Durability of Response

The Applicant's Position:

In the pivotal study (Study UTX-TGR-205), 31 of the 69 subjects with MZL were exposed to umbralisib for at least 12 months. No separate analyses were carried out on these subsets of subjects. A Kaplan-Meier plot of DOR was used to provide estimated DOR with continued umbralisib treatment. For subjects with MZL, the DOR rate at 12 months was 65.9% (Figure 4).

Figure 4: Kaplan-Meier Plot of DOR for Subjects With MZL Based on IRC Assessment (ITT Population) – Responders Only



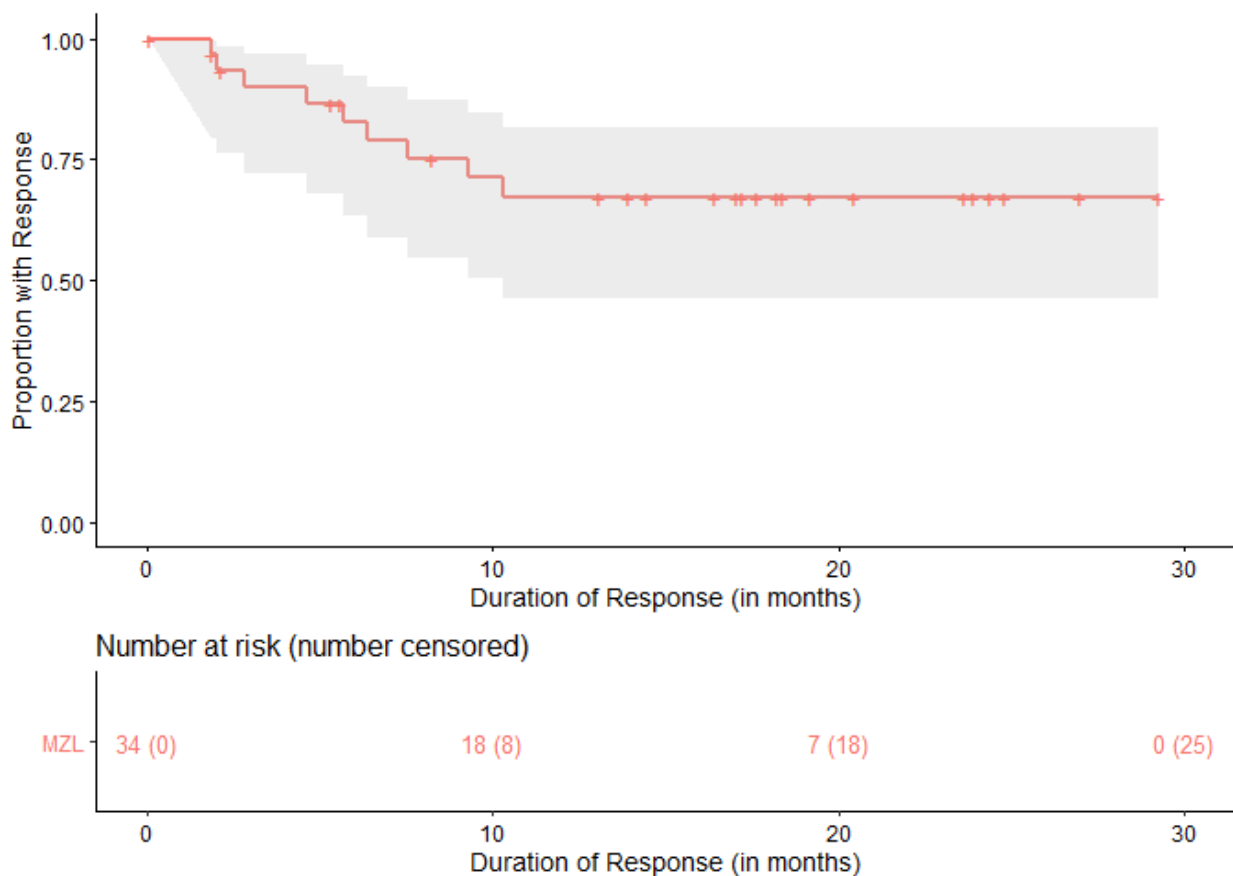
Source: CSR Study UTX-TGR-205, Figure 14.2.2.1

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Abbreviations: CI, confidence interval; CSR, clinical study report; DOR, duration of response; IRC, Independent Review Committee; ITT, intent-to-treat; MZL, marginal zone lymphoma; NE, not evaluated; No., number; NR, not reached.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the duration of response (DoR). The Kaplan Meier curve for the updated DoR based on the 9/11/2020 submission is provided in the figure below with the 95% CI bands. As mentioned previously, the point estimate of the median DoR remains unchanged [NR (95%CI: 10.3, NR)].



Source: *adtte.xpt, reviewer generated*

8.1.3. Supportive Study for Efficacy - Study TGR-1202-101

The Applicant's Position:

Study TGR-1202-101 is a completed, Phase I, first-in-human, open-label study of umbralisib, administered as a single agent to subjects with relapsed or refractory

hematologic malignancies. The study included eligible subjects aged 18 years or older with histologically confirmed Hodgkin lymphoma, B-cell NHL, peripheral T cell lymphoma, CLL, SLL, MZL, or other B-cell lymphoproliferative disorders whose disease had relapsed after, or was refractory to, at least 1 previous treatment regimen.

This study consisted of a dose-escalation phase and a dose-expansion phase. The dose-escalation phase used a traditional 3+3 design to determine the MTD. Subjects were to receive umbralisib daily in the absence of disease progression, unacceptable toxicity, or withdrawal from treatment. In the initial dose-escalation phase, subjects received (b) (4) umbralisib under a fasted condition starting at 50 mg orally QD with increasing doses for each subsequent cohort until the MTD was identified. For the majority of the study, subjects received (b) (4) umbralisib, which was subsequently used in Study UTX-TGR-205 and Study TGR-1202-202. Each treatment cycle was 4 weeks (28 days), with the first efficacy evaluation at 8 weeks (± 7 days) and at 8-week intervals thereafter. After Cycle 12, restaging was performed every 6 months at the discretion of the treating physician on a subject-by-subject basis secondary to the clinical presentation of the subject. Disease assessments were conducted by treating investigators. Subjects with PD or unacceptable toxicity were discontinued, and subjects achieving stable disease or better were allowed to continue daily treatment with umbralisib. Subjects on umbralisib who received benefit at the conclusion of this study were eligible to enroll in an open-label extension study, Study UTX TGR-501, to continue to receive single agent umbralisib.

The primary objective of this study was to evaluate safety and MTD of umbralisib in subjects with hematologic malignancies and to evaluate the PK effects of umbralisib. The secondary objectives of the study included evaluation of ORR and DOR in subjects with hematologic malignancies treated with umbralisib.

Of the 90 subjects enrolled in this study, 5 subjects had MZL. Treatment was discontinued for all subjects: 2 subjects due to PD and 1 subject each due to AE, other (lack of improvement in disease burden), and subject request to discontinue treatment. The median age was 62.0 years (range: 43 to 76 years). The mean duration of exposure to umbralisib was 15.2 months (range: 4.2 to 24.6 months); 3 of the 5 subjects were exposed for ≥ 12 months.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.1.4. Efficacy Results - Study TGR-1202-101

The Applicant's Position:

Results from the Phase I dose expansion phase of Study TGR-1202-101 provide additional support for efficacy of umbralisib in subjects with MZL. However, because of the small number of subjects in this study and the differences in response evaluation and dosing of umbralisib, direct comparison with the MZL cohort in Study UTX-TGR-205 is not feasible.

Of the 5 MZL subjects enrolled in this study, 1 subject achieved PR, yielding ORR of 20.0%. The disease control rate (DCR) was 100%. Median (95% CI) DOR was not estimable.

The FDA's Assessment:

The FDA's assessment of efficacy was based primarily on Study UTX-TGR-205. The efficacy data from Study UTX-TGR-101 is descriptive and considered supportive.

8.1.5. Supportive Study for Efficacy - Study TGR-1202-202

The Applicant's Position:

Study TGR-1202-202 is an ongoing Phase II study designed to evaluate the efficacy and safety of single agent umbralisib 800 mg QD in previously treated subjects with non-follicular iNHL. Subjects were required to have non-follicular iNHL (MZL and Waldenstrom's macroglobulinemia) that relapsed or were refractory following at least 1 prior standard therapy regimen. The primary objective was to evaluate the ORR (CR+PR+very good partial response +minor response) and DOR for umbralisib in subjects with relapsed or refractory non follicular iNHL. The secondary objectives were to determine the PFS of umbralisib in subjects with relapsed or refractory non-follicular iNHL, to evaluate time to treatment failure with umbralisib, and to evaluate the safety profile of umbralisib. Disease assessments were conducted by treating investigators.

As of the cutoff date of 01 September 2019, a total of 8 subjects with MZL were enrolled in the study, of whom 4 subjects were discontinued from the study and 4 subjects were ongoing. The median age was 73 years (range: 58 to 82 years). Most of the subjects had nodal (50.0%) or extranodal (37.5%) MZL disease. Stage at diagnosis was IV for 37.5% of subjects. The mean duration of exposure to umbralisib was 8.0 months (range: 2 to 18 months). Six of the 8 subjects were exposed to umbralisib for <12 months, and 2 subjects were exposed to umbralisib ≥12 months.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.1.6. Efficacy Results - Study TGR-1202-202

The Applicant's Position:

Preliminary efficacy results from the Phase II Study TGR-1202-202 provide additional support for efficacy of umbralisib in subjects with MZL. However, because of the small number of subjects in this study and the differences in response evaluation and dosing of umbralisib, direct comparison with the MZL cohort in Study UTX-TGR-205 is not feasible.

For the 8 MZL subjects as of the cutoff date for efficacy (30 November 2019), the ORR was 37.5%, with CR in 12.5% of subjects and PR in 25.0% of subjects. The DCR was 87.5%. For the 2 responders with more than 1 response assessment and no disease progression as of the data cutoff date, the DOR was censored at the last tumor assessment and were estimated as 3.0 and 7.2 months.

The FDA's Assessment:

The FDA's assessment of efficacy was based primarily on Study UTX-TGR-205. The efficacy data from Study UTX-TGR-202 is descriptive and considered supportive.

8.1.7. Integrated Review of Effectiveness

The FDA's Assessment:

Not applicable, the primary efficacy data for umbralisib is from Study UTX-TGR-205 as reviewed in the above sections

8.1.8. Assessment of Efficacy Across Trials

The Applicant's Position:

Study UTX-TGR-205 was the pivotal study. Data from this study provide primary support for efficacy of umbralisib in subjects with MZL. Data from the other 2 studies (TGR-1202-101 and TGR-1202-202) that included subjects with MZL provide additional support for efficacy of umbralisib in subjects with MZL. However, because of the small number of subjects in these 2 studies and the differences in response evaluation and dosing of umbralisib, direct comparison with the MZL cohort in Study UTX-TGR-205 is not feasible, and efficacy results are instead presented side by side in Table 15. DOR and TTR were not calculated for TGR-1202-101 and TGR-1202-202 because of the limited number of subjects.

Table 15: Efficacy Results (Response Rate) - Subjects With MZL

Endpoint	Statistic	UTX-TGR-205 (N=69)	TGR-1202-101 (N=5)	TGR-1202-202 (N=8)
ORR (CR+PR)	n (%)	34 (49.3)	1 (20.0)	3 (37.5)
	95% CI	37.0, 61.6	0.5, 71.6	8.5, 75.5

Endpoint	Statistic	UTX-TGR-205 (N=69)	TGR-1202-101 (N=5)	TGR-1202-202 (N=8)
CR	n (%)	11 (15.9)	0	1 (12.5)
	95% CI	8.2, 26.7	--	0.3, 52.7
DCR (ORR+stable disease)	n (%)	57 (82.6)	5 (100.0)	7 (87.5)
	95% CI	71.6, 90.7	0. 52.2	47.3, 99.7

Source: CSR Study UTX-TGR-205, Table 14.2.1.1, Table 14.2.2.1, and Table 14.2.3.1; CSR Study TGR-1202-101, Table 14.2.1.1 and Table 14.2.1.2; CSR Study TGR-1202-202, Table 14.2.1.

Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; DCR, disease control rate; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached; ORR, overall response rate; PR, partial response.

Note: Responses in Study UTX-TGR-205 were assessed by independent central review, while Study TGR-1202-101 and TGR-1202-202 were by investigator assessment.

The FDA's Assessment:

The FDA's assessment of efficacy was based on Study UTX-TGR-205.

8.1.9. Integrated Assessment of Effectiveness

The Applicant's Position:

The primary study to characterize the efficacy of umbralisib in MZL is Study UTX-TGR-205. Two additional studies with single agent umbralisib included subjects with MZL: Study TGR-1202-101 (5 subjects with MZL) and Study TGR-1202-202 (8 subjects with MZL).

A comparison of the efficacy results across studies was not conducted due to the limited number of subjects with MZL enrolled outside of the pivotal study UTX-TGR-205 as well as the differences in response evaluation and dosing of umbralisib. Given the minimal number of additional subjects with MZL for these 2 studies, interpretation of these results will be limited and will not meaningfully contribute to the description of efficacy.

Unlike Study UTX-TGR-205, Study TGR-1202-101 did not require MZL subjects to be relapsed following prior anti-CD20-based therapy. Unlike Study UTX-TGR-205, Study TGR-1202-202 did not require MZL subjects to be relapsed following prior anti-CD20-based therapy and allowed subjects to have prior treatment with a PI3K inhibitor.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that the data from the three trials cannot be pooled together due to the differences in the response evaluation, dosing, inclusion/exclusion criteria of the three trials. The evaluation of efficacy is based on the data from UTX-TGR-205.

The efficacy of umbralisib is based on data from 69 patients with MZL from a cohort of

the UTX-TGR-205 trial, an open-label, multi-center, single-arm, multi-cohort trial. Patients with MZL were required to have prior treatment with 1 or more lines of therapy, including at least 1 anti-CD20-based regimen (either as monotherapy or chemoimmunotherapy). The trial excluded patients with prior exposure to a PI3K inhibitor. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) based on the 2007 International Working Group criteria for Malignant Lymphoma using computerized tomography (CT). Secondary endpoints included duration of response and progression-free survival.

Of the 69 patients with MZL [extranodal (N=38), nodal (N=20), and splenic (N=11)], the median age was 67 years (range: 34 to 88 years), 52% were female, 83% were White, 7% were Black, 3% were Asian, and 97% had a baseline ECOG performance status of 0 or 1. Patients had a median number of prior lines of therapy of 2 (range: 1 to 6), with 26% being refractory to their last therapy. The median follow-up time was 20.3 months (range 15.0 to 28.7 months). The ORR per IRC was 49% (95% CI: 37.0, 61.6), with 16% achieving a complete response. The median duration of response was not reached (95% CI: 9.3, not evaluable). Of the 34 patients that responded, 65% maintained a response at 6 months, 50% at 9 months, and 38% at 12 months.

The data in patients with MZL support the determination that umbralisib has clinically meaningful activity in adult patients with relapsed or refractory MZL after at least one prior anti-CD20-based regimen.

8.2. Review of Safety

The Applicant's Position:

Safety data for subjects exposed to single agent umbralisib from the pivotal Study UTX-TGR-205 as of the cutoff date of 01 September 2019 were integrated with data from 4 other studies (Studies TGR-1202-101, TGR-1202-202, UTX-TGR-103, and UTX-TGR-501) to form an integrated database (IDB), which included a total of 371 subjects (82 subjects with MZL, 147 subjects with FL, and 142 subjects with other hematologic malignancies) hereafter referred to as the Umbralisib Safety Population.

Safety data from Study TGR-1202-102, a completed Phase I study in 32 subjects with solid tumor cancers, and safety data from 6 clinical pharmacology studies in healthy subjects (Studies TGR 1202-PK101, TGR 1202-PK102, TGR-1202-901, TGR-1202-902, TGR-1202-904, and TGR-1202-908) were not integrated with the other studies.

Data from the IDB allow for an informed assessment of the safety profile of umbralisib

800 mg QD and an evaluation of the overall benefit-risk in subjects with MZL. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.1. Safety Review Approach

The Applicant's Position:

The Umbralisib Safety Population included all subjects who received at least 1 dose of single agent umbralisib at doses ≥ 800 mg and was used for all analyses for single agent umbralisib. Pooled safety analyses included TEAEs, laboratory assessments, vital signs, and subgroup analyses (gender [male, female], age group [<65 years, ≥ 65 years], race [Caucasian, non-Caucasian], geographic region [US, non-US], prior lines of therapy [<2 , ≥ 2], prior lenalidomide therapy [yes, no], previous treatment with lenalidomide in combination with anti-CD20 therapy [yes, no], eGFR at baseline [mildly decreased, moderately decreased, severely decreased renal function, or end stage renal disease], and hepatic impairment [mild, moderate, severe]). Physical examinations and ECGs were not pooled and were examined by study.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The FDA reviewed data from the pivotal trial as well as the Safety Pool population (N = 371) and the 120-day Safety update, extending data collection to January 2020.

Safety endpoints listed below were used to evaluate the safety and tolerability of single agent umbralisib in this population of patients with MZL and patients with hematologic malignancies:

- Incidence and severity of all Treatment-emergent adverse events (TEAE)
- Grade 3-5 TEAEs
- Serious adverse events
- TEAEs leading to treatment modifications
- Adverse events of Special Interest
- Clinical laboratory test abnormalities, including lab shift analysis
- Prior therapies

The frequency of TEAEs was tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1. The NCI CTCAE version 4.03 was used to grade and summarize adverse events.

To inform the safety review, FDA used grouped preferred terms for more sensitive and informative safety analyses. The FDA preferred terms are listed in Section 19.5

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

Overall, 371 subjects received at least 1 dose of umbralisib, 82 subjects with MZL, 147 subjects with FL, 74 subjects with DLBCL/MCL, 43 subjects with CLL/SLL, and 25 subjects with other tumor types (Table 16). The median duration of exposure to umbralisib was 5.91 months (range: 0.1 to 75.1 months). A total of 92 subjects (24.8%) were exposed to umbralisib for 12 to <24 months, and 15 subjects (4.0%) were exposed for ≥24 months.

Table 16: Summary of Umbralisib Administration and Extent of Exposure (Umbralisib Safety Population)

Extent of Exposure	UTX-TGR-205	Pooled	
	MZL (N=69)	MZL (N=82)	Total (N=371)
Duration (months)			
Mean (SD)	10.27 (6.97)	10.31 (7.03)	9.06 (9.66)
Median	9.43	9.43	5.91
Minimum, maximum	0.2, 23.0	0.2, 24.6	0.1, 75.1
Duration, n (%)			
<3 months	13 (18.8)	16 (19.5)	111 (29.9)
3 to <6 months	14 (20.3)	16 (19.5)	76 (20.5)
6 to <12 months	11 (15.9)	14 (17.1)	77 (20.8)
12 to <18 months	16 (23.2)	19 (23.2)	56 (15.1)
18 to <24 months	15 (21.7)	16 (19.5)	36 (9.7)
≥24 months	0	1 (1.2)	15 (4.0)

Source: Table 2.7.4.1.2.1

Abréviations: MZL, marginal zone lymphoma; SD, standard deviation.

Note: Duration of exposure (months)=(date of last dose - date of first dose + 1)/30.4375.

Dose Modifications

Overall in the Umbralisib Safety Population (N=371), 57.4% of subjects had at least 1 dose adjustment (46.4% of subjects due to AEs). Umbralisib dose was reduced in 16.7% of subjects (13.2% of subjects due to AEs), umbralisib dosing was interrupted in 52.6% of subjects (43.7% of subjects due to AEs), and umbralisib was withdrawn in 21.8% of subjects (14.8% of subjects due to AEs).

The FDA's Assessment:

The FDA agrees with the Applicant's description of exposure. A median exposure of 9.4 months in patients with MZL and approximately 6 months in patents with hematologic malignancies provides sufficient data to support the evaluation of safety. However, there is a paucity of data to evaluate long-term toxicity.

For dose modifications, the following table below depicts umbralisib treatment modifications due to treatment-emergent adverse events per FDA review.

Table 17: Umbralisib Treatment Modifications Due to Adverse Events – FDA Review

Treatment Modifications due to Adverse Events	UTX-TGR-205 MZL N = 69 %	Safety Pool N = 371 %
Any TEAE leading to <u>discontinuation</u>	24.6%	15.4%
Any TEAE leading to dose <u>interruption</u>	59.4%	45.3%
Any TEAE leading to dose <u>reduction</u>	10.1%	10.5%
Abbreviations: MZL, Marginal zone lymphoma; TEAE, Treatment-emergent adverse event Source: FDA review of ADSL (Subject-level Analysis) Dataset and ADAE (Adverse Events Analysis) Dataset		

Source: ADSL (Subject-level Analysis Dataset), ADAE (Adverse Events Analysis Dataset)

Relevant characteristics of the safety population:

The Applicant's Position:

The Umbralisib Safety Population included subjects with MZL, FL, and other hematologic malignancies from 5 studies. Overall, the median age was 67 years (range: 22 to 95 years); 56.3% of subjects were male, 82.7% of subjects were White, and 72.8% of subjects were enrolled in the US. The ECOG performance status was 0 or 1 for most of the subjects (96.0%).

For subjects with MZL, the median age was 68 years (range: 34 to 88 years); 47.6% of subjects were male, 81.7% of subjects were White, and 63.4% of subjects were enrolled in the US.

Overall, the median number of prior systemic therapy was 2 (range: 1 to 14); 76.5% of subjects had ≥ 2 prior lines of therapy, and 49.1% of subjects had ≥ 3 prior lines of therapy. For subjects with MZL, the median number of prior systemic therapy was 2 (range: 1 to 7); 53.7% of subjects had ≥ 2 prior lines of therapy, and 30.5% of subjects had ≥ 3 prior lines of therapy.

Overall, 11.9% of subjects had prior lenalidomide therapy, and 7.8% of subjects had prior lenalidomide plus anti-CD20 therapy.

Median time since the most recent progression was 2.1 months (range: 0.3 to 447.4 months); 55.8% of subjects relapsed from prior treatment (progression of disease occurring greater than 6 months after last treatment), and 39.1% of subjects were refractory to prior treatment (progression during or within 6 months of completing prior therapy).

Overall, at baseline, the percentage of subjects with mild, moderate, and severe renal impairment were 53.6%, 26.1%, and 0.5% of subjects, respectively. No subjects had severe hepatic impairment, 14.8% of subjects had mild hepatic impairment, and 0.5% of subjects had moderate hepatic impairment.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on data for subjects exposed to single agent umbralisib from the pivotal Study UTX-TGR-205 as of the cutoff date of 01 September 2019 and from 4 other studies (Studies TGR-1202-101, TGR-1202-202, UTX-TGR-103, and UTX-TGR-501). Further details are provided in Section 8.2. This population allows for an informed assessment of the safety profile of umbralisib and a judgment of the overall benefit-risk in subjects with MZL.

The FDA's Assessment:

The safety database was acceptable for review. The initial submission did not include toxicity grades in the laboratory (ADLB) dataset. An information request was sent to the Applicant to enable a lab-shift analysis by the reviewers.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the case report forms and AE databases were consistent.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Categorization of Adverse Event

The Applicant's Position:

Each AE term was mapped to a SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. The AE severity was graded using Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

A TEAE was defined as an AE that first occurred or worsened in intensity from the first dose of study drug through 30 days after the last dose of study drug. The AEs that started before the first dose of study drug but considered related to study drug by the Investigator were assumed worsened in intensity during treatment and therefore were reported as TEAEs. The analysis of AEs included subjects with any TEAE, serious TEAE, CTCAE Grade ≥ 3 TEAE, TEAEs that led to death, TEAEs that led to discontinuation of study drug, TEAEs that led to dose reduction or interruption of study drug, AESIs, and drug-related AESIs. In addition, the number and percentage of subjects with TEAEs, serious TEAEs, TEAEs leading to discontinuation of study drug, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to death were summarized by period of exposure to umbralisib (<3 months, 3 to <6 months, 6 to <12 months, 1 to <2 years, and ≥ 2 years).

Adverse events of special interest (AESIs) were predefined in the integrated SAP; the criteria used to define AESIs were drug causality assessment, serious adverse event (SAE) rate, severity grade, frequency of TEAEs, class effect, discontinuation rate, and clinical context. All AESIs had SAEs (at least possibly related) plus one or more of the other criteria. Standardized MedDRA Queries relevant to the AESI list were used to select any additional PTs associated with AESI.

The Umbralisib Safety Population (N=371) supported predominantly by the pivotal UTX-TGR-205 study, provide the primary source for adverse drug reaction (ADR) determination. Safety data were reviewed systematically for TEAEs irrespective of Investigator's causality assessment, which includes serious TEAEs, TEAEs leading to dose modification, and AESIs. This was

accompanied by individual case reviews of selected events. New or worsening laboratory parameters were also analyzed.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Routine Clinical Tests

The Applicant's Position:

Laboratory assessments were pooled for the Umbralisib Safety Population and included changes from baseline, laboratory abnormalities based on CTCAE grade, shifts from baseline to post-baseline worst value based on CTCAE grade for hematology and serum chemistry (including liver function tests) parameters measured in the clinical trials.

The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with umbralisib. Subjects were questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by the subjects during or between visits or through physical examination, laboratory test results, or other assessments. Further to the standard safety evaluations outlined above, AE categories expected to be associated with umbralisib were also analyzed.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.4 Safety Results

Deaths

The Applicant's Position:

Overall, 4 deaths due to AEs (pleural effusion, septic shock, myocardial infarction, and pneumonia legionella) were reported, and all 4 subjects died within 30 days of last dose of umbralisib (Table 18). The events of pleural effusion, septic shock, and myocardial infarction were considered not related to umbralisib; pneumonia legionella was considered unlikely related to umbralisib.

Other deaths include death due to PD in 22 subjects (5.9%) and death due to "other/unknown/missing" after 30 days of last dose of umbralisib in 3 subjects (0.8%) due to heart failure, myelodysplasia, and respiratory failure.

Table 18: Summary of Deaths (Umbralisib Safety Population)

Primary Cause of Death	UTX-TGR-205	Pooled	
	MZL (N=69) n (%)	MZL (N=82) n (%)	Total (N=371) n (%)
All deaths	2 (2.9)	3 (3.7)	29 (7.8)
Progressive disease	1 (1.4)	2 (2.4)	22 (5.9)
Adverse event	0	0	4 (1.1)
Other/unknown/missing	1 (1.4)	1 (1.2)	3 (0.8)
Death within 30 days of last dose of umbralisib	0	1 (1.2)	11 (3.0)
Progressive disease	0	1 (1.2)	7 (1.9)
Adverse event	0	0	4 (1.1)

Source: Table 2.7.4.2.3.1

Abbreviations: MZL, marginal zone lymphoma.

Note: No deaths were reported in subjects in the “Other” cohort.

The FDA’s Assessment:

The FDA disagrees with the Applicant’s contention that no deaths in patients with MZL were related to an adverse event. In the table above, the patient listed as death due to other/unknown/missing was adjudicated by FDA as a death due to an adverse event. Patient (b) (6) an 88 year-old female with MZL, received the first dose of umbralisib on (b) (6) (b) (6), and the final dose on (b) (6). Relevant past medical history included hypertension and hypothyroidism. On study day 37, she presented with facial edema with erythematous lesions on her upper back and extremities and umbralisib was interrupted. Umbralisib was restarted on study day 39 and discontinued again on day 45 due to continued symptoms. The event progressed to a grade 3 serious adverse event of exfoliative dermatitis requiring hospitalization. The patient continued treatment for exfoliative dermatitis and was discharged after partial improvement. Umbralisib was interrupted on study day 45 and permanently discontinued on study day 72. On study day 73, the patient was readmitted with grade 3 heart failure, grade 3 staphylococcal sepsis, severe edema of right hand and both legs, and continuation of the exfoliative dermatitis. The patient developed worsening and ultimately fatal complications secondary to toxicity. The temporal sequence of development of exfoliative dermatitis followed by staphylococcal bacteremia and sepsis and organ dysfunction provides support that the event can be considered related to umbralisib.

Serious Adverse Events

The Applicant's Position:

Overall, serious TEAEs were reported in 95 subjects (25.6%), including 27 subjects (32.9%) with MZL (Table 19). The most frequently reported serious TEAEs (at least 2% of total pooled subjects) were pneumonia (3.0% of subjects) and diarrhea (2.4% of subjects). Serious TEAEs reported in at least 2 subjects with MZL were diarrhea (4 subjects), pneumonia (3 subjects), and anemia (3 subjects).

Table 19: Summary of Serious TEAEs (at Least 1% Total by PT) by SOC and PT (Umbralisib Safety Population)

System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	MZL (N=69) n (%)	MZL (N=82) n (%)	Total (N=371) n (%)
Any serious TEAE	26 (37.7)	27 (32.9)	95 (25.6)
Infections and infestations			
Pneumonia	3 (4.3)	3 (3.7)	11 (3.0)
Sepsis	1 (1.4)	1 (1.2)	5 (1.3)
Urinary tract infection	0	0	4 (1.1)
Gastrointestinal disorders			
Diarrhea	4 (5.8)	4 (4.9)	9 (2.4)
Colitis	0	1 (1.2)	4 (1.1)
Respiratory, thoracic, and mediastinal disorders			
Pleural effusion	0	0	4 (1.1)
Metabolism and nutrition disorders			
Dehydration	1 (1.4)	1 (1.2)	4 (1.1)
Hypercalcemia	0	0	4 (1.1)
General disorders and administration site conditions			
Pyrexia	1 (1.4)	1 (1.2)	4 (1.1)
Renal and urinary disorders			
Acute kidney injury	0	0	4 (1.1)

Source: Table 2.7.4.2.4.1.1

Abbreviations: CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MZL, marginal zone lymphoma; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

Serious TEAEs related to umbralisib were reported in 44 subjects (11.9%) overall, including 21 subjects (25.6%) with MZL. The most frequently reported serious TEAEs related to umbralisib (at least 1% of total pooled subjects) were pneumonia (1.9% of subjects), diarrhea (1.9% of subjects), and sepsis (1.1% of subjects). Serious TEAEs related to umbralisib reported in at least 2 subjects with MZL were diarrhea (3 subjects), pneumonia (2 subjects), and anemia (2 subjects).

Grade ≥ 3 serious TEAEs were reported in 82 subjects (22.1%) overall, including 24 subjects (29.3%) with MZL. Of these, 41 subjects (11.1%) had Grade ≥ 3 serious TEAEs related to umbralisib, including 19 subjects (23.2%) with MZL.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's description of all-cause serious TEAEs in 371 patients with hematologic malignancies. Overall, serious TEAEs were reported in 98 subjects (26.4%). For additional information, SAEs are shown in the table below using grouped preferred terms (Section 19.5), which allows for increased sensitivity and informative analyses. There was a higher incidence of any grade SAEs in the MZL cohort compared to the safety pool (39.1% versus 26.4%) with diarrhea/colitis and sepsis more pronounced. In patients with MZL, the most common SAEs were diarrhea/colitis (5.8%), sepsis, pneumonia, and anemia (4.3% each).

Table 20: Summary of Serious Adverse Events – FDA Review

Serious Adverse Events	UTX-TGR-205 MZL (N = 69) n (%)		Safety Pool (N = 371) n (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any SAE	27 (39.1%)	24 (34.7%)	98 (26.4%)	84 (22.6%)
Diarrhea/colitis	4 (5.8%)	2 (2.8%)	12 (3.2%)	9 (2.4%)
Sepsis	3 (4.3%)	3 (4.3%)	7 (1.8%)	7 (1.8%)
Neutropenia	1 (1.4%)	1 (1.4%)	2 (0.5%)	2 (0.5%)
Pneumonia	3 (4.3%)	2 (2.8%)	13 (3.7%)	12 (3.2%)
Anemia	3 (4.3%)	1 (1.4%)	3 (0.8%)	3 (0.8%)
Lower respiratory tract infection	2 (2.8%)	1 (1.4%)	3 (0.8%)	2 (0.5%)
Febrile neutropenia	2 (2.8%)	2 (2.8%)	4 (1.1%)	4 (1.1%)

Rash	2 (2.9%)	2 (2.8%)	2 (0.5%)	2 (0.5%)
Source: FDA review of ADAE dataset				

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Overall, TEAEs led to discontinuation of umbralisib in 57 subjects (15.4%), including 18 subjects (22.0%) with MZL (Table 21). The most frequently reported TEAEs leading to discontinuation of umbralisib (at least 2% of total pooled subjects) were diarrhea (3.8% of subjects), ALT increased (2.7% of subjects), and AST increased (2.7% of subjects).

TEAEs leading to discontinuation of umbralisib considered related to umbralisib were reported in 46 subjects (12.4%) overall, including 15 subjects (18.3%) with MZL. The most frequently reported TEAEs leading to discontinuation of umbralisib considered related to umbralisib (at least 2% of total pooled subjects) were diarrhea (3.5% of subjects), ALT increased (2.7% of subjects), and AST increased (2.7% of subjects).

Table 21: Summary of TEAEs Leading to Discontinuation of Umbralisib (at Least 1% Total by PT) by SOC and PT (Umbralisib Safety Population)

System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	MZL (N=69) n (%)	MZL (N=82) n (%)	Total (N=371) n (%)
Any TEAE leading to discontinuation	16 (23.2)	18 (22.0)	57 (15.4)
Gastrointestinal disorders			
Diarrhea	2 (2.9)	2 (2.4)	14 (3.8)
Colitis	1 (1.4)	2 (2.4)	4 (1.1)
Investigations			
Alanine aminotransferase increased	3 (4.3)	4 (4.9)	10 (2.7)
Aspartate aminotransferase increased	3 (4.3)	4 (4.9)	10 (2.7)
General disorders and administration site conditions			
Fatigue	1 (1.4)	1 (1.2)	4 (1.1)
Blood and lymphatic system disorders			
Neutropenia	1 (1.4)	1 (1.2)	4 (1.1)

Source: Table 2.7.4.2.4.2.1

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Abbreviations: MZL, marginal zone lymphoma; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

The FDA's Assessment:

The following table presents the FDA's analysis of the drug discontinuation data, including the specific AEs responsible for treatment discontinuation.

Table 22: Treatment Discontinuation Due to Adverse Events – FDA Review

Outcome/event	UTX-TGR-205 MZL (N = 69) %	Safety pool N=371 %
Any TEAE leading to discontinuation	24.6%	15.4%
Reason for discontinuation		
Diarrhea/colitis	5.1%	4.8%
Transaminase elevation	4.3%	3.2%
Neutropenia	1.4%	1.1%
Fatigue	1.4%	1.1%
Source: FDA review of ADAE dataset		

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Overall, TEAEs leading to umbralisib dose reduction were reported in 39 subjects (10.5%), including 9 subjects (11.0%) with MZL (Table 23). The most frequently reported TEAEs leading to umbralisib dose reduction (at least 1% of total pooled subjects) were diarrhea (2.2% of subjects), nausea (1.6% of subjects), neutropenia (1.6% of subjects), ALT increased (1.1% of subjects), and fatigue (1.1% of subjects).

TEAEs leading to umbralisib dose reduction related to umbralisib were reported in 34 subjects (9.2%) overall, including 7 subjects (8.5%) with MZL. The most frequently reported TEAEs leading to umbralisib dose reduction related to umbralisib (at least 1% of total pooled subjects) were diarrhea (2.2% of subjects), nausea (1.6% of subjects), neutropenia (1.6% of subjects), and fatigue (1.1% of subjects).

Table 23: Summary of TEAEs Leading to Umbralisib Dose Reduction (at Least 1% Total by PT) by SOC and PT (Umbralisib Safety Population)

System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	MZL (N=69) n (%)	MZL (N=82) n (%)	Total (N=371) n (%)
Any TEAE leading to dose reduction of umbralisib	7 (10.1)	9 (11.0)	39 (10.5)
Gastrointestinal disorders			
Diarrhea	2 (2.9)	2 (2.4)	8 (2.2)
Nausea	1 (1.4)	1 (1.2)	6 (1.6)
Blood and lymphatic system disorders			
Neutropenia	0	1 (1.2)	6 (1.6)
Investigations			
Alanine aminotransferase increased	1 (1.4)	1 (1.2)	4 (1.1)
General disorders and administration site conditions			
Fatigue	0	0	4 (1.1)

Source: Table 2.7.4.2.4.3.1

Abbreviations: MZL, marginal zone lymphoma; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

Overall, TEAEs leading to umbralisib dose interruption were reported in 168 subjects (45.3%), including 47 subjects (57.3%) with MZL. The most frequently reported TEAEs leading to umbralisib dose interruption (at least 2% of total pooled subjects) were diarrhea (11.9% of subjects), vomiting (4.9% of subjects), neutropenia (4.9% of subjects), ALT increased (4.6% of subjects), AST increased (4.3% of subjects), nausea (3.8% of subjects), pneumonia (2.7% of subjects), upper respiratory tract infection (2.2% of subjects), and pyrexia (2.2% of subjects).

TEAEs leading to umbralisib dose interruption related to umbralisib were reported in 131 subjects (35.3%) overall, including 42 subjects (51.2%) with MZL. The most frequently reported TEAEs leading to umbralisib dose interruption related to umbralisib (at least 1% of total pooled subjects) were diarrhea (10.8% of subjects), neutropenia (4.9% of subjects), ALT increased (4.3% of subjects), AST increased (4.0% of subjects), vomiting (4.0% of subjects), nausea (3.2% of subjects), pneumonia (1.3% of subjects), thrombocytopenia (1.3% of subjects), fatigue (1.1% of subjects), and decreased appetite (1.1% of subjects).

The FDA's Assessment:

Overall, all-cause TEAEs leading to umbralisib dose reduction in the safety pool were reported in 39 subjects (10.5%). The most common reasons were diarrhea/colitis (2.2%), nausea (1.6%),

and neutropenia (1.6%). Adverse events leading to umbralisib dose interruption in the safety pool were reported in 162 subjects (43.6%), most often due to diarrhea/colitis (12.3%), vomiting (4.9%), neutropenia (4.9%) and transaminase elevation (4.6%).

In patients with MZL, all-cause TEAEs leading to umbralisib dose reduction were reported in 7 subjects (10.1%). The most common reasons were diarrhea/colitis (2.9%), nausea (1.4%), transaminase elevation (1.4%), and fatigue (1.4%). Adverse events leading to umbralisib dose interruption in this group were reported in 41 subjects (59.4%) overall, which were mostly diarrhea/colitis (20.3%), transaminase elevation (8.7%), and neutropenia (5.8%).

Table below demonstrates the most common TEAEs leading to umbralisib dose reduction and interruption using grouped preferred terms (Section 19.5), which allows for increased sensitivity and informative analyses.

Table 24: Adverse Events Leading to Dose Reduction and Interruption - FDA Review

Outcome/event	UTX-TGR-205 MZL MZL (N = 69) %	Safety pool (N = 371) %
Any TEAE leading to dose reduction	10.1%	10.5%
Reason for dose reduction		
Diarrhea/colitis	2.9%	2.2%
Nausea	1.4%	1.6%
Transaminase elevation	1.4%	1.1%
Headache	0	1.6%
Neutropenia	0	1.6%
Fatigue	1.4%	1.1%
Any TEAE leading to dose interruption	59.4%	43.6%
Reason for dose interruption		

Diarrhea/colitis	20.3%	12.3%
URI	2.9%	2.5%
Vomiting	4.3%	4.9%
Transaminase elevation	8.7%	4.6%
Neutropenia	5.8%	4.9%
Musculoskeletal pain	1.4%	1.7%
Abdominal pain	2.9%	1.8%
Fatigue	1.4%	2.1%
Nausea	4.3%	2.8%
Pneumonia	4.3%	2.7%
Rash	2.8%	1.6%
Sepsis	1.4%	1.9%
Source: FDA review of ADAE dataset		

Significant Adverse Events

The Applicant's Position:

The significant AEs reported are described in other sections of this document.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Treatment-Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Most Frequent TEAEs

Overall, the most common TEAEs (at least 20% of total pooled subjects) were diarrhea (52.3% of subjects), nausea (41.5% of subjects), fatigue (31.8% of subjects), and vomiting (23.2% of subjects) (Table 25). For subjects with MZL, the most common TEAEs were diarrhea (61.0% of subjects), nausea (34.1% of subjects), fatigue (31.7% of subjects), AST increased (28.0% of subjects), ALT increased (24.4% of subjects), headache (23.2% of subjects), decreased appetite (22.0% of subjects), and cough (22.0% of subjects).

Table 25: Summary of Common TEAEs (at Least 10% Total by PT) by SOC and PT (Umbralisib Safety Population)

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System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	MZL (N=69) n (%)	MZL (N=82) n (%)	Total (N=371) n (%)
Any TEAE	69 (100.0)	82 (100.0)	366 (98.7)
Gastrointestinal disorders			
Diarrhea	43 (62.3)	50 (61.0)	194 (52.3)
Nausea	23 (33.3)	28 (34.1)	154 (41.5)
Vomiting	15 (21.7)	16 (19.5)	86 (23.2)
Constipation	6 (8.7)	7 (8.5)	39 (10.5)
Abdominal pain	6 (8.7)	8 (9.8)	38 (10.2)
General disorders and administration site conditions			
Fatigue	21 (30.4)	26 (31.7)	118 (31.8)
Pyrexia	7 (10.1)	10 (12.2)	47 (12.7)
Edema peripheral	11 (15.9)	13 (15.9)	39 (10.5)
Nervous system disorders			
Dizziness	10 (14.5)	13 (15.9)	65 (17.5)
Headache	17 (24.6)	19 (23.2)	60 (16.2)
Infections and infestations			
Upper respiratory tract infection	10 (14.5)	11 (13.4)	46 (12.4)
Metabolism and nutrition disorders			
Decreased appetite	16 (23.2)	18 (22.0)	65 (17.5)
Hypokalemia	6 (8.7)	7 (8.5)	39 (10.5)
Respiratory, thoracic, and mediastinal disorders			
Cough	16 (23.2)	18 (22.0)	72 (19.4)
Investigations			
Alanine aminotransferase increased	17 (24.6)	20 (24.4)	56 (15.1)
Aspartate aminotransferase increased	20 (29.0)	23 (28.0)	55 (14.8)
Blood creatinine increased	8 (11.6)	10 (12.2)	39 (10.5)
Blood and lymphatic system disorders			
Neutropenia	10 (14.5)	11 (13.4)	53 (14.3)
Anemia	6 (8.7)	7 (8.5)	41 (11.1)

Psychiatric disorders			
Insomnia	10 (14.5)	11 (13.4)	47 (12.7)

Source: Table 2.7.4.2.1.2

Abbreviations: MZL, marginal zone lymphoma; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

TEAEs of at Least Grade 3

Overall, 189 subjects (50.9%) had Grade ≥ 3 TEAEs. Of these, 124 subjects (33.4%) had Grade ≥ 3 TEAEs related to umbralisib. The most frequently reported Grade ≥ 3 TEAEs (at least 5% of total pooled subjects) were neutropenia (11.3% of subjects), diarrhea (7.3% of subjects), ALT increased (5.7% of subjects), and AST increased (5.7% of subjects). The most frequently reported Grade ≥ 3 TEAEs related to umbralisib (at least 5% of total pooled subjects) were neutropenia (8.9% of subjects), diarrhea (6.7% of subjects), ALT increased (5.4% of subjects), and AST increased (5.4% of subjects).

Adverse Drug Reactions

The Umbralisib Safety Population, supported predominantly by the pivotal Study UTX-TGR-205, provide the primary source for ADR determination. Safety data were reviewed systematically for TEAEs irrespective of Investigator's causality assessment, which includes serious TEAEs, TEAEs leading to dose modification, and AESIs, observed in the Umbralisib Safety Population. This was accompanied by individual case reviews of selected events. New or worsening laboratory parameters were also analyzed. Each TEAE and laboratory parameter evaluated for ADR determination were assessed against pre-specified criteria as follows: frequency, severity, and seriousness; clinical experience to date with umbralisib; observed dose-response relationship; association with mechanism of action of umbralisib as an inhibitor of PI3K δ and CK1 ϵ ; consistency with non-clinical findings with umbralisib; underlying malignancy, comorbidities, or concurrent illness; and/or clinically meaningful shift for laboratory parameter.

Common adverse reactions reported in $\geq 10\%$ of subjects with MZL, FL, and other hematologic malignancies treated with umbralisib are summarized in Table 26. ADRs of any grade were reported in 351 subjects (94.6%), and ADRs of Grade 3 and Grade 4 were reported in 135 subjects (36.4%) and 31 subjects (8.4%), respectively. The most frequently reported ADRs of any grade ($\geq 20\%$) were diarrhea (52.3%), nausea (41.5%), fatigue (38.8%), musculoskeletal pain (28.6%), and vomiting (23.2%); none of these were of Grade 4.

Table 26: Adverse Reactions Reported in at Least 10% of Subjects With MZL, FL, and Other Hematologic Malignancies (Umbralisib Safety Population)

NDA Multi-disciplinary Review and Evaluation NDA 213176
UKONIQ (umbralisib)

System Organ Class Preferred Term or Groups	Umbralisib (N=371)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any adverse drug reaction	351 (94.6)	135 (36.4)	31 (8.4)
Blood and lymphatic system disorders			
Anemia ^a	42 (11.3)	18 (4.9)	2 (0.5)
Neutropenia (including febrile neutropenia) ^b	53 (14.3)	34 (9.2)	18 (4.9)
Gastrointestinal disorders			
Abdominal pain ^c	66 (17.8)	7 (1.9)	0
Constipation	39 (10.5)	1 (0.3)	0
Diarrhea	194 (52.3)	27 (7.3)	0
Nausea	154 (41.5)	4 (1.1)	0
Vomiting	86 (23.2)	1 (0.3)	0
General disorders and administration site conditions			
Fatigue ^d	144 (38.8)	15 (4.0)	0
Peripheral edema ^e	50 (13.5)	2 (0.5)	0
Pyrexia	47 (12.7)	0	0
Hepatobiliary disorders			
Transaminase elevation ^f	63 (17.0)	24 (6.5)	4 (1.1)
Infections and infestations			
Upper respiratory tract infection ^g	49 (13.2)	0	0
Investigations			
Blood creatinine increased	39 (10.5)	1 (0.3)	0
Metabolism and nutrition disorders			
Decreased appetite	65 (17.5)	5 (1.3)	0
Hypokalemia	39 (10.5)	9 (2.4)	1 (0.3)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain ^h	106 (28.6)	7 (1.9)	0
Psychiatric disorders			
Insomnia	47 (12.7)	1 (0.3)	0
Respiratory, thoracic, and mediastinal disorders			

NDA Multi-disciplinary Review and Evaluation NDA 213176
UKONIQ (umbralisib)

System Organ Class Preferred Term or Groups	Umbralisib (N=371)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Dyspnea ⁱ	37 (10.0)	6 (1.6)	0
Skin and subcutaneous tissue disorders			
Rash ^j	52 (14.0)	8 (2.2)	0

Source: Table 2.7.4.6.1

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma.

Note: Summary based on treatment-emergent adverse event with the worst grade. Any grade=Grades 1 to 4 or missing.

Grouped term for reactions with multiple preferred terms:

^a Anemia and hemoglobin decreased

^b Neutropenia and febrile neutropenia

^c Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness

^d Fatigue and asthenia

^e Edema peripheral and peripheral swelling

^f Alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, and hepatic enzyme increased

^g Upper respiratory tract infection and viral upper respiratory tract infection

^h Musculoskeletal pain, back pain, myalgia, pain in extremity, musculoskeletal discomfort, musculoskeletal chest pain, neck pain, groin pain, spinal pain, bone pain, non-cardiac chest pain, pain in jaw, and limb discomfort

ⁱ Dyspnea and dyspnea exertional

^j Rash, rash maculopapular, rash pruritic, rash erythematous, and rash macula

The FDA's Assessment:

Based on the use of grouped of preferred terms (Section 19.5), the following table provides a summary of the most common adverse events.

Overall, in the safety pool, the most common TEAEs (at least 10% of total pooled subjects) were diarrhea/colitis (52.3%), nausea (41.5%), fatigue (39.4%), musculoskeletal pain (28.3%) and vomiting (23.2%). For patients with MZL, the most common TEAEs were diarrhea/colitis (62.3%), musculoskeletal pain (35%), nausea (33.3%), increased transaminases (30.4%), and rash (30%).

The incidence of Grade ≥3 adverse events was 51.2% and 59.4% in the safety pool and patients with MZL, respectively. The most common Grade ≥3 adverse events in the safety pool and in patients with MZL were neutropenia (11.3%, 13%), diarrhea/colitis (8.4%, 11.6%) and increased transaminases (6.5%, 11.6%), respectively.

Table 27: Summary of Common (≥10%) Treatment Emergent Adverse Events – FDA Review

NDA Multi-disciplinary Review and Evaluation NDA 213176
UKONIQ (umbralisib)

Preferred Term	UTX-TGR-205 MZL (N=69) n (%)		Safety Pool (N=371) n (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any TEAE	69 (100.0)	41 (59.4)	366 (98.7)	190 (51.2)
Diarrhea/Colitis	43 (62.3)	8 (11.6)	194 (52.3)	31 (8.4)
Musculoskeletal pain	24 (35)	2 (3)	104 (28.3)	9 (2.4)
Nausea	23 (33.3)	0	154 (41.5)	4 (1)
Transaminase increased	21 (30.4)	8 (11.6)	64 (17.2)	24 (6.5)
Rash	20 (30)	3 (4.3)	70 (18.9)	10 (3)
Edema	17 (24.6)	2 (3)	58 (15.6)	5 (1.3)
Headache	17 (24.6)	2 (3)	61 (16.4)	5 (1.3)
Decreased appetite	16 (23.2)	1 (1.4)	65 (18)	5 (1.3)
Cough	17 (24.6)	0	85 (23)	0
Vomiting	16 (23.2)	0	87 (23.2)	1 (1)
Upper respiratory tract infection	15 (22)	0	57 (16.4)	0
Abdominal pain	10 (14.5)	1 (1.4)	68 (18.3)	7 (2)
Neutropenia	10 (14.5)	9 (13)	53 (14.2)	42 (11.3)
Dizziness	10 (14.5)	0	68 (18.3)	0
Insomnia	10 (14.5)	0	48 (13)	1 (1)
Blood creatinine increased	8 (11.6)	0	40 (10.8)	1 (1)
Confusional state	8 (11.6)	0	17 (4.6)	0
Hyperuricemia	8 (11.6)	1 (1.4)	14 (3.8)	4 (1.1)
Dyspnea	7 (10.1)	0	39 (10.5)	6 (2)
Pyrexia	7 (10.1)	0	47 (12.7)	4 (1.1)
Urinary tract infection	7 (10.1)	1 (1.4)	29 (7.8)	7 (2)
Taste disorder	12 (17.3)	0	40 (10.8)	0
Fatigue	29 (42)	2 (3)	146 (39.4)	15 (4)
Hypokalemia	6 (8.7)	1 (1.4)	39 (10.5)	10 (3)

Abbreviations: MZL, Marginal zone lymphoma; PT, preferred term; TEAE, treatment-emergent adverse event

Source: FDA review of the ADAE dataset

Laboratory Findings

The Applicant's Position:

Hematological and chemistry parameters were reviewed as CTCAE version 4.03-derived new or worsening abnormalities from baseline. The frequency cut-off for inclusion in the laboratory abnormality ADR table was based on frequency and severity. Based on the observed data with umbralisib, the cutoff was determined to be $\geq 20\%$ any grade plus $\geq 5\%$ Grade ≥ 3 new or worsening laboratory abnormality, and these data are provided in Table 28.

Table 28: Treatment-emergent Laboratory Abnormalities With Umbralisib (at Least 20% of Subjects and at Least 5% of Subjects With Grade ≥ 3) (Umbralisib Safety Population)

Laboratory Parameter	Number of Evaluable Subjects	Umbralisib (N=371)		
		Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematology				
Leukocytes decreased	369	143 (38.8)	19 (5.1)	7 (1.9)
Neutrophils decreased	368	135 (36.7)	33 (9.0)	30 (8.2)
Hemoglobin decreased	369	112 (30.4)	20 (5.4)	0
Lymphocytes decreased	369	89 (24.1)	37 (10.0)	16 (4.3)
Chemistry				
Aspartate aminotransferase increased	369	111 (30.1)	22 (6.0)	0
Alanine aminotransferase increased	369	107 (29.0)	21 (5.7)	4 (1.1)

Source: Table 2.7.4.6.3.1

The FDA's Assessment:

In the MZL cohort, the most common grade 3-4 lab shift abnormalities were neutropenia (19%), ALT increase (10%) and AST increase (10%). No patient developed grade 3-4 increase in creatinine despite a large number of patients with any grade increase in creatinine. A similar trend was seen in the safety pool.

Table 29: Treatment Emergent Laboratory Abnormalities - FDA Laboratory Shift Analysis

Laboratory Parameter	UTX-TGR-205		Safety Pool	
	MZL (N = 69)		(N = 371)	
	%		%	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematologic				
Neutropenia	33%	19%	36%	17%
Thrombocytopenia	30%	6%	25%	5%
Anemia	22%	4%	30%	5%
Chemistry				
Creatinine increase	84%	0	77%	0
ALT increase	43%	10%	29%	7%
AST increase	41%	10%	30%	6%
ALT, alanine aminotransferase; AST, aspartate aminotransferase Source: FDA review of ADLB (laboratory) dataset				

Vital Signs

The Applicant's Position:

Vital sign results were not pooled due to the heterogeneity of assessment schedule across studies. In general, the changes from baseline were not clinically meaningful. Of the TEAEs associated with vital signs, the most frequently reported in the Umbralisib Safety Population were pyrexia (12.7%), hypertension (7.0%), and weight decreased (7.0%).

The FDA's Assessment:

The FDA agrees with the Applicant's position

Electrocardiograms (ECGs)

The Applicant's Position:

ECG data were summarized by study for Study TGR-1202-101 and Study TGR-1202-102. No pooled analyses based on IDB were performed due to limited data and heterogeneity of assessment schedules across studies. Of the TEAEs associated with ECG parameters, the most frequently (at least 1% total) reported in the Umbralisib Safety Population were atrial fibrillation (1.3%) and sinus tachycardia (1.1%). No TEAEs of supraventricular tachycardia or ventricular extrasystoles were reported.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

QT

The Applicant's Position:

A concentration-QTc analysis based on data from the 32 subjects of Cohort S (umbralisib monotherapy) in Study TGR-1202-102 was conducted to characterize the relationship of the change from baseline QTc interval with umbralisib plasma concentration. The concentration QTc analysis did not reveal a significant relationship or risk of ≥ 20 ms corrected QT interval by Fredericia (QTcF) prolongation at the time points evaluated. The predicted Δ QTcF was higher at the 4-hour post dose time point than for other time points, reaching 3.6 ms with a 90% CI upper bound of 10.2 ms.

The FDA's Assessment:

The FDA disagrees with the Applicant's position that there is no risk of QTc prolongation with umbralisib. The Applicant's exposure-corrected QT interval (QTc) analyses were conducted using steady state exposure ($C_{max,ss}$) data in Study TGR-1202-102. The geometric mean C_{max} on Cycle 2 Day 1 was 4012 ng/mL (n=20), which was lower than the therapeutic exposure (7266 ng/mL) obtained from PPK analysis. The 1200 mg QD dose group in Study TGR-1202-102 did not provide higher exposure (4172 ng/mL) as compared to the 800 mg QD dose group. Thus, the Applicant's QT assessment was not adequate to extrapolate the risk of QTc prolongation to the higher exposure range. The FDA agrees that there were no large mean increases (i.e., 20 msec) with umbralisib treatment.

Immunogenicity

The Applicant's Position:

There are no immunogenicity data about umbralisib in this application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.4. Analysis of Submission-Specific Safety Issues

Overall, TEAEs of special interest were reported in 288 subjects (77.6%), including 71 subjects (86.6%) with MZL (Table 30).

Table 30: Summary of TEAEs of Special Interest (at Least 5% Total by PT) by Category and PT (Umbralisib Safety Population)

AE Special Interest/ Preferred Term	UTX-TGR-205	Pooled	
	MZL (N=69) n (%)	MZL (N=82) n (%)	Total (N=371) n (%)
At least 1 TEAE of special interest	62 (89.9)	71 (86.6)	288 (77.6)
Diarrhea			
Diarrhea	43 (62.3)	50 (61.0)	194 (52.3)
Hepatic dysfunction			
Alanine aminotransferase increased	17 (24.6)	20 (24.4)	56 (15.1)
Aspartate aminotransferase increased	20 (29.0)	23 (28.0)	55 (14.8)
Neutropenia			
Neutropenia	10 (14.5)	11 (13.4)	53 (14.3)
Rash			
Rash	7 (10.1)	7 (8.5)	31 (8.4)
Anemia			
Anemia	6 (8.7)	7 (8.5)	41 (11.1)
Thrombocytopenia			
Thrombocytopenia	5 (7.2)	5 (6.1)	34 (9.2)
Pneumonia			
Pneumonia	5 (7.2)	5 (6.1)	22 (5.9)

Source: Table 2.7.4.2.4.6.1

Abbreviations: AE, adverse event; MZL, marginal zone lymphoma; PT, preferred term; TEAE, treatment-emergent adverse event.

Note: AE sorting is done by decreasing frequency of system organ class and AE of special interest based on the total column.

8.2.5.1 Diarrhea

The Applicant's Position:

Overall in the Umbralisib Safety Population, the most frequently reported TEAE of special interest was diarrhea (194 subjects [52.3%]), including 50 subjects (61.0%) with MZL (Table 30). A total of 27 subjects (7.3%) had Grade ≥ 3 diarrhea, including 8 subjects (9.8%) with MZL. A total of 165 subjects (44.5%) had a TEAE of diarrhea that was considered related to umbralisib, including 41 subjects (50.0%) with MZL. Of these, 25 subjects (6.7%) reported Grade ≥ 3 diarrhea related to umbralisib, including 8 subjects (9.8%) with MZL. There were no Grade 4 TEAEs of diarrhea.

8.2.5.2 Hepatic Dysfunction

The Applicant's Position:

Overall in the Umbralisib Safety Population, ALT increased was reported by a total of 56 subjects (15.1%), including 20 subjects (24.4%) with MZL (Table 30). A total of 21 subjects (5.7%) had Grade ≥ 3 ALT increased, including 7 subjects (8.5%) with MZL. A total of 45 subjects (12.1%) had a TEAE of ALT increased that was considered related to umbralisib, including 20 subjects (24.4%) with MZL. Of these, 20 subjects (5.4%) reported Grade ≥ 3 ALT increased related to umbralisib, including 6 subjects (7.3%) with MZL. Grade 4 TEAEs of ALT increased were reported by a total of 4 subjects (1.1%), including 1 subject (1.2%) with MZL.

Overall in the Umbralisib Safety Population, AST increased was reported by a total of 55 subjects (14.8%), including 23 subjects (28.0%) with MZL (Table 30). A total of 21 subjects (5.7%) had Grade ≥ 3 AST increased, including 7 subjects (8.5%) with MZL. A total of 45 subjects (12.1%) had a TEAE of AST increased that was considered related to umbralisib, including 21 subjects (25.6%) with MZL. Of these, 20 subjects (5.4%) reported Grade ≥ 3 AST increased related to umbralisib, including 6 subjects (7.3%) with MZL. There were no Grade 4 TEAEs of AST increased.

8.2.5.3 Neutropenia

The Applicant's Position:

Overall in the Umbralisib Safety Population, neutropenia was reported by a total of 53 subjects (14.3%), including 11 subjects (13.4%) with MZL (Table 30). A total of 42 subjects (11.3%) had Grade ≥ 3 neutropenia, including 10 subjects (12.2%) with MZL. A total of 42 subjects (11.3%) had a TEAE of neutropenia that was considered related to umbralisib, including 8 subjects (9.8%) with MZL. Of these, 33 subjects (8.9%) reported Grade ≥ 3 neutropenia related to umbralisib, including 7 subjects (8.5%) with MZL. Grade 4 TEAEs of neutropenia were reported by a total of 18 subjects (4.9%), including 5 subjects (6.1%) with MZL.

8.2.5.4 Rash

The Applicant's Position:

Overall in the Umbralisib Safety Population, rash was reported by a total of 31 subjects (8.4%), including 7 subjects (8.5%) with MZL (Table 30). A total of 2 subjects (0.5%) had Grade ≥ 3 rash, none were subjects with MZL. There were no Grade 4 TEAEs of rash. There were no TEAEs of rash that were considered related to umbralisib.

8.2.5.5 Anemia

The Applicant's Position:

Overall in the Umbralisib Safety Population, anemia was reported by a total of 41 subjects (11.1%), including 7 subjects (8.5%) with MZL (Table 30). A total of 18 subjects (4.9%) had Grade ≥ 3 anemia, including 5 subjects (6.1%) with MZL. A total of 22 subjects (5.9%) had a TEAE of anemia that was considered related to umbralisib, including 3 subjects (3.7%) with MZL. Of these, none of the Grade ≥ 3 TEAEs of anemia were considered related to umbralisib. Grade 4 TEAEs of anemia were reported by a total of 2 subjects (0.5%), including 1 subject (1.2%) with MZL.

8.2.5.6 Thrombocytopenia

The Applicant's Position:

Overall in the Umbralisib Safety Population, thrombocytopenia was reported by a total of 34 subjects (9.2%), including 5 subjects (6.1%) with MZL (Table 30). A total of 11 subjects (3.0%) had Grade ≥ 3 thrombocytopenia, including 2 subjects (2.4%) with MZL. A total of 22 subjects (5.9%) had a TEAE of thrombocytopenia that was considered related to umbralisib, including 4 subjects (4.9%) with MZL. Of these, none of the Grade ≥ 3 TEAEs of thrombocytopenia were considered related to umbralisib. Grade 4 TEAEs of thrombocytopenia were reported by a total of 8 subjects (2.2%), including 2 subjects (2.4%) with MZL.

8.2.5.7 Pneumonia

The Applicant's Position:

Overall in the Umbralisib Safety Population, pneumonia was reported by a total of 22 subjects (5.9%), including 5 subjects (6.1%) with MZL (Table 30). A total of 11 subjects (3.0%) had Grade ≥ 3 pneumonia, including 2 subjects (2.4%) with MZL. Overall, there was 1 Grade 4 TEAE of pneumonia reported by 1 subject (0.3%); there were no subjects with MZL who reported a Grade 4 TEAE of pneumonia. There were no TEAEs of pneumonia that were considered related to umbralisib.

The FDA's Assessment:

The information below summarizes the FDA review of adverse events of special interest with umbralisib and include diarrhea/colitis, hepatotoxicity, rash, neutropenia, anemia,

thrombocytopenia, pneumonia, infection, and pneumonitis.

Table 31: Summary of Adverse Events of Special Interest – FDA Review

AE Special Interest/ Preferred Term	UTX-TGR-205		Safety Pool	
	MZL (N=69) n (%)		(N=371) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
At least 1 TEAE of special interest	62 (89.9)	30 (43.5)	288 (77.6)	166 (44.8)
Diarrhea/colitis	43 (62.3)	5 (7.2)	194 (52.3)	27 (7.3)
Hepatotoxicity	21 (30.4)	8 (12)	70 (18.9)	25 (6.7)
Neutropenia	11 (16)	9 (13)	53 (14.3)	52 (14.1)
Rash	42 (60.9)	6 (9)	70 (18.9)	10 (2.6)
Anemia	6 (8.7)	4 (5.7)	42 (11.3)	20 (5.4)
Thrombocytopenia	6 (8.7)	2 (2.9)	35 (9.4)	11 (3)
Pneumonia	6 (8.7)	2 (2.9)	24 (6.5)	13 (3.5)
Sepsis	3 (4.3)	3 (4.3)	8 (2.2)	8 (2.2)
Pneumonitis	2 (2.9)	1 (1.4)	4 (1.1)	2 (0.5)
Source: FDA review of ADAE dataset				

Table 32: Incidence of Adverse Events of Special Interest by Prior Lines of Therapy - FDA Review

Adverse events of special interest	All Heme N=371				Risk Difference
	# prior therapies				
	≤2 N=189		≥3 N=182		
	n	%	n	%	
Diarrhea/colitis					
All-grade events	106	56%	88	48%	8
Grade ≥3	23	12%	7	4%	8
Hepatotoxicity					

Adverse events of special interest	All Heme N=371				Risk Difference
	# prior therapies				
	≤2 N=189		≥3 N=182		
	n	%	n	%	
All-grade events*	65	34%	49	27%	7
Grade ≥3*	17	9%	8	4%	5
Pneumonitis					
All-grade events	4	2%	0	0	2
Grade ≥3	2	1%	0	0	1
Rash					
All-grade events	44	23%	21	12%	11
Grade ≥3	8	4%	2	1%	3
Infection					
All-grade events	85	45%	75	41%	4
Grade ≥3	17	9%	20	11%	-2
*Based on laboratory data					
Source: FDA review of ADAE and ADLB datasets					

Adverse Events of Special Interest

The FDA's incidence of AESIs, differed in some instances due to grouping of preferred terms, consistent throughout this review. In the following section, the FDA considerations are provided for each AESI. Any grade AESIs occurred in 62 patients (90%) with MZL in the UTZ-TGR-205 MZL cohort (N = 69).

Diarrhea

Diarrhea or colitis is an important identified risk for patients who receive treatment with umbralisib. The Applicant identified events of diarrhea or colitis based on selected MedDRA preferred terms for diarrhea or colitis. Because the clinical presentation of diarrhea or colitis overlaps, FDA used a grouped MedDRA PT (Appendix 19.4) to evaluate the incidence and pattern of umbralisib-associated diarrhea or colitis.

Diarrhea/colitis was the most common toxicity reported in the safety pool (52.3%), as well as the MZL population in UTX-TGR-205 (62.3%). Grade 3 diarrhea/colitis occurred in 7.3% and 7.2% of patients in the safety pool and MZL cohort, respectively.

Based on the 371 patients in the safety pool, the incidence of any grade diarrhea/colitis reported as a SAE was 3.2% (2.4% grade ≥3). Diarrhea or colitis led to dose interruption in 12.3%, dose reduction in 2.2%, and treatment discontinuation in 4.8% of patients. It is one of

the most common reasons for treatment modification. For all grade diarrhea or colitis, the median time to onset was 1 month, with 75% occurring within 2.8 months. For patients with grade ≥ 3 diarrhea or colitis, the median time to onset was 4.5 months, with 75% occurring within 8 months.

Based on the data, there is no established standard of treatment for umbralisib-associated diarrhea or colitis. Labeling will include a Warning and Precaution for diarrhea or colitis and dose modifications to ensure safe use of the drug. Patients should be aware that umbralisib should be discontinued in the event of severe diarrhea or colitis.

Hepatotoxicity

Based on lab-shift analyses in the safety pool population (N = 371), any grade transaminase elevation occurred in 29% (ALT) and 30% (AST) of the population, and grade 3-4 toxicities were 7% and 6% respectively. These incidences were higher in the UTX-TGR-205 MZL population in which 43% (ALT) and 41% (AST) of patients experienced any grade AST/ALT elevation with 10% reaching severity of grade 3-4. In the safety pool, the median onset of grade 3-4 hepatotoxicity was 2 months, with 75% occurring by 3 months. Transaminase elevation led to umbralisib dose interruption in 4.6%, dose reduction in 1.1%, and treatment discontinuation in 3.2%. The Applicant reported no cases of liver failure in patients with hematologic malignancies. The study did not enroll patients with moderate or severe hepatic dysfunction.

Given the concerns for hepatotoxicity with umbralisib, labeling will include hepatotoxicity as a Warning and Precaution to ensure safe use of umbralisib. The pattern of umbralisib-associated hepatotoxicity, specific monitoring procedures, and dose modifications will need to be included in labeling to inform healthcare providers and patients.

Rash

In the safety pool, one patient developed a fatal case of Grade 3 exfoliative dermatitis. The event of exfoliative dermatitis led to bacteremia and sepsis and multi-organ failure. In the MZL cohort of study UTX-TGR-205, 39% of the patients developed all grade rash. The incidence in the safety pool of any grade rash was 18.9%, with 3% experiencing Grade 3 rash events. Rash lead to umbralisib dose interruption in 1.6% of the patients.

In addition, severe cutaneous reactions, including SJS, TEN, and DRESS, are a known class effect with PI3K inhibitors. Based on a fatal case of exfoliative dermatitis with umbralisib, the incidence of cutaneous reactions, and the known class effect, a Warning and Precaution for severe cutaneous reactions should be included in labeling.

Neutropenia

Based on lab-shift analyses in the safety pool population, any grade neutropenia occurred in 36% of the population, and grade 3-4 neutropenia of 17%. In patients with MZL, any grade

neutropenia was 33%, with 19% being Grade 3-4.%

For the 371 patients in the safety pool, the median time to onset of grade 3-4 neutropenia was 2 months, with 75% occurring by 3.7 months. Neutropenia led to umbralisib dose interruption in 5%, reduction in 2%, and discontinuation in 1%.

Given the concerns for Grade 3-4 neutropenia coupled with the potential risk for infection with umbralisib, labeling will include neutropenia as a Warning and Precaution to ensure safe use of umbralisib. The pattern of umbralisib-associated neutropenia, monitoring procedures, and dose modifications will need to be included in labeling to inform healthcare providers and patients.

Anemia

Based on lab-shift analysis data in the safety pool population, any grade anemia occurred in 30% of the population and grade 3-4 anemia in 5%. In patients with MZL, any grade anemia was 22%, with 4% being Grade 3-4.

Thrombocytopenia

Based on lab-shift analysis data in the safety pool population, any grade thrombocytopenia occurred in 25% of the population and grade 3-4 thrombocytopenia in 5%. In patients with MZL, any grade thrombocytopenia was 30%, with 6% being Grade 3-4. In patients that developed thrombocytopenia, there was no association with clinically significant bleeding event.

Pneumonia

Overall in the umbralisib safety population, pneumonia was reported 6.5% of the patients, including 3.5% with Grade ≥ 3 pneumonia. In the MZL cohort of study UTX-TGR-205, 8.7% and 2.9% of the patients had any grade and Grade ≥ 3 pneumonia, respectively. Incidence of SAE in the safety population and MZL cohort were 0.8% and 4.3%, respectively.

Infection

Though not included as an AESI, infection is a significant issue with umbralisib use. In the safety pool of 371 patients, there were 160 patients (43%) with the reported event of infection, with 37 (20%) of grade 3-4 severity. There were two deaths attributable to infection. These included pneumonia legionella and sepsis. Sepsis occurred in eight patients (2%) and led to two deaths.

Given the concerns for the risk of infection and the incidence of Grade 3-4 neutropenia, labeling will include infection as a Warning and Precaution to ensure safe use of umbralisib.

Pneumonitis

In the Safety Population, pneumonitis was reported in 1% of patients, with <1% being Grade 3. Pneumonitis was reported as a SAE and led to treatment discontinuation in 2 patients (<1%) each, respectively.

8.2.5. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable.

The FDA's Assessment:

There were no clinical outcome or patient-reported outcome data submitted with this application.

8.2.6. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses were conducted to identify potential safety issues restricted to particular subpopulations; no clinically meaningful differences were observed as compared to the overall Umbralisib Safety Population.

Sex

Overall, diarrhea, nausea, and vomiting were reported more frequently in female subjects than male subjects. Neutropenia was reported with a similar incidence between male and female subjects overall but more frequently in male than female subjects with MZL. The observed differences by gender were not considered clinically meaningful.

Age

Overall, Grade ≥ 3 TEAEs, serious TEAEs, and TEAEs leading to discontinuation of umbralisib were reported more frequently in subjects in the age group ≥ 65 years than subjects < 65 years (54.5% versus 46.3%, 31.6% versus 17.9%, and 18.2% versus 11.7%, respectively). Nausea was reported more frequently in subjects in the age group ≥ 65 years than subjects < 65 years (44.0% versus 38.3%) overall and in subjects with MZL (41.2% versus 22.6%). Neutropenia and anemia were reported more frequently in subjects in the age group ≥ 65 years than subjects < 65 years (17.2% versus 11.7% and 15.3% versus 6.2%, respectively) overall and in subjects with FL (18.9% versus 8.2% and 14.9% versus 4.1%, respectively). The observed differences by age were not considered clinically meaningful.

Race

The incidences of TEAEs, serious TEAEs, and TEAEs leading to discontinuation of umbralisib were similar between White and Non-White subjects. Vomiting was reported more frequently in Non-White than White subjects (28.1% versus 22.1%) overall and in subjects with MZL (26.7%

versus 17.9%). The incidence of hepatic dysfunction and rash were also higher in Non-White than White subjects (23.4% versus 17.9% and 18.8% versus 13.0%, respectively). The observed differences by race were not considered clinically meaningful.

The FDA's Assessment:

There was limited representation of racial or ethnic minorities in the MZL population of UTX-TGR-205 with few African American (7.2%) or Asian (2.9%) patients to allow generalization of these results. In addition, only 2.9% were of Hispanic/Latino ethnicity. This reflects an overall limitation in the data as it applies to the US population and a postmarketing commitment was issued to address this concern (Section 13).

8.2.7. Specific Safety Studies/Clinical Trials

The Applicant's Position:

There were no special safety studies or clinical trials in this application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

There were no analyses for second primary malignancies in the application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

Umbralisib has not been studied in pregnant or lactating women. Based on findings in animals and its mechanism of action, umbralisib can cause fetal harm when administered to a pregnant woman. The presence of umbralisib in human milk and its effects on the breastfed child or on milk production have not been investigated.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

There were no children enrolled in any study submitted with this application. The safety of umbralisib in pediatric patients has not been established.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Two subjects reported an accidental overdose as a TEAE with one subject taking 1600 mg and the other subject taking 1200 mg instead of 800 mg. For both subjects, no action was taken.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable. Umbralisib is not currently registered or approved in the US or in any other country.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.10. Integrated Assessment of Safety

The Applicant's Position:

The safety of single agent umbralisib was evaluated in 371 subjects, including 82 subjects with MZL. Key safety findings were as follows:

- Death due to TEAEs were reported in 4 subjects (1.1%), and none were in subjects with MZL.

- The common TEAEs of diarrhea, nausea, fatigue, and vomiting were reported at similar rates across duration of exposure groupings suggesting that these TEAEs occurred at generally the same rate regardless of the duration of exposure to umbralisib.
- Common ADRs of any grade ($\geq 10\%$) were reported in 94.6% of subjects, and ADRs of Grade 3 and Grade 4 were reported in 36.4% and 8.4% of subjects, respectively. The most frequently reported adverse reactions of any grade ($\geq 20\%$) were diarrhea (52.3%), nausea (41.5%), fatigue (38.8%), musculoskeletal pain (28.6%), and vomiting (23.2%); none of these were of Grade 4.
- Overall, TEAEs of special interest were reported in 77.6% of subjects. The most frequently reported TEAEs of special interest (at least 10% of total pooled subjects) were diarrhea (52.3% of subjects), ALT increased (15.1% of subjects), AST increased (14.8% of subjects), neutropenia (14.3% of subjects), and anemia (11.1% of subjects).
- The most frequently reported laboratory abnormalities with umbralisib treatment ($>30\%$ of subjects and at least 5% of subjects with Grade ≥ 3) were leukocytes decreased (38.8%, Grade 3: 5.1%), neutrophils decreased (36.7%, Grade 3: 9.0%), hemoglobin decreased (30.4%, Grade 3: 5.4%), and AST increased (30.1%, Grade 3: 6.0%).

In conclusion, single agent umbralisib was well tolerated and had a manageable safety profile in the overall and MZL populations.

The FDA's Assessment:

The FDA agrees with the Applicant's position that the safety data demonstrates that umbralisib demonstrated a tolerable safety profile in patients with marginal zone lymphoma. Although, given the median exposure of 9.4 months in patients with MZL and approximately 6 months in patients with hematologic malignancies, there is limited data to support longer-term safety.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There are no major statistical issues identified from this submission. The trials included in the review of this application were designed to be single arm open-label studies with different study objectives. No statistical inference on comparison was conducted. The primary efficacy endpoint was the overall response rate (CR + PR). The single-arm aspect of the analyses limits the ability to perform any comparative evaluations.

There were insufficient number of patients in the race and ethnicity demographic subgroups to provide an assessment of efficacy in this patient subpopulation.

In the absence of a control arm, it was difficult to interpret the time-to-event endpoint of PFS in these trials. The results of the analysis were descriptive and considered exploratory.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The benefit-risk assessment is favorable for umbralisib for the treatment of adult patients with relapsed or refractory marginal zone lymphoma who have received one prior systemic therapy, including an anti-CD20-based regimen.

Efficacy:

Efficacy of umbralisib in adult patients with previously treated marginal zone lymphoma (MZL) is based on the results from a single-arm cohort of Study UTX-TGR-205, a multicenter, single-arm, open-label, multi-cohort trial, which included 69 patients with MZL. The scheduled umbralisib dose was 800 mg by mouth daily until progressive disease or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) based on the 2007 International Working Group criteria using computerized tomography (CT). Among the 69 patients with MZL, the median follow-up time was 20.3 months (range 15.0 to 28.7 months). The ORR per IRC was 49% (95% CI: 37.0, 61.6], with 16% achieving a complete response. The median duration of response was not reached.

Safety:

The safety profile was supported by analysis of the 69 patients with marginal zone lymphoma from the study UTX-TGR-205 and a combined safety database of 371 patients with hematologic malignancies [marginal zone lymphoma (22%), follicular lymphoma (40%), diffuse large B-cell lymphoma or mantle cell lymphoma (20%), and other hematologic malignancies (18%)] who received umbralisib doses $\geq$ 800 mg daily.

In the 69 patients with MZL, the median duration of treatment was 9.4 months (range 5 days to 23 months) and the most common adverse events ($\geq$ 20% of patients) were increased creatinine, diarrhea-colitis, AST/ALT increased, fatigue, neutropenia, nausea, musculoskeletal pain, thrombocytopenia, cough, headache, rash, decreased appetite, upper respiratory tract infection, anemia, edema, and vomiting. Grade $\geq$ 3 adverse events occurred in 62% and those occurring in at least 5% of the MZL population included diarrhea-colitis, AST/ALT increased, and neutropenia. Adverse events that led to treatment discontinuation occurred in 23% of patients, most often due to AST/ALT increased and diarrhea-colitis.

The primary safety issues identified with umbralisib include serious, including fatal, infections and cutaneous reactions, and serious diarrhea or colitis, hepatotoxicity, and neutropenia. In the 371 patients with hematologic malignancies, 51% of patients experienced a grade 3 or 4

toxicity, the most common including neutropenia (17%), diarrhea-colitis (8%), and increased AST/ALT (6%). Fifteen percent of patients discontinued umbralisib due to an adverse event, most often due to diarrhea-colitis and increased AST/ALT.

Benefit-Risk:

In the single-arm cohort with 69 patients with MZL, patients had to of received prior treatment with 1 or more lines of therapy, including at least 1 anti-CD20-based regimen. The median number of prior systemic therapies was 2 (range 1 to 6) with 22% refractory to their last therapy. The ORR of 49% with associated durability and a tolerable safety profile constitutes a meaningful clinical benefit and a favorable benefit-risk for these patients. To support accelerated approval, the efficacy data is considered in the context of available therapy for patients with MZL in the 2nd line setting and beyond. Available therapy includes rituximab and the immunotherapy combination rituximab plus lenalidomide, which provides response rates ranging from 44% to 65% with associated durability (Table 1). Thus, the ORR of 49% with durability for umbralisib provides data to support a clinically meaningful therapeutic benefit in the context of available therapy for patients with relapsed or refractory MZL in the 2nd line setting and beyond.

Therefore, the benefit-risk of umbralisib is deemed favorable to support accelerated approval under 21 CFR 314.510 Subpart H for the following indication:

- Treatment of adult patients with relapsed or refractory marginal zone lymphoma who have received at least one prior anti-CD20-based regimen.

X

X

Laura Fernandes, PhD
Primary Statistical Reviewer

Yu-Te Wu, PhD
Statistical Team Leader

X

X

Candis Morrison, PhD, CRNP
Primary Clinical Reviewer

Nicholas Richardson, DO, MPH
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented to the Oncologic Drugs Advisory Committee or other external consultants because umbralisib is not first-in-class, and the application did not raise new efficacy or safety issues for the recommended indications.

10 Pediatrics

The Applicant's Position:

The efficacy and safety of umbralisib in pediatric patients have not been studied. Umbralisib has an orphan drug designation for treatment of MZL based on Request # 2019-6800 for splenic marginal zone, Request # 2019-6874 for extranodal MZL, and Request # 2019-6875 for nodal MZL were granted on 11 April 2019. Due to the orphan drug designation of umbralisib for MZL, it is exempt from Pediatric Research Equity Act requirements. This information was submitted in Section 1.9.1 of the NDA Application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

11 Labeling Recommendations

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

Data:

Summary of Significant Labeling Changes		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Highlights of Prescribing Information		FDA revised Highlights to align with Format and Content with Selected Requirements of Prescribing Information (SRPI) as per regulations (21 CFR 201.56 and 201.57) and FDA Guidances.
1. Indications and Usage	UKONIQ is indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.	Indication for marginal zone lymphoma revised based on the trial population enrolled correlating with the data supporting a favorable benefit-risk profile and the comparative efficacy evaluation in the context of available therapy. Accelerated approval language modified per recommendations found in the Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry .
2. Dosage and Administration		
2.1 Recommended	The recommended dose of UKONIQ is	FDA generally agreed with

Dosage	800 mg taken orally (b) (4) (b) (4) once daily (b) (4) (b) (4) with food. Tablets should be swallowed whole. Do not chew the tablets. (b) (4)	proposal but made changes to align with current labeling practices. FDA added dosage instructions for patients who vomit because vomiting occurred in >15% of patients.
2.2 (b) (4) (b) (4)	(b) (4)	Deleted this section (b) (4)
2.3 Dosage Modifications for Adverse Reactions	(b) (4) (b) (4)	Revised tables to add cross-references to related information in sections 5 and 6 and removed (b) (4) (b) (4) Added dosage modifications for infections, diarrhea, thrombocytopenia, and severe cutaneous reactions to support new W&P and ARs.
3. Dosage Forms and Strengths	(b) (4) green, film-coated, oval-shaped, 200-mg tablet (b) (4) with "L474" on one side and plain on the other.	Edited to align with recommendations in Draft Guidance for Industry: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for

		Human Prescription Drug and Biological Products – Content and Format
4. Contraindications	None	FDA agreed.
5. Warnings and Precautions		
5.1 Infections	Serious, including fatal (b) (4), infections occurred in (b) (4) patients treated with UKONIQ (b) (4) (b) (4). For Grade 3 or (b) (4) infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. (b) (4) monitor (b) (4) for CMV infection (b) (4) UKONIQ in patients with a history of CMV infection.	Revised to describe infections in a pooled safety population of 335 adults with hematological malignancies as described in Section 6 Adverse Reactions; this pooled safety approach applies to all adverse reactions described in Section 5 Warnings and Precautions. Added risk mitigation strategies where appropriate per 21 CFR 201.57 (c)(6)(i). Added recommendations for prophylaxis and dosage modifications for <i>Pneumocystis jirovecii</i> (PJP). Added recommendations for monitoring, prophylaxis, and dosage modifications for cytomegalovirus (CMV).
5.2 Neutropenia	Serious (b) (4) neutropenia occurred in (b) (4) patients treated with UKONIQ (b) (4) (b) (4) The median time to onset for neutropenia (b) (4) (b) (4) Withhold, reduce dose, or discontinue UKONIQ depending on the severity and	Revised to describe neutropenia in the pooled safety population and to include recommendations for monitoring.

	persistence of neutropenia	
5.3 Non-Infectious Colitis	Serious non-infectious colitis occurred in (b) (4) patients treated with UKONIQ (b) (4). The median time to onset for any grade (b) (4) (b) (4) (b) (4) Upon resolution (b) (4), resume UKONIQ at a reduced dose. Discontinue UKONIQ for life-threatening colitis.	Added diarrhea to this Warning and Precaution subsection such that it reads: Diarrhea or Colitis. Revised to describe colitis in pooled safety population. Added median time to onset. Modified risk mitigation strategies to include withholding until resolved, providing supportive care, resuming at a reduced dose, and discontinuing for recurrent Grade 3 diarrhea or recurrent colitis of any grade.
5.4 Hepatotoxicity	Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in (b) (4) (b) (4) (b) (4) The median time to onset (b) (4) Monitor hepatic function during treatment with UKONIQ. (b) (4) (b) (4)	Revised to describe hepatotoxicity using the pooled safety population based on the lab dataset, (b) (4)
5.5 Severe Cutaneous		Added a Warning & Precaution subsection for

Reactions		Severe Cutaneous Reactions because there were cases of grade 3 cutaneous reactions, including a fatal case of exfoliative dermatitis. Described these adverse reactions in the pooled safety population and included appropriate risk mitigation strategies.
5.6 Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5		Added a Warning and Precaution subsection based on regulation (21 CFR 201.20(b)).
5.7 Embryo-Fetal Toxicity	Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of umbralisib to pregnant mice during the period of organogenesis (b) (4) (b) (4) (b) (4) (b) (4) Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least (b) (4) after the last dose.	FDA generally agreed but changed the duration of contraception to one month based on information on non-genotoxic drugs in the Guidance to Industry – Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations . Additional edits were made to align with current OOD labeling practices.
6. Adverse Reactions		
6.1 Clinical Trials	(b) (4)	Modified this subsection to

Experience	(b) (4)	align with current OOD labeling practices. Described the pooled safety population of 335 adult patients used to inform the Warnings and Precautions section and based the remaining discussion of safety on the 221 patients with FL and MZ who received the recommended dosage. Added descriptions of serious adverse reactions, fatal adverse reactions, and dosage modifications. Revised laboratory table to populate from the laboratory dataset, (b) (4) (b) (4) Reordered terms in tables to be listed in descending order per 21 CFR 201.57(c)(7)(ii). (b) (4)
(b) (4)		
8. Use in Specific Populations		

8.1 Pregnancy	<u>Risk Summary:</u> Based on findings from animal studies and the mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. <u>Data:</u> Animal Data	Revised risk summary and data based on review of nonclinical data and for consistency with current labeling practices.
8.2 Lactation	<u>Risk Summary:</u> There are no data on the presence of umbralisib in human milk, the effects on the breastfed child, or (b) (4) milk production. Because of the potential for serious adverse reactions from umbralisib in a breastfed child, advise lactating women not to breastfeed while taking UKONIQ and for (b) (4) after the last dose.	Shortened the duration not to breastfeed based on elimination half-life.
8.3 Females and Males of Reproductive Potential	(b) (4)	Revised duration of contraception based on guidance as described in Warnings and Precaution subsection 5.7
8.4 Pediatric Use	Safety and effectiveness of UKONIQ have not been established in pediatric patients.	FDA agreed.
8.5 Geriatric Use	(b) (4)	Modified this section to align with 21 CFR 201.57(c)(9)(v) and draft geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry .

		Revised the percentage of 65 years and older and added 75 years and older for the pooled safety population of 221 patients with MZL or FL who received the recommended dosage.
8.6 Renal Impairment		Added this section to inform healthcare providers (HCP) that no dosage adjustments are recommended in patients with mild or moderate renal impairment and that Ukoniq has not been studied in patients with severe renal impairment based on 21 CFR 201.57(c)(9)(vi).
8.7 Hepatic Impairment		Added this subsection to inform HCP that the recommended dosage has not been established in patients with mild hepatic impairment and that Ukoniq has not been studied in patients with moderate or severe hepatic impairment based on 21 CFR 201.57(c)(9)(vi).
11. Description	(b) (4)	Revised to add pharmacologic or therapeutic class as required by 21 CFR 201.57(c)(12)(i). Used established pharmacologic class (EPC) for consistency with Highlights. Added pKa or pH value for the drug substance based on 21 CFR

		201.57(c)(12)(ii).
12. Clinical Pharmacology		
12.1 Mechanism of Action		(b) (4) Revised to include inhibition of the ABL1 mutant and deleted (b) (4) (b) (4)
12.2 Pharmacodynamics		Added <u>Exposure- Response Relationships</u> heading to describe exposure-response relationship between umbralisib and overall response rate and safety and the time course of pharmacodynamic response based on 21 CFR 201.57 (c)(13)(i)(B). Modified the <u>Cardiac Electrophysiology</u> section to read: “The effect of UKONIQ on QT interval has not been fully characterized.” because the QTc assessment was inadequate to characterize the effects of umbralisib on the QT interval.
12.3 Pharmacokinetics		Revised description of the pharmacokinetics of umbralisib in patients with

	(b) (4)	cancer based on FDA review of the results of the various clinical pharmacology studies. Omitted
		(b) (4)
		Added description of meal as recommended in the Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry.
13. Nonclinical Toxicology		
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Carcinogenicity studies have not been conducted with umbralisib.	Edited the fertility information to reflect the study design and findings.
14. Clinical Studies	(b) (4)	Revised description of the study and population to align with current labeling. Deleted (b) (4)
		(b) (4)
		Removed (b) (4)
		(b) (4)

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		(b) (4)
16. How Supplied/Storage and Handling	(b) (4)	Removed (b) (4)
17. Patient Counseling Information		Edited to align with the remaining sections of labeling, including adding diarrhea, cutaneous reactions, thrombocytopenia, infertility, Yellow No. 5, vomited doses, and modifying advice for contraception.

The Applicant's Position:

The final USPI for UKONIQ reflects several changes from the version originally submitted by the Applicant.

The FDA's Assessment:

The FDA made changes to several sections of the USPI as described above. Additionally, the Applicant proposed Patient Labeling; FDA determined that a Medication Guide would be required in place of the proposed Patient Labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team and Division of Risk Management (DRISK) agree that a REMS is not necessary for the safe use of umbralisib. There are no additional risk management strategies needed beyond recommended labeling and an associated Medication Guide.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends five postmarketing requirements (PMR) and two postmarketing commitments (PMC). The goal of the postmarketing requirements are to confirm clinical benefit in patients with FL and MZL, determine a safe and appropriate dose in patients with moderate to severe hepatic impairment, characterize QTc prolongation risk with umbralisib, and evaluate drug-drug interactions. The postmarketing commitments are to provide information on racial and ethnic minorities consistent with the U.S. FL and MZL population and evaluate the PK of umbralisib with a strong CYP3A inducer.

Postmarketing Requirements

1. Conduct a randomized, Phase 3 clinical trial that verifies and describes the clinical benefit of umbralisib in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for interpretation of the results in these patient populations. Patients should be randomized to receive immunotherapy with or without umbralisib. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate

Final Protocol Submission:	06/2021
Trial Completion:	12/2026
Final Report Submission:	06/2027

2. Conduct a clinical pharmacokinetic study to determine a safe and appropriate dose of umbralisib in patients with moderate to severe hepatic impairment. Design and conduct the study in accordance with the FDA Guidance for Industry titled [Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	09/2021
Trial Completion:	03/2024
Final Report Submission:	09/2024

3. Conduct a clinical study to characterize QTc prolongation risk with umbralisib at steady-state maximal concentrations. The QT study can be conducted as a dedicated study or as a sub-study of ongoing trials. Design and conduct the QT study in accordance with

the ICH E14 Guidances for industry titled [E14 Clinical Evaluation of QT/QTc](#) and [E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers \(R3\) Guidance for Industry](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	06/2021
Study Completion:	12/2026
Final Report Submission:	06/2027

4. Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of umbralisib on the single dose pharmacokinetics of a sensitive CYP2C8, CYP2C9, CYP2C19, and CYP3A and P-gp substrate to address the potential for excessive drug toxicity. Design and conduct the study in accordance with the FDA Guidance for Industry entitled [Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	09/2021
Study Completion:	10/2024
Final Report Submission:	04/2025

5. Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of a strong CYP3A and a moderate CYP2C9 inhibitor on the single dose pharmacokinetics of umbralisib to address the potential for excessive drug toxicity. Design and conduct the study in accordance with the FDA Guidance for Industry entitled [Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	09/2021
Study Completion:	12/2024
Final Report Submission:	06/2025

Postmarketing Commitment

6. Submit a final report containing data from clinical trials, post-marketing reports, compassionate use/expanded access program, real-world evidence, and other sources to further characterize the safety and efficacy of umbralisib monotherapy and in

combination with immunotherapy among U.S. racial and ethnic minority patients with follicular lymphoma or marginal zone lymphoma.

Final Report Submission: 06/2028

7. Conduct a clinical pharmacokinetic study with repeat doses of a strong CYP3A inducer on the single dose pharmacokinetics of umbralisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the study in accordance with the FDA Guidance for Industry entitled [Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry.](#)

Draft Protocol Submission: 06/2021

Final Protocol Submission: 09/2021

Study Completion: 12/2023

Final Report Submission: 06/2024

14 Division Director (DHOT) (NME ONLY)

X

Haleh Saber, PhD, MS

15 Division Director (OCP)

X

Brian Booth, PhD

16 Division Director (DBIX)

X

Thomas Gwise, PhD

17 Division Director (Clinical)

X

Nicole Gormley, MD

18 Office Director (or designated signatory authority)

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

19 Appendices

19.1. References

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19.2. Financial Disclosure

The Applicant's Position:

Covered Clinical Study (Name and/or Number):* UTX-TGR-205

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>1592</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
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: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>1</u> Sponsor of covered study: <u>0</u>		
Is an attachment provided with details	Yes ☒	No ☐ (Request details from

of the disclosable financial interests/arrangements:		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) <u>0</u>		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

19.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

No additional nonclinical data reviewed.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Plasma, feces and urine concentrations or amount of umbralisib were measured in clinical pharmacology trials (TGR-1202-902, TGR-1202-PK101, TGR-1202-PK102, TGR-1202-908, TGR-1202-901, TGR-1202-904) and clinical trials (TGR-1202-101, UTX-TGR-205, TGR-1202-102). Based on results of human mass-balance Study TGR-1202-902, umbralisib is the predominant circulating moiety (79%) in plasma.

For all moieties measured, is free, bound, or total measured?

The total plasma or serum concentrations of umbralisib were measured in the clinical trials. The average binding of umbralisib is about 99.7-99.8%.

Bioanalytical methods

The bioanalytical method validations and performance for measurements of umbralisib concentrations in all clinical trials are summarized in Table 33 (plasma method MET126) and in Table 35 (serum method MET193v1). The plasma method was modified to provide an alternative assay range, i.e., from 1.00 – 2000 ng/mL to 10.0 – 10000 ng/mL. This change was partially validated and is summarized in Table 34 (method MET126 Addendum 1).

Table 33: Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126)

Bioanalytical method validation report name, amendments, and hyperlinks	Analytical method and validation report for the determination of TGR-1202 (base) in human plasma by LC/MS/MS. Method report MET126 and Addendum 3 .		
Method description	The method used an analog internal standard, RP-5182. An aliquot of each plasma sample (100 µL) was added to internal standard solution in methanol (750 µL), mixed, and centrifuged. Supernatant was analyzed by LC-MS/MS. Analyte separation was performed with a Synergi Polar RP column with a mobile phase of 25:75 0.1% formic acid in water and acetonitrile run isocratically at a flow rate of 0.4 mL/min. Analytes were detected using an Applied Biosystems Sciex API-3000 triple quadrupole mass spectrometer using turbo ion spray in positive ionization mode.		
Materials used for standard calibration curve and concentration	Umbralisib tosylate, lot number: RP-5307/F/1905/45/PTSA. Stock solution: 1.0 mg/mL in methanol.		
Validated assay range	1.08 to 2029.85 ng/mL (and 10.00 to 10060.27 ng/mL [NEBA/STY202]; see Error! Reference source not found.). APPEARS THIS WAY ON ORIGINAL		
Material used for QCs & concentration	Umbralisib tosylate, lot number: RP-5307/F/1905/45/PTSA. Stock solution: 1.0 mg/mL in methanol.		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	Acetonitrile, HPLC grade (J.T.Baker, cat # 9012-03) Water, HPLC grade (Milli-Q® purified water prepared in-house) Formic Acid (Fisher, cat # A118p-500) Human Plasma, lot BRH647681, 682, & 683 (Bio-Reclamation, NY, cat# HMPLLIHP), anti-coagulant Li-heparin		
Regression model & weighting	Linear, weighted 1/x ²		
Validation parameters	Method validation summary		Source Location
Calibration curve performance during	Number of standard calibrators from LLOQ to ULOQ	9	MET126, Table 3 , Table 4 , and Table 5

accuracy & precision	Cumulative accuracy (%bias) from LLOQ to ULOQ umbralisib	NR (within run bias was -6.8% to 4.7%)	MET126, Table 3 , Table 4 , and Table 5
	Cumulative precision (%CV) from LLOQ to ULOQ umbralisib	NR	NA

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 4 QCs</u> QCs umbralisib	-2.1% to 1.6%	MET126, Table 9
	<u>Inter-batch %CV</u> QCs umbralisib	≤4.7%	MET126, Table 9
	<u>Total error (TE)</u> QCs umbralisib	NR	NA
Selectivity & matrix effect	No interference (bias=2.7%) was observed at the retention time of umbralisib from 6 lots of blank matrix.		MET126, Table 15
Interference & specificity	NR		NA
Hemolysis effect	NR		NA
Lipemic effect	NR		NA
Dilution linearity & hook effect	4-fold dilution of 6238.53 ng/mL QC (bias=7.2%, CV=0.3%), Hook effect not applicable		MET126, Table 10
Bench-top/process stability	4 hours at room temperature umbralisib		MET126, Table 13
Freeze-thaw stability	3 cycles umbralisib		MET126, Table 12
Long-term storage	1145 days at -70°C and 33 days at -20°C umbralisib		MET126 Addendum 3, Table 2 and Table 3
Parallelism	NA umbralisib		NA
Carry over	Sample to sample carryover was evaluated by running a blank or wash after the highest standard and assessing the relative peak area of this blank versus the signal at LLOQ. Carryover was not observed at the retention time of umbralisib. umbralisib		MET126, Section 5.2

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-101 Bioanalytical report: TGR-1202-101 NEBA/STY202		
Assay passing rate	100%	STY202, Table 3
Standard curve performance	Cumulative bias range (calibrator set 1): -5.7% to 2.0% Cumulative bias range (calibrator set 2): -2.4% to 1.8% Cumulative bias range (calibrator set 3): -4.1% to 1.8% Cumulative bias range (calibrator set 4): -2.2% to 1.6% Cumulative precision (calibrator set 1): ≤4.6% CV Cumulative precision (calibrator set 2): ≤7.0% CV Cumulative precision (calibrator set 3): ≤7.7% CV Cumulative precision (calibrator set 4): ≤6.1% CV	STY202, Table 5
QC performance	Cumulative bias range (QC set 1): -7.6% to 2.4% Cumulative bias range (QC set 2): -2.0% to 1.6% Cumulative bias range (QC set 3): -2.1% to 2.4% Cumulative bias range (QC set 4): -1.8% to 6.9% Cumulative precision (QC set 1): ≤5.4% CV Cumulative precision (QC set 2): ≤6.3% CV Cumulative precision (QC set 3): ≤8.1% CV Cumulative precision (QC set 4): ≤5.4% CV TE: NA (LBA only)	STY202, Table 6
Method reproducibility	Incurred sample reanalysis was performed in approximately 11% of non-zero study samples and 100% were within ±20% of the original result.	STY202, Section 2.3 and Table 8
Study sample analysis/stability	All samples were analyzed within 216 days after collection (within established stability of 1145 days).	STY202, Section 4

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-102 Bioanalytical report: TGR-1202-102 NEBA/STY272, Amendment 1 and Amendment 2		
Assay passing rate	100%	STY272, Table 1

Standard curve performance	Cumulative bias range (calibrator set 1): -1.3% to 1.0% Cumulative bias range (calibrator set 2): -6.0% to 2.6% Cumulative bias range (calibrator set 3): -2.8% to 2.1% Cumulative bias range (calibrator set 4): -8.8% to 11.8% Cumulative bias range (calibrator set 5): -9.0% to 9.9% Cumulative precision (calibrator set 1): $\leq 11.9\%$ CV Cumulative precision (calibrator set 2): $\leq 6.9\%$ CV Cumulative precision (calibrator set 3): $\leq 5.9\%$ CV Cumulative precision (calibrator set 4): $\leq 11.6\%$ CV Cumulative precision (calibrator set 5): $\leq 4.0\%$ CV	STY272, Table 12 , Table 13 , Table 14 , Table 15 , and Table 16 , and Amendment 2, Table 1
QC performance	Cumulative bias range (QC set 1): -4.4% to -0.5% Cumulative bias range (QC set 2): -9.5% to 4.1% Cumulative bias range (QC set 3): -1.8% to 6.3% Cumulative bias range (QC set 4): -1.2% to 2.6% Cumulative bias range (QC set 5): 1.9% to 9.8% Cumulative precision (QC set 1): $\leq 10.7\%$ CV Cumulative precision (QC set 2): $\leq 5.8\%$ CV Cumulative precision (QC set 3): $\leq 7.2\%$ CV Cumulative precision (QC set 4): $\leq 7.0\%$ CV Cumulative precision (QC set 5): $\leq 9.5\%$ CV TE: NA (LBA only)	STY272, Table 18 , Table 19 , Table 20 , Table 21 , and Table 22 , and Amendment 1, Table 1
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of non-zero study samples and 92% were within $\pm 20\%$ of the original result.	STY272, Table 25
Study sample analysis/stability	All samples were analyzed within 440 days after collection (within established stability of 1145 days).	STY272, Section 4

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-PK101 Bioanalytical report: TGR-1202-PK101 NEBA/STY219		
Assay passing rate	100%	STY219, Table 3
Standard curve performance	Cumulative bias range: -4.6% to 2.5% Cumulative precision: $\leq 7.2\%$ CV	STY219, Table 5
QC performance	Cumulative bias range: -4.1% to 0.3% Cumulative precision: $\leq 3.6\%$ CV TE: NA (LBA only)	STY219, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 11% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY219, Table 8

Study sample analysis/stability	All samples were analyzed within 37 days after collection (within established stability of 1145 days).	STY219, Section 4
Method performance in Study TGR-1202-PK102 Bioanalytical report: TGR-1202-PK102 NEBA/STY221		
Assay passing rate	100%	STY221, Table 3
Standard curve performance	Cumulative bias range: -5.4% to 2.5% Cumulative precision: $\leq 6.6\%$ CV	STY221, Table 5
QC performance	Cumulative bias range: -3.6% to 2.1% Cumulative precision: $\leq 4.3\%$ CV TE: NA (LBA only)	STY221, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 11% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY221, Table 8
Study sample analysis/stability	All samples were analyzed within 29 days after collection (within established stability of 1145 days).	STY221, Section 4
Method performance in Study TGR-1202-901 Bioanalytical report: TGR-1202-901 NEBA/STY341		
Assay passing rate	100%	STY341, Table 3
Standard curve performance	Cumulative bias range: -4.2% to 3.7% Cumulative precision: $\leq 5.4\%$ CV	STY341, Table 5
QC performance	Cumulative bias range: -0.4% to 2.7% Cumulative precision: $\leq 3.0\%$ CV TE: NA (LBA only)	STY341, Table 6
Method reproducibility	Not required	NA
Study sample analysis/stability	All samples were analyzed within 14 days after collection (within established stability of 1145 days).	STY341, Section 4

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-904 Bioanalytical report: TGR-1202-904 NEBA/STY367		
Assay passing rate	100%	STY367, Table 3
Standard curve performance	Cumulative bias range: -10.5% to 5.4% Cumulative precision: $\leq 4.9\%$ CV	STY367, Table 5

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QC performance	Cumulative bias range: -1.2% to 8.4% Cumulative precision: $\leq 8.0\%$ CV TE: NA (LBA only)	STY367, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY367, Table 8
Study sample analysis/stability	All samples were analyzed within 67 days after collection (within established stability of 1145 days).	STY367, Section 4
Method performance in Study TGR-1202-908 Bioanalytical report: TGR-1202-908 NEBA/STY371		
Assay passing rate	100%	STY371, Table 3
Standard curve performance	Cumulative bias range: -8.7% to 4.0% Cumulative precision: $\leq 7.8\%$ CV	STY371, Table 5
QC performance	Cumulative bias range: 1.1% to 5.5% Cumulative precision: $\leq 7.0\%$ CV TE: NA (LBA only)	STY371, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of non-zero study samples and 97% were within $\pm 20\%$ of the original result.	STY371, Table 8
Study sample analysis/stability	All samples were analyzed within 41 days after collection (within established stability of 1145 days).	STY371, Section 4
Method performance in Study UTX-TGR-205 Bioanalytical report: UTX-TGR-205 NEBA/STY360		
Assay passing rate	100%	STY360, Table 1
Standard curve performance	Cumulative bias range: -7.3% to 4.0% Cumulative precision: $\leq 10.6\%$ CV	STY360, Table 7
QC performance	Cumulative bias range: 8.4% to 11.8% Cumulative precision: $\leq 7.0\%$ CV TE: NA (LBA only)	STY360, Table 9
Method reproducibility	Incurred sample reanalysis was performed in 10.7% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY360, Table 13
Study sample analysis/stability	All samples were analyzed within 827 days after collection (within established stability of 1145 days).	STY360, Section 3

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study UTX-TGR-205 (extra samples) Bioanalytical report: UTX-TGR-205 NEBA/STY360 ADD-1

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Assay passing rate	67%	STY360 ADD-1, Table 1
Standard curve performance	Cumulative bias range: -6.8% to 5.8% Cumulative precision: $\leq 9.5\%$ CV	STY360 ADD-1, Table 3
QC performance	Cumulative bias range: 3.5% to 12.9% Cumulative precision: $\leq 9.1\%$ CV TE: NA (LBA only)	STY360 ADD-1, Table 6
Method reproducibility	Not performed.	NA
Study sample analysis/stability	All samples were analyzed within 1140 days after collection (within established stability of 1145 days).	STY360 ADD-1, Section 3

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; HPLC=high performance liquid chromatography; LBA=ligand binding assay; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LLOQ=lower limit of quantification; MRD=minimum required dilution; NA=not applicable; NR=not reported; QC=quality control; TE=total error; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

Table 34: Summary of Method Modification and Partial Validation Results (Method MET126, Reported in TGR-1201-101 NEBA/STY202)

Bioanalytical method validation report name and hyperlinks	The partial validation of the determination of umbralisib in human plasma is reported in the bioanalytical report for Study TGR-1202-101 (NEBA/STY202): Bioanalytical report for the analysis of TGR-1202 in human plasma (protocol HEMREF31/TGR-1202-101) Report: NEBA/STY202, Section 6.1.3		
Changes in method	The existing validated method (MET126 [Table 33 :]) had a range of approximately 1.00 to 2000 ng/mL. A new range of approximately 10.0 to 10000 ng/mL was implemented for the analysis of clinical samples with high concentrations of umbralisib.		
New validated assay range if any	10.00 to 10060.27 ng/mL		
Validation parameters	Partial validation performance		Source location
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	NR	NA
	Cumulative precision (%CV) from LLOQ to ULOQ	NR	NA
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 4 QCs</u>	-5.6% to 8.9%	STY202, Section 6.1.3
	<u>Inter-batch %CV</u>	≤11.6%	STY202, Section 6.1.3
	<u>Percent total error (TE)</u>	NR	NA
Cross-validation	NA		NA
List other parameters	NA		NA

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; LLOQ=lower limit of quantification; NA=not applicable; NR=not reported;
QC=quality control; TE=total error; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

Table 35: Summary Method Performance for the Determination of Umbralisib Concentrations in Human Serum (Method MET193)

Bioanalytical method validation report name, amendments, and hyperlinks	Analytical method and validation report for determination of TGR-1202 in human serum by LC/MS/MS. Method report MET193 and Addendum 1 .		
Method description	The method used an analogue internal standard, RP-5182. An aliquot of each serum sample (100 µL) was added to internal standard solution in methanol (750 µL), mixed, and centrifuged. Supernatant was analyzed by LC-MS/MS. Analyte separation was performed with a Phenomenex Synergi Polar RP column with a mobile phase of 25:75 0.1% formic acid in water and acetonitrile run isocratically at a flow rate of 0.4 mL/min. Analytes were detected using an Applied Biosystems Sciex API-3000 triple quadrupole mass spectrometer using turbo ion spray in positive ionization mode.		
Materials used for standard calibration curve & concentration	Umbralisib, lot number: TGR-21506. Stock solution: 1.0 mg/mL in methanol.		
Validated assay range	10.69 to 10175.95 ng/mL		
Material used for QCs & concentration	Umbralisib, lot number: TGR-21506. Stock solution: 1.0 mg/mL in methanol.		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	Acetonitrile HPLC Grade Methanol HPLC Grade HPLC grade Water Formic acid, 88% Human Serum, Source: Bioreclamation Inc.		
Regression model & weighting	Linear, weighted 1/x ²		
Validation parameters	Method validation summary		Source Location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	9	MET193, Table 3 , Table 4 , and Table 5
	Cumulative accuracy (%bias) from LLOQ to ULOQ umbralisib	NR (within run bias was -12.9% to 10.6%)	MET193, Table 3 , Table 4 , and Table 5

	Cumulative precision (%CV) from LLOQ to ULOQ umbralisib	NR	NA

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Serum (Method MET193) - Continued

QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 4 QCs</u> QCs umbralisib	-10.6% to 2.0%	MET193, Table 9
	<u>Inter-batch %CV</u> QCs umbralisib	≤7.1%	MET193, Table 9
	<u>Total error</u> QCs umbralisib	NR	NA
Selectivity & matrix effect	No interference (bias=12.6%) was observed at the retention time of umbralisib from 6 lots of blank matrix.		MET193, Table 15
Interference & specificity	NR		NA
Hemolysis effect	NR		NA
Lipemic effect	NR		NA
Dilution linearity & hook effect	4-fold dilution of 33822.58 ng/mL QC (Bias=-10.4%, CV=2.2%), Hook effect not applicable		MET193, Table 11
Bench-top/process stability	6 hours at room temperature umbralisib		MET193, Table 16
Freeze-thaw stability	3 cycles umbralisib		MET193, Table 15
Long-term storage	301 days at -70°C and 27 days at -20°C (Further long-term stability testing is ongoing) umbralisib		MET193 Addendum 1, Table 1 and Table 2
Parallelism	NA umbralisib		NA
Carry over	Sample to sample carryover was evaluated by running a blank or rinse after the highest standard of each analyte and assessing the relative peak height of this blank versus the signal at LLOQ. In the six instances from 3 batches the carryover was less than 15% of the LLOQ. umbralisib		MET193, Section 5.4.3

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Serum (Method MET193) - Continued

Method performance in Study UTX-TGR-205 Bioanalytical report: UTX-TGR-205 NEBA/STY360		
Assay passing rate	100%	STY360, Table 1
Standard curve performance	Cumulative bias range: -2.7% to 1.7% Cumulative precision: ≤5.5% CV	STY360, Table 8
QC performance	Cumulative bias range: -8.4% to 0.1% Cumulative precision: ≤7.6% CV TE: NA (LBA only)	STY360, Table 10
Method reproducibility	Incurred sample reanalysis was performed in 10.2% of non-zero study samples and 95% were within ±20% of the original result.	STY360, Table 14
Study sample analysis/stability	All samples were analyzed within 808 days after collection (further long-term stability testing is ongoing [currently established for 301 days]).	STY360, Section 3
Method performance in Study UTX-TGR-205 (extra samples) Bioanalytical report: UTX-TGR-205 NEBA/STY360 ADD-1		
Assay passing rate	75%	STY360 ADD-1, Table 1
Standard curve performance	Cumulative bias range: -4.1% to 4.6% Cumulative precision: ≤9.5% CV	STY360 ADD-1, Table 4
QC performance	Cumulative bias range: -12.3% to -4.2% Cumulative precision: ≤17.0% CV TE: NA (LBA only)	STY360 ADD-1, Table 6
Method reproducibility	Not performed.	NA
Study sample analysis/stability	All samples were analyzed within 1142 days after collection (further long-term stability testing is ongoing [currently established for 301 days]).	STY360 ADD-1, Section 3

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; HPLC=high performance liquid chromatography; LBA=ligand binding assay; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LLOQ=lower limit of quantification; MRD=minimum required dilution; NA=not applicable; NR=not reported; QC=quality control; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Serum (Method MET193) - Continued

Bioanalytical method validation report name and hyperlinks	Cross validation of TGR-1202 in human plasma and human serum. Method report MET126 Addendum 1 .		
Changes in method	Methods for the determination of umbralisib in human plasma (MET126) and for the determination of umbralisib in human serum (MET193) were fully validated. This cross validation was to demonstrate the equivalency of the 2 methods when human serum QC samples were quantified using a human plasma calibration curve.		
New validated assay range if any	9.72 to 10024.78 ng/mL (no change)		
Validation parameters	Cross-validation performance		Source Location
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	NR (within run bias was -10.2% to 12.5%)	MET126 Addendum 1, Table 1
	Cumulative precision (%CV) from LLOQ to ULOQ	NR	NA
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 3 QCs</u>	-3.7% to 1.8%	MET126 Addendum 1, Table 2
	<u>Inter-batch %CV</u>	≤11.3%	MET126 Addendum 1, Table 2
	<u>Percent total error (TE)</u>	NR	NA
Cross-validation	Acceptable results obtained from serum QCs analyzed using a plasma calibration curve.		NA
List other parameters	NA		NA

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; LLOQ=lower limit of quantification; NA=not applicable; NR=not reported; QC=quality control; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

There were 6 PK samples that had concentration measurements for both plasma and serum matrices (Table 36). Using the standard acceptance criteria for incurred sample reproducibility (within $\pm 20\%$), 4 of the 6 samples met the acceptance criteria. The results suggest that there appears to be no difference in the concentrations determined in the two matrices although the sample size is small.

Table 36: Umbralisib Concentrations in Plasma and Serum at the Same Nominal Timepoint (Study UTX-TGR-205)

Subject	Nominal Timepoint	Concentration, ng/mL		Deviation, %
		Plasma	Serum	
(b) (6)	Cycle 2, predose	4470	3890	-14.9
	Cycle 3, predose	8790	7460	-17.8
	Cycle 6, predose	8240	8010	-2.9
	Cycle 1, predose	<LLOQ	<LLOQ	0
	Cycle 2, predose	4690	3710	-26.4
	Cycle 2, pre-dose	11200	<LLOQ	ND
Count				6
Failure count (>20% deviation)				2
Mean deviation, %				-15.5
Minimum, %				-26.4
Maximum, %				-2.9

Source: Addendum-1 to Study NEBA/STY360, [Table 7](#) and [Table 8](#).

Abbreviations: LLOQ=lower limit of quantification; ND = not determinable.

Of note: Except for Subject (b) (6), the average of the plasma and serum concentrations at the same timepoint was used in the PPK analysis.

19.4.2. Pharmacometrics Review

A population pharmacokinetics (PPK) model was developed by the Applicant to characterize the PK of umbralisib in patients with select hematologic malignancies, previously treated indolent NHL, MCL, or DLBCL and healthy subjects. Subjects intrinsic and extrinsic factors which influence the PK and PK variability of umbralisib were identified. Individual umbralisib exposure metrics were generated for subsequent exposure-response (E-R) analyses for efficacy and safety. In this review, the FDA Pharmacometrics Reviewer validated the Applicant's PPK model and E-R analyses for both efficacy and safety.

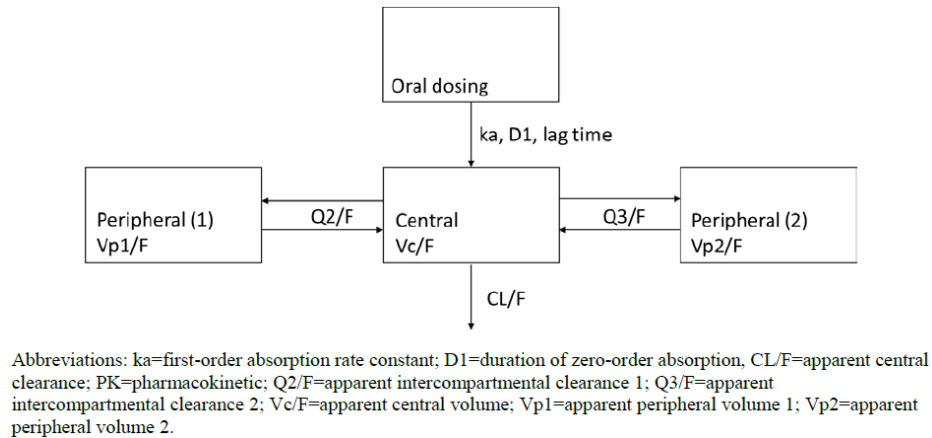
1. Population PK analyses

Three clinical trials were included in the PPK analyses: Study 101, 205 and 1102. Total of 2014 PK samples collected from 247 subjects across the three studies were included in the final population PK analysis. Concentration range for the analysis was from 1.08 to 16061.5 ng/mL. In Study 101, the subjects with select hematologic malignancies were administered with (b) (4) umbralisib with the dose range of 50 to 1800 mg QD under fasted or fed condition. In Study 205, the subjects with previously treated indolent NHL, MCL or DLBCL were administered with (b) (4) umbralisib at the dose level of 800 mg QD under fed condition. In Study 1102, the healthy subjects were administered with (b) (4) or (b) (4) umbralisib at the dose level of 200 mg QD under fasted condition.

The intrinsic and extrinsic factors of healthy subjects versus subjects with hematological malignancies, disease type (MZL vs FL vs others), age, baseline body weight (BW), sex race (White vs non-White), hepatic function, renal function, and coadministration of strong cytochrome P450 (CYP) 3A inhibitors, strong CYP3A inducers, or acid-reducing agents (ARAs) were evaluated.

The PK of umbralisib following oral administration was adequately described by a three-compartment disposition model with combined first- and zero-order absorption (Figure 5).

Figure 5: Structure of the PK Model for Umbralisib



Source: Applicant's population PK and E-R study report

The equations for the final model are presented as below:

$$CL/F \text{ (L/h)} = 15.5 \times e^{\eta_{CL}}$$

$$Vc/F \text{ (L)} = 312 \times e^{\eta_{Vc}} \times (0.205 \text{ if healthy subject})$$

$$F = 1 \\ \times (0.702 \text{ if in Study 1102}) \\ \times (1.41 \text{ if in Study 205}) \\ \times (1.93 \text{ if DP containing (b) (4) DS}) \\ \times (1.38 \text{ if fed condition with DP containing (b) (4) DS in Study 101})$$

The PK parameter estimates of the final model are presented in .

Table 37.

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Table 37: Parameters of the Final Umbralisib PPK Model

Parameter	Estimate	BSV ^a (CV%)	Shrinkage ^b (%)	Bootstrap (N=1000)		
				Median	2.5% CI	97.5% CI
Fixed effect						
Duration of zero-order absorption, D1 (h)	2.02	-	-	2.02	1.25	2.27
First-order absorption rate, ka (1/h)	0.404	-	-	0.409	0.325	0.473
Apparent clearance, CL/F (L/h)	15.5	51.9	8.78	15.4	13.5	17.6
Apparent central volume, Vc/F (L)	312	185	36.7	311	215	446
Apparent intercompartmental clearance 1, Q2/F (L/h)	151	-	-	150	125	184
Apparent peripheral volume 1, Vp1/F (L)	1990	-	-	1990	1630	2390
Apparent intercompartmental clearance 2, Q3/F (L/h)	9.88	-	-	9.93	6.24	15.1

Parameter	Estimate	BSV ^a (CV%)	Shrinkage ^b (%)	Bootstrap (N=1000)		
				Median	2.5% CI	97.5% CI
Apparent peripheral volume 2, Vp2/F (L)	2300	-	-	2390	1570	3704
Absorption lag time, Tlag ^c (h)	0.208	-	-	0.208	0.208	0.208
Covariate effect						
Study 1102 on residual error	0.763	-	-	0.753	0.645	0.864
Study 205 on residual error	0.497	-	-	0.492	0.389	0.606
Study 1102 on F	0.702	-	-	0.707	0.597	0.832
Study 205 on F	1.41	-	-	1.41	1.22	1.62
(b) (4) DS on F	1.93	-	-	1.94	1.80	2.09
Fed condition with (b) (4) DS in Study 101 on F	1.38	-	-	1.38	1.06	1.75
Reduction in Vc/F for healthy subjects	-0.795	-	-	-0.788	-0.873	-0.618
Residual error						
Proportional residual error (SD)	0.438	-	5.77	0.436	0.407	0.466
Others						
Covariance of CL/F and Vc/F ^d	0.006	-	-	0.003	-0.164	0.160
Half-life, t _{1/2} alpha (h)	1.10	-	-	-	-	-
Half-life, t _{1/2} beta (h)	59.5	-	-	-	-	-
Half-life, t _{1/2} gamma (h)	317	-	-	-	-	-

Abbreviations: BSV=between-subject variability; CI=confidence interval; CV%=percent coefficient of variation; DS=drug substance; F=relative oral bioavailability; (b) (4) SD=standard deviation; Tlag=absorption lag time; (b) (4) Vc/F=apparent central volume.

^a Estimates for random effects and BSV are presented in CV% and based on the estimated variances, calculated as $\sqrt{(\exp[\text{variance}^2] - 1) \times 100}$.

^b Shrinkage (%) is calculated as $100 \times (1 - \text{SD}[\text{ETA}]/\sqrt{[\text{variance}]})$.

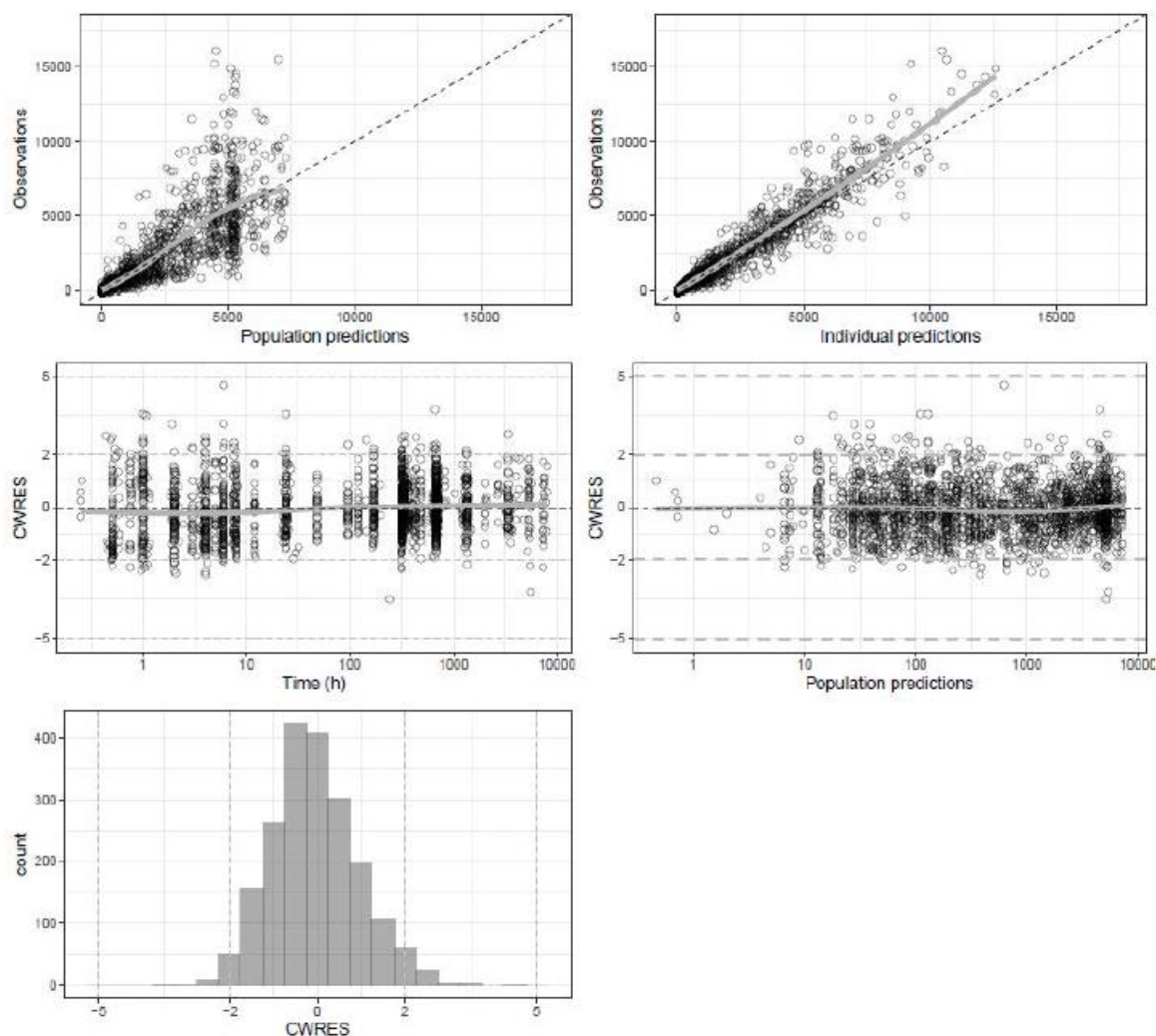
^c Tlag estimate was fixed during the final model development.

^d The correlation coefficient between CL/F and Vc/F was estimated as 0.968.

Source: Applicant's population PK and E-R study report

The goodness-of-fit (GOF) diagnostic plots and pcVPCs are shown in Figure 6 and Figure 7.

Figure 6: GOF Diagnostics of the Umbralisib Final Model

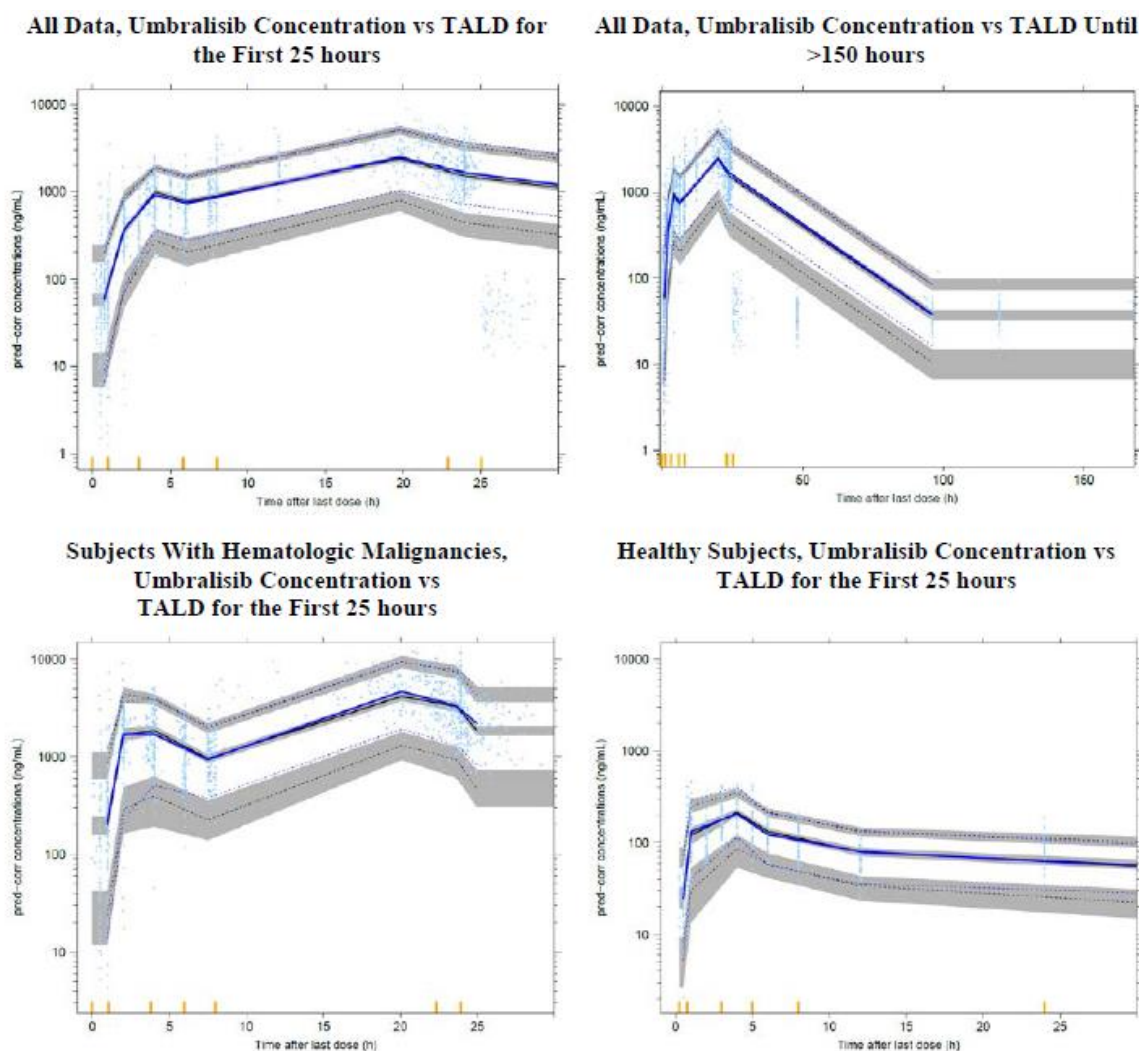


Abbreviations: CWRES=conditional weighted residuals; GOF=goodness-of-fit.

Note: Circles are individual data points, and solid gray lines are smoothed regression lines. In the CWRES versus time and population predictions, dashed black lines show the boundaries of the CWRES ± 2 and ± 5 intervals.

Source: Applicant's population PK and E-R study report

Figure 7: pcVPC for the Umbralisib Final Model



Abbreviations: pcVPC=prediction-corrected visual predictive check; PI=prediction interval; pred-con=prediction-corrected; TALD=time after last dose; vs=versus.

Note: Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% PI for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals.

Source: Applicant's population PK and E-R study report

The Applicant evaluated the impact of concomitant acid reducing agents (ARAs) and strong CYP3A4 inhibitors using population PK analysis to support the labeling claim. For ARAs coadministration, the PPK analysis included 20 subjects who had quantifiable umbralisib concentrations during the period of co-administration of ARAs. Out of the 20 subjects, 6 subjects had intense PK and 14 subjects had sparse PK. For strong CYP3A4 inhibitors, 10 subjects were included in the PPK analysis. Out of the 10 subjects, 4 subjects had intense PK

and 6 subjects had sparse PK. As shown in Table 38, the change in objective function values (OFV) relative to the base model were all statistically non-significant ($p>0.01$). Thus, the Applicant determined that the use of concomitant strong CYP3A4 inhibitors and ARAs had no clinically meaningful impact on the PK of umbralisib.

Table 38: Results of Model Evaluation

Description	Run number	OFV	Δ OFV compared to run056
Base model	run056_6	23053.551	-
Including CYP3A4 effect on CL/F	run059_6	23053.347	-0.204
Including ARA effect on CL/F	run060_6	23053.491	-0.06
Including ARA effect on F*	run061_6	23047.497	-6.054
Including CYP3A4 effect on F*	run062_6	23053.504	-0.047

Abbreviations: ARA=acid-reducing agent; CL/F=apparent clearance; OFV=objective function value.

Source: Applicant's response to Clin Pharm IR

In addition, the Applicant assessed the impact of mild/moderate renal and mild hepatic impairment on the PK of umbralisib using the PPK analysis. As shown in Table 39, no statistically significant effects were detected for mild hepatic impairment (N=6), mild (N=121) and moderate (N=62) renal impairment on the PK of umbralisib.

Table 39: Model-predicted geometric mean (CV%) of umbralisib exposure metrics by subgroup following administration of 800 mg QD in MZL and FL populations

Parameters	Cmin C1 ng/mL GM (CV%)	Cminss ng/mL GM (CV%)	Cmax C1 ng/mL GM (CV%)	Cmaxss ng/mL GM (CV%)	AUC C1 ng·h/mL GM (CV%)	AUCss ng·h/mL GM (CV%)	Cavss ng/mL GM (CV%)
Hepatic function							
Normal (N=241)	443 (48.0)	3585 (73.3)	1417 (41.8)	5026 (56.3)	16181 (44.1)	97549 (67.3)	4065 (67.3)
Mild impairment (N=6)	499 (35.8)	4283 (84.3)	1441 (36.3)	5806 (62.1)	17440 (31.8)	115426 (75.9)	4809 (75.9)
Renal function							
Normal (N=64)	344 (57.6)	2631 (84.4)	1252 (46.9)	3946 (63.4)	13061 (51.9)	72665 (77.5)	3028 (77.5)
Mild impairment (N=121)	486 (41.0)	4114 (69.0)	1479 (40.5)	5593 (54.7)	17442 (38.8)	110990 (63.5)	4625 (63.5)
Moderate impairment (N=62)	486 (37.8)	3837 (56.1)	1482 (35.3)	5312 (42.1)	17560 (35.5)	104451 (50.9)	4352 (50.9)

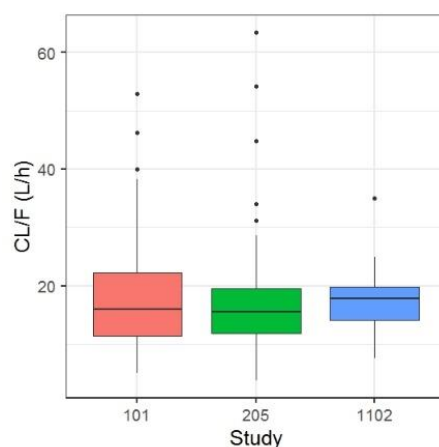
Source: adapted from Applicant's population PK report Table 4-14

The effects of severe renal impairment and moderate to severe hepatic impairment are not evaluated.

Reviewer's comment:

The Applicant's PPK analysis is acceptable for describing the PK of umbralisib in the healthy subjects and select hematologic malignancies patients. The CL of umbralisib estimated by the Applicant's PPK model across different studies are comparable (Figure 8).

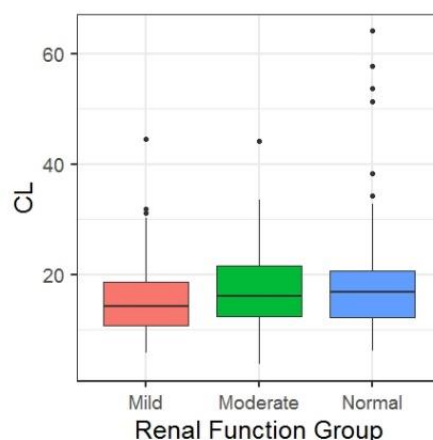
Figure 8: Clearance of umbralisib estimated by the final PPK model across different studies



Source: Reviewer's analysis

The evaluations of the impact of mild/moderate renal impairment on the PK of umbralisib using PPK analysis appear to be reasonable. In the Applicant's PPK analysis for renal impairment, the renal function was categorized based on eGFR estimated by Modification of Diet in Renal Disease (MDRD). FDA Reviewer also evaluated the CL in different renal function groups categorized by creatinine clearance estimated by Cockcroft-Gault equation. As shown in Figure 9, the CL of umbralisib across different renal function groups based on creatinine clearance was comparable, further supporting (b) (4) that no dose adjustment would be needed for mild/moderate renal impairment subjects.

Figure 9: Clearance of umbralisib across different renal function groups categorized by creatinine clearance estimated by Cockcroft-Gault equation



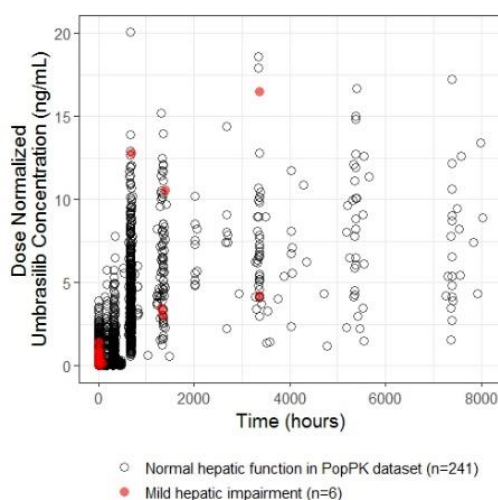
Note: normal renal function: ≥ 90 mL/min ($n=116$); mild renal impairment: 60 – 89 mL/min ($n=85$); moderate renal impairment: 30-59 mL/min ($n=46$).

Source: Reviewer's analysis

In the Applicant's evaluation of the impact of concomitant strong CYP3A4 inhibitors and acid reducing agents (ARAs), the frequency and dosing time of the co-administrated strong CYP3A4 inhibitors and ARAs were not clearly provided. In addition, out of the 10 subjects who were co-administrated with strong CYP3A4 inhibitors, only 4 of them had intense PK, while 6 subjects only had sparse PK of 1-3 PK samples; out of 20 subjects who were co-administrated with ARAs, only 5 of them had intense PK, while 14 subjects only had sparse PK of mostly 1-3 PK samples. Based on the limited PK data and information on the administration time of concomitant medications, the Applicant's proposal of no dose adjustment for concomitant administration of strong CYP3A4 inhibitors or ARAs is not acceptable based on PPK analysis. As the Applicant conducted dedicated study (TGR-1202-904) to evaluate the effect of ARAs, the result from that study should be used to inform the decision of dose adjustment with co-administrated ARAs.

In the Applicant's evaluation of impact of mild hepatic impairment, only 6 patients with mild hepatic impairment were included. Out of the 6 patients, 4 of them had only 1 PK sample. Although the observed dose-normalized umbralisib concentrations from mild hepatic impairment patients were within the range of those from normal hepatic function patients (Figure 10), the available data were limited to conclude the effect of mild hepatic impairment on PK of umbralisib.

Figure 10: Comparison of umbralisib observed concentrations between normal hepatic function and mild hepatic impairment patients



Source: Reviewer's analysis

2. Exposure-Efficacy Analyses in MZL Population

The Applicant conducted exposure-response (E-R) analysis for efficacy in MZL population. Table 40 summarizes the studies and dose levels included in the E-R analyses. For both MZL and FL populations, multiple dose levels were included in the exposure-efficacy analyses.

Table 40: Summary of studies and dose levels by disease populations included in the exposure-efficacy analyses

	MZL Population (N=37)
Studies	Study 101 (n=5) and 205 (n=32)
Dose level	800mg (n=33), 1000mg (n=1) and 1200mg (n=3)

Source: adapted from Applicant's population PK and PK/PD study report

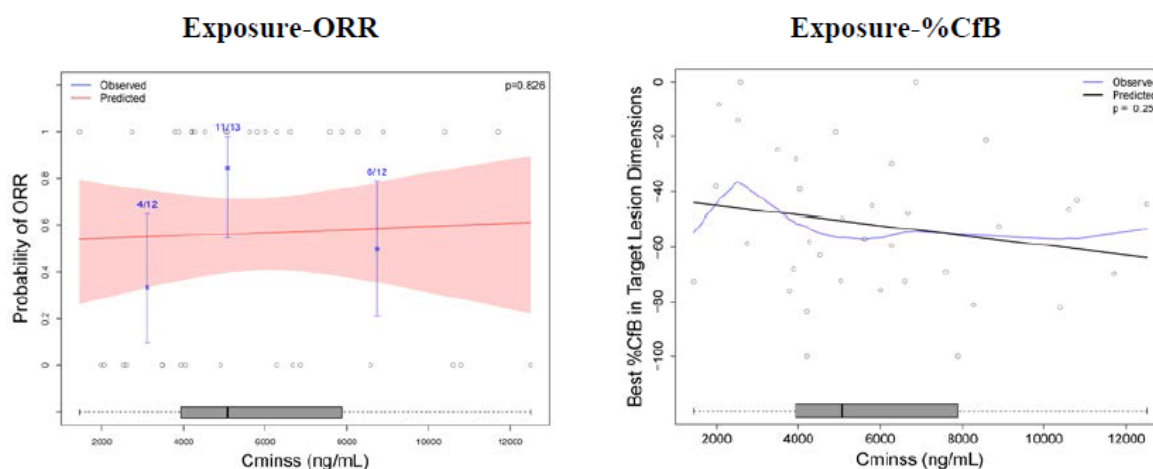
2.1 E-R Analysis for Efficacy in MZL Population

In the E-R analysis for efficacy in MZL population, subjects were primarily male (54%), White (73%), aged 34 to 81 years, had body weight of 49 to 165 kg, and had an Eastern Cooperative Oncology Group (ECOG) performance score of 0 (54%).

No significant exposure-efficacy relationships for ORR, TTR, DOR, PFS, and %CfB were identified (Figure 11). Thus, no further modeling was performed by the Applicant. From the univariate E-R analysis, the model predicted ORR at 800 mg QD was 56.9% (90% CI: 43.2, 69.8) (Table 41) and

the model predicted probability of best %CfB in target lesion dimensions was -52.3% (90% CI: -60.1, -44.3) (Table 42).

Figure 11: Relationship between exposure-ORR and exposure-%CfB in target lesion dimensions in MZL population



Abbreviations: %CfB=percent change from baseline; Cminss=minimum concentration at steady state; MZL=marginal zone lymphoma; ORR=objective response rate.

Note: Horizontal boxplot below shows the exposure distribution for the 800 mg dose group. The p-value is for the slope of the logistic (left panel) or linear (right panel) fit.

Source: Applicant's population PK and PK/PD study report

Table 41: Model-predicted ORR by dose in MZL population

Umbralisib Dose (mg QD)	Model-Predicted Mean Rate (%) Estimate (90% CI)
400	55.0 (35.8, 73.1)
600	55.9 (41.1, 70.1)
800	56.9 (43.2, 69.8)
1000	57.8 (41.5, 71.6)
1200	58.8 (37.9, 74.7)

Abbreviations: CI=confidence interval; MZL=marginal zone lymphoma; QD=once daily.

Note: Simulations were based on all subjects in the exposure-ORR MZL analysis set and used subject-specific exposures. The 90% CI was based on model uncertainty and exposure variability.

Source: Applicant's population PK and PK/PD study report

Table 42: Model-predicted %CfB by dose in MZL population

Umbralisib Dose (mg QD)	Model-Predicted Mean Rate (%) Estimate (90% CI)
400	-47.0 (-57.5, -35.9)
600	-49.6 (-57.7, -41.1)
800	-52.3 (-60.1, -44.3)
1000	-55.0 (-64.6, -46.3)
1200	-57.7 (-70.5, -46.4)

Abbreviations: %CfB=percent change from baseline; CI=confidence interval; MZL=marginal zone lymphoma; N=number of subjects; QD=once daily.

Note: Simulations were based on all subjects in the exposure-%CfB analysis set (N=36) and used subject-specific exposures. The 90% CI was based on model uncertainty and exposure variability.

Source: Applicant's population PK and PK/PD study report

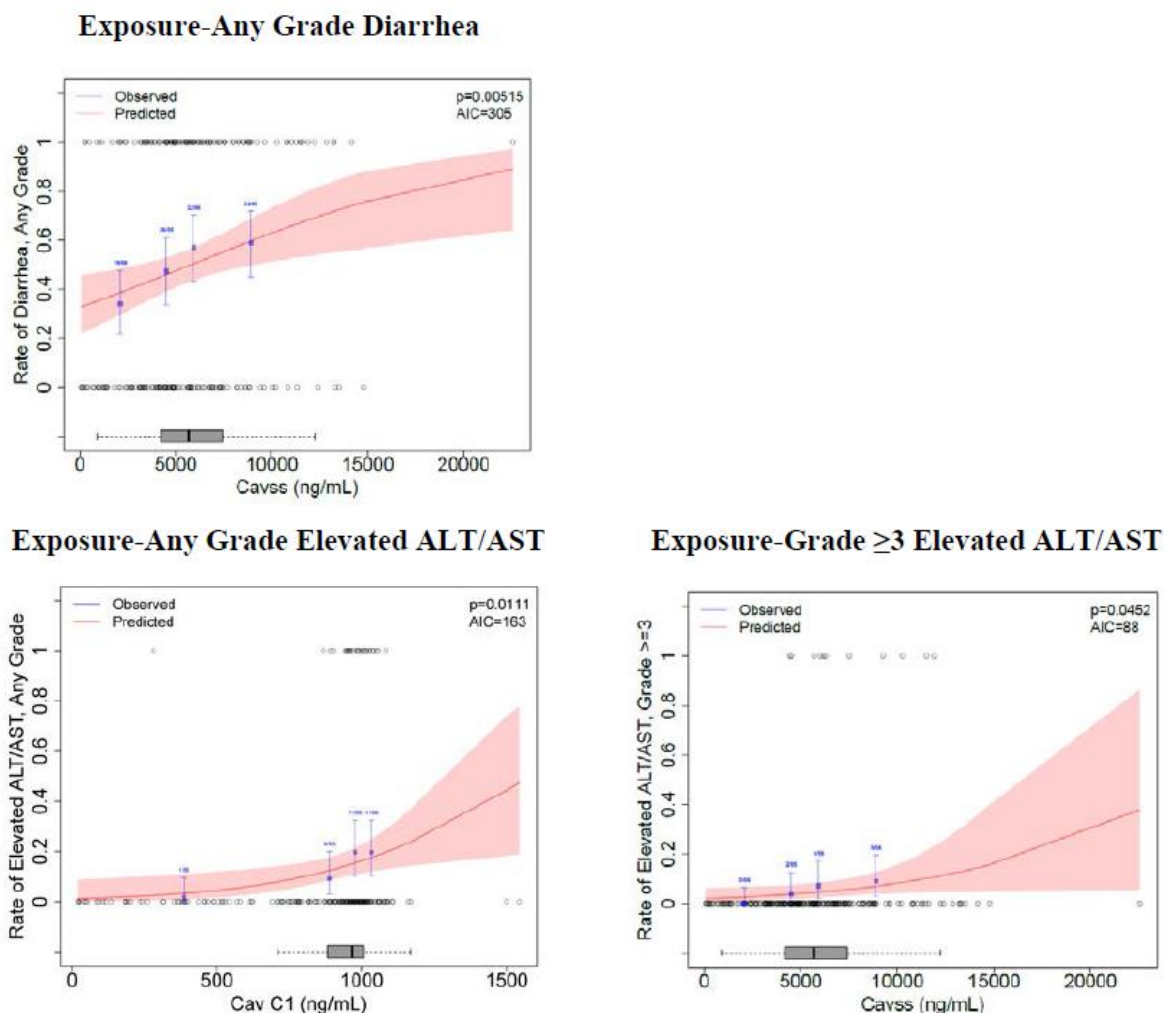
Reviewer's comments:

The Applicant's E-R analyses for efficacy are acceptable. The flat E-R relationship for efficacy in MZL population indicates that the efficacy plateau has been reached at the dose level ≥ 800 mg.

3. E-R Analyses for Safety

The exposure-safety dataset included 223 subjects (N=83 from Study 101 and N=140 from Study 205). Of the safety-endpoints evaluated, the AESI with an incidence rate $\geq 10\%$ were diarrhea, elevated ALT/AST, rash, neutropenia, pneumonia, and anemia. Among these AESI, only diarrhea (any grade) and elevated ALT/AST (any grade and Grade ≥ 3) were statistically correlated with umbralisib exposure (Figure 12).

Figure 12: Relationships between exposure and diarrhea or elevated ALT/AST



Abbreviations: AIC=Akaike information criterion; ALT=alanine aminotransferase; AST=aspartate aminotransferase; Cav C1=Cycle 1, Day 1 average concentration; Cavss=average concentration at steady state. Note: Horizontal boxplot below shows the exposure distribution for the 800 mg dose group. The p-value is for the slope of the logistic regression fit.

Source: Applicant's population PK and PK/PD study report

For any grade diarrhea, following the covariate analysis, a statistically significant effect of sex on the intercept of the relationship was identified and retained in the final model. For C_{avg} -any grade elevated ALT/AST, following the covariate analysis, statistically significant effects of ECOG and MZL on the slope of the relationship were identified and retained in the final model. No E-R relationships were identified for any grade rash, neutropenia, anemia, thrombocytopenia and pneumonia.

Reviewer's comment:

The Applicant's E-R analyses for safety are acceptable. The positive E-R relationships for diarrhea and elevated ALT/AST indicated that increasing the dose in MZL/FL population may lead to higher incidence of adverse events.

4. Integrated E-R Analyses

The Applicant conducted simulation to predict the probability of key efficacy and safety endpoint rates for doses ranging from 400 to 1200 mg QD in MZL and FL populations (Table 43). For exposure-efficacy analysis for FL population, detail refers to Pharmacometrics Review in Appendix in FL Assessment Aid. Figure 13 shows the relative change in event rates relative to the 800 mg QD dose.

For MZL population, similar ORR was projected at different doses, higher rates of diarrhea and ALT/AST elevation were predicted at higher doses. For FL population, there was a substantial reduction in ORR and tumor shrinkage projected at doses lower than 800 mg QD. On the other hand, any grade and Grade ≥ 3 diarrhea was projected to modestly increase by <30%, while any grade and Grade ≥ 3 elevated ALT/AST were projected to increase by 62% and 32% for the 1000 mg QD dose, and by 131% and 72% for the 1200 mg QD dose.

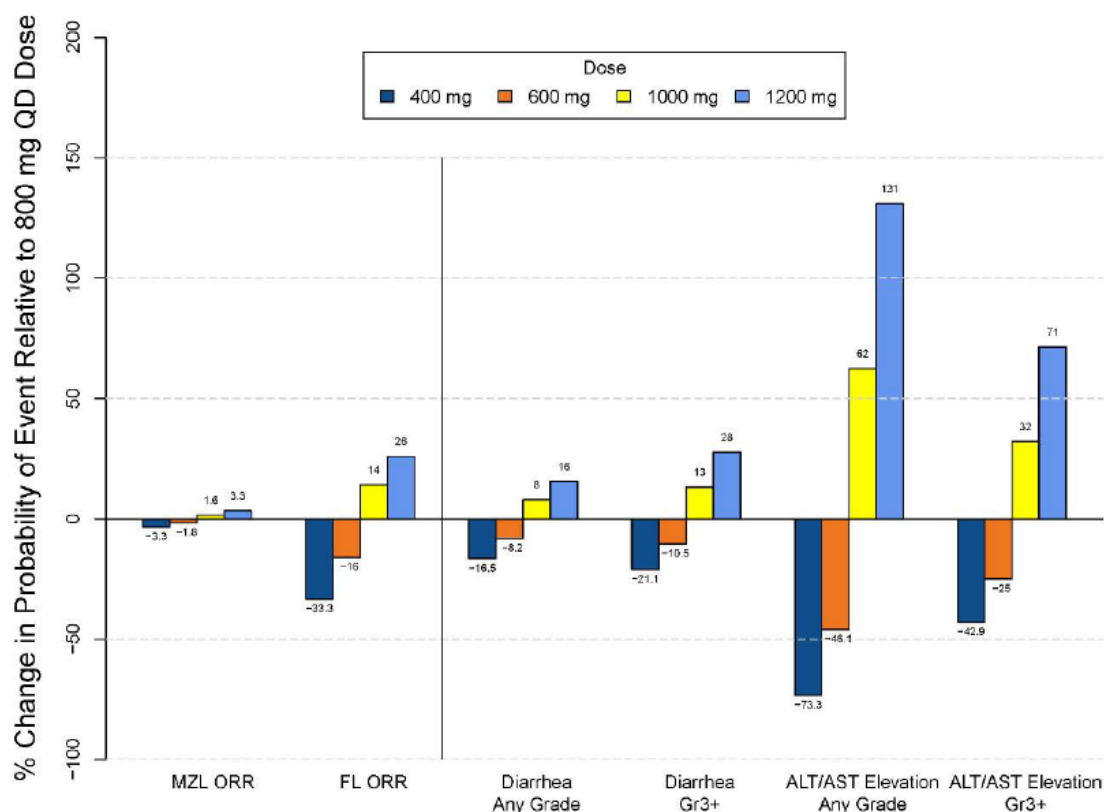
Table 43: Model-projected probabilities of key efficacy and safety endpoints by dose group

Umbralisib Dose (mg QD)	Model-Predicted Rate (%) Estimate (90% CI)					
	ORR-MZL	ORR-FL	Diarrhea Any Grade	Diarrhea Grade ≥ 3	Elevated ALT/AST Any Grade	Elevated ALT/AST Grade ≥ 3
400	55.0 (35.8, 73.1)	37.4 (26.6, 50.5)	43.9 (37.1, 51.2)	6.0 (3.5, 10.3)	4.4 (1.6, 12)	3.2 (1.6, 6.5)
600	55.9 (41.1, 70.1)	47.1 (37.2, 57.2)	48.3 (42.5, 54.1)	6.8 (4.4, 10.6)	8.9 (5.3, 14.9)	4.2 (2.5, 7.4)
800	56.9 (43.2, 69.8)	56.1 (46.2, 65.1)	52.6 (46.4, 58.2)	7.6 (5.1, 11.9)	16.5 (12.3, 22.2)	5.6 (3.4, 9.5)
1000	57.8 (41.5, 71.6)	64.0 (53.1, 73.0)	56.8 (49.1, 63.3)	8.6 (5.4, 14.6)	26.8 (17.7, 39.6)	7.4 (4.3, 13.1)
1200	58.8 (37.9, 74.7)	70.7 (58.2, 79.7)	60.8 (51.3, 68.3)	9.7 (5.3, 18.3)	38.1 (21, 59.3)	9.6 (4.9, 18.3)

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; CI=confidence interval; FL=follicular lymphoma; MZL=marginal zone lymphoma; ORR=objective response rate; QD=once daily.

Source: Applicant's population PK and PK/PD study report

Figure 13: Percent change in key efficacy and safety endpoints relative to 800 mg QD, stratified by dose group in MZL and FL population



Source: Applicant's population PK and PK/PD study report

Reviewer's comment:

Based on the Applicant's simulation, a lower dose in MZL population may provide better safety profile while maintaining efficacy. However, there is no efficacy data available at doses lower than 800 mg QD in the MZL patients to discern that. For FL population, while the reduced efficacy at lower doses, and increased risk of diarrhea and ALT/AST elevation at higher doses appear to support the proposed 800 mg QD regimen, these projections were potentially limited by small number of subjects at doses outside of 800 mg in the E-R analysis dataset, particularly for efficacy.

In conclusion, the Applicant developed a PPK model that reasonably described the PK behavior of umbralisib in MZL and FL patients. The PK of umbralisib following oral administration was adequately described by a three-compartment model combined with first- and zero-order absorption after a lag time and first-order elimination. Flat E-R relationships were observed for MZL population while positive E-R relationships were identified for ORR, TTR and %CfB in target

lesion dimensions in FL population, with potential uncertainties due to limited number of subjects at doses outside of 800 mg QD. Positive E-R relationships were observed for diarrhea and elevated ALT/AST.

19.4.3. Physiologically Based Pharmacokinetic (PBPK) Modeling Analysis

Executive Summary

The objective of this review is to evaluate the adequacy of the applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate

- the inhibitory potential of umbralisib on the pharmacokinetics (PK) of substrates of CYP2C8, CYP2C9 and CYP2C19
- the inhibitory and induction potential of umbralisib on the PK of midazolam, a sensitive CYP3A substrate

The Division of Pharmacometrics has reviewed the PBPK analyses report (R_TGT/1/B) submitted with NDA 213176, responses to FDA's information requests (IRs) submitted on July 24th and 31st, 2020, and the modeling supporting files, and concluded that the effects of umbralisib on CYP3A, CYP2C8, CYP2C9 and CYP2C19 could not be confidently predicted using the PBPK modeling approach. The potential of drug-drug interactions (DDIs) of umbralisib with substrates of these enzymes cannot be ruled out.

Background

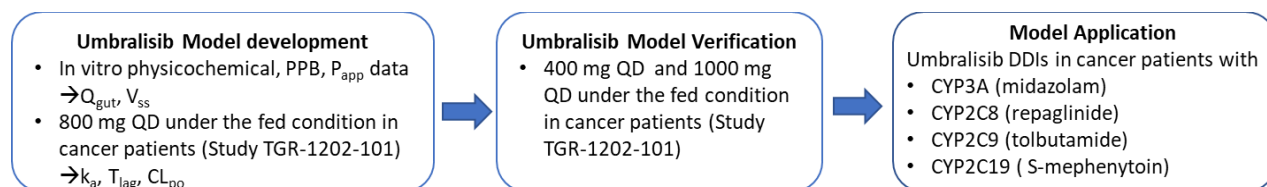
The proposed umbralisib dosing regimen is 800 mg once daily with food. The maximal dose examined is 1200 mg once daily with food. Following oral administration of umbralisib (b) (4) once daily under the fed condition, umbralisib AUC and C_{max} increased approximately dose proportionally across the dose range of 200-mg to 1000-mg on cycle 1 day1 (C1D1) and C2D1, and steady-state was achieved by C3D1. Umbralisib had a long half-life (166 h) and its accumulation ratio ranged from 5.2 to 11.3 for $AUC_{0-\infty}$ and 2.8 to 5.9 for C_{max} across the doses from 200- to 1200-mg.

Umbralisib was determined in vitro to be an inhibitor and inducer of CYP3A, and an inhibitor of CYP2C8, CYP2C9 and CYP2C19. The applicant intended to use a PBPK modeling approach to evaluate the potential of drug interactions of umbralisib with the substrates of these CYP enzymes. Refer to the Clinical Pharmacology review section for detail information on umbralisib regarding its ADME properties, in vitro and clinical studies used in PBPK modeling.

Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 18 Certara, Sheffield, UK). A scheme of the PBPK simulation strategy is shown in the figure below, which summarizes the studies used for model development and verification, and model applications in DDI predictions with CYP substrates. The model structure, model optimization and final model parameters for the umbralisib PBPK model are summarized in the table below. For prediction of DDIs with umbralisib as a perpetrator, Simcyp library substrate files of midazolam, repaglinide, tolbutamide, S-mephenytoin were used without any modifications. All simulations were completed using the sim-Healthy Volunteer population aged 20-50 years with 50% female subjects under the fed condition. All DDI simulations were conducted after 168 days of hypothetical QD umbralisib administration to ensure a maximum systemic umbralisib exposure for DDI prediction.

Figure 14: PBPK Modeling and Simulation Strategy



Source: This flow chart was generated by the reviewer.

Table 44: Final Input Parameters for Umbralisib in its PBPK Model

PARAMETER	Umbralisib	Reference
Physicochemical and Blood Binding		
MW (gm/mol)	571.5	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
logP _{ow}	5.52	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
Compound type	Monoprotic base	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
pKa	2.71	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
B:P	0.78	Predicted by Simulator
f _{up}	0.003	Mean of (5 µM) 12F158-rhiz - Human plasma protein binding, (2 µM) DMPK-5264-PB-01 - Preclinical and human plasma binding
Absorption		
Model	First Order	
P _{app} (x10 ⁻⁶ cm/s)	6.59	OPT-2017-164: 10 µM TGR-1202 + 3 µM elacridar A → B in P-gp expressing MDCK
P _{eff, max} (x10 ⁻⁶ cm/s)	0.825	Predicted by Simulator
f _{up, gut}	1.00	Fit-for-purpose assumption – worst-case scenario for perpetrator DDI prediction objective
Q _{gut} (L/hours)	5.56	Predicted by Simulator
k _s (hours ⁻¹)	0.99	Parameter Estimation (ka-flag-full-pbpbk pwkz)
T _{lag} (hours)	0.77	Parameter Estimation (ka-flag-full-pbpbk pwkz)
f _a	1.00	Fit-for-purpose assumption
Distribution		
Model	full PBPK	Fit-for-purpose
V _{ss} (L/kg) Method 2	60.5	Method 2 estimate resulted in improved fit over Method 1 (12.0 L/kg)
Elimination		
Model	Global Clearance	Fit-for-purpose
CL _{oral} (L/hours)	6.3	34% of oral clearance calculated from dose and AUC0-24h on C2D1 (11.6 L/hours) in TGR-1202-101 800 mg DP containing micronized DS in fed subjects
Interaction		
CYP2C8 K _i (µM)		(b) (4)
CYP2C9 K _i (µM)		
CYP2C19 K _i (µM)		
CYP3A4 K _i (µM)		
CYP2C8 f _{u, mic}		
CYP2C9 f _{u, mic}		
CYP2C19 f _{u, mic}		
CYP3A4 f _{u, mic}		
CYP3A4 EC ₅₀ (µM)		
Calibrated CYP3A4		
Ind _{max}		
CYP3A4 f _{u, app}		

Abbreviation: PDR = Pharmaceutical Development Report

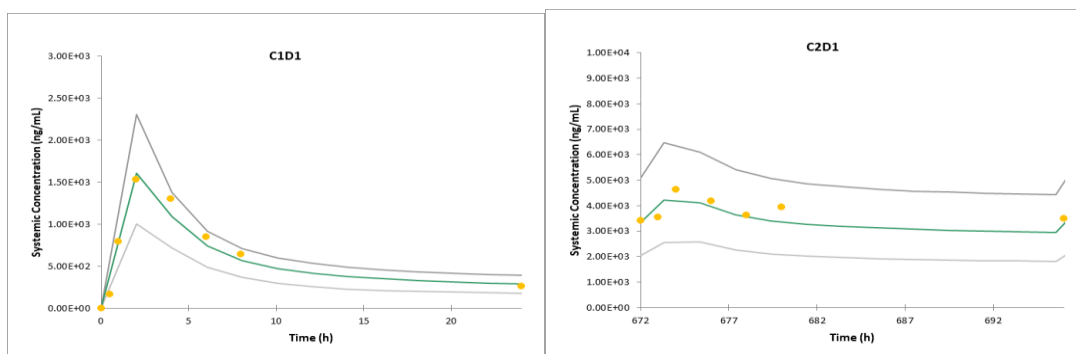
Source: Table 3.26 in the PBPK report (R_{TGT}/1/B)

Results

1. Can the PBPK model adequately describe the PK profiles of umbralisib?

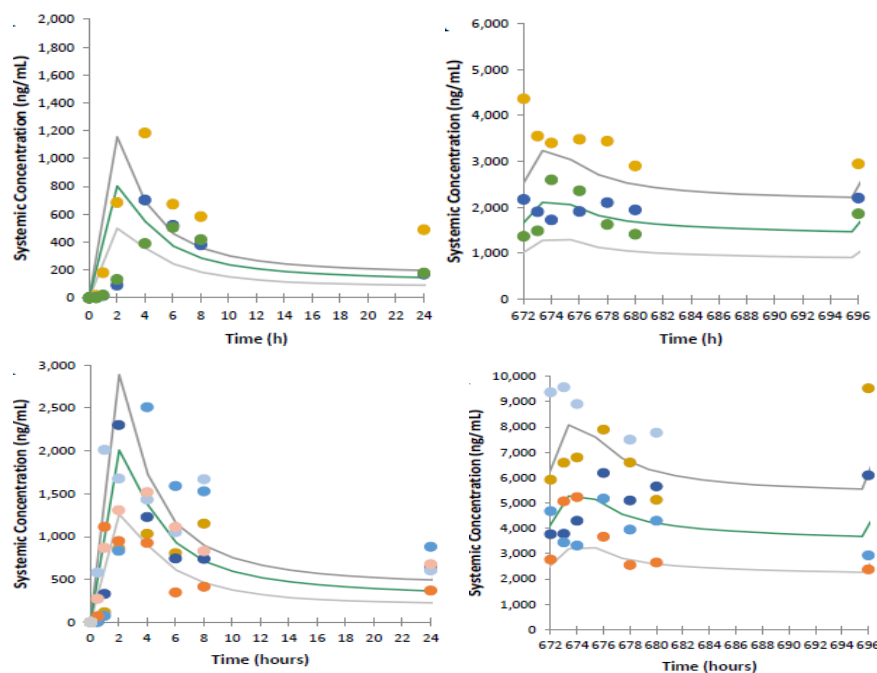
Yes, the PBPK model of umbralisib described umbralisib PK following administration of multiple doses of umbralisib in cancer patients (Figures 15 - 16 and Table 45).

Figure 15: Mean simulated (green lines) and observed (dots) PK profiles of umbralisib following 800 mg of umbralisib once daily in cancer patients (TGR-1202-101) on C1D1 (left) and C2D1 (right)



Source: Figure 4-1-1 and Figure 4-1-2 in the PBPK report (R_TGT/1/B). The grey lines represent the 5th and 95th percentiles of the total simulated population PK.

Figure 16: Predicted mean (green lines) and observed (dots) PK profiles following 400- (upper pane) and 1000-mg (lower panel) umbralisib once daily in cancer patients (TGR-1202-101) on C1D1 (left) and C2D1 (right).



Source: Figure 4-2-1 to Figure 4-2-4 in the PBPK report (R_TGT/1/B)

Table 45: Predicted and observed PK parameters following multiple doses of umbralisib once daily in cancer patients (TGR-1202-101) on C1D1 and C2D1

Dose (mg)		C1D1			C2D1		
		T _{max} (h)	C _{max} (ng/ml)	AUC _{0-24h} (h*ng/ml)	T _{max} (h)	C _{max} (ng/ml)	AUC _{0-24h} (h*ng/ml)
800	observed	2.1 (2-3.6)	1830 (23)	14200 (11)	3.9 (2.1-23)	4920 (50)	68700 (64)
	simulated	1.9 (1.2-2.9)	1610 (24)	13200 (19)	1.9 (1.3-2.9)	4360 (28)	76000 (33)
	sim/obs	0.9	0.88	0.93	0.49	0.89	1.11
400	PopPK	4 (4-6)	750 (45)	8830 (42)	0.0 (0-2.1)	2910 (37)	53200 (31)
	predicted	1.9 (1.2-2.9)	806 (24)	6600 (19)	1.9 (1.3-2.9)	2180 (28)	38000 (33)
	pred/obs	0.48	1.07	0.75	ND	0.75	0.71
1000	PopPK	3 (0.9-7.8)	1680 (36)	20700 (39)	4 (2-4)	6920 (36)	126000 (50)
	predicted	1.9 (1.2-2.9)	2020 (24)	16500 (19)	1.9 (1.3-2.8)	5440 (28)	95000 (33)
	pred/obs	0.63	1.2	0.8	0.48	0.79	0.75

C_{max} and AUC_{0-24h}: Geometric mean; T_{max}: median

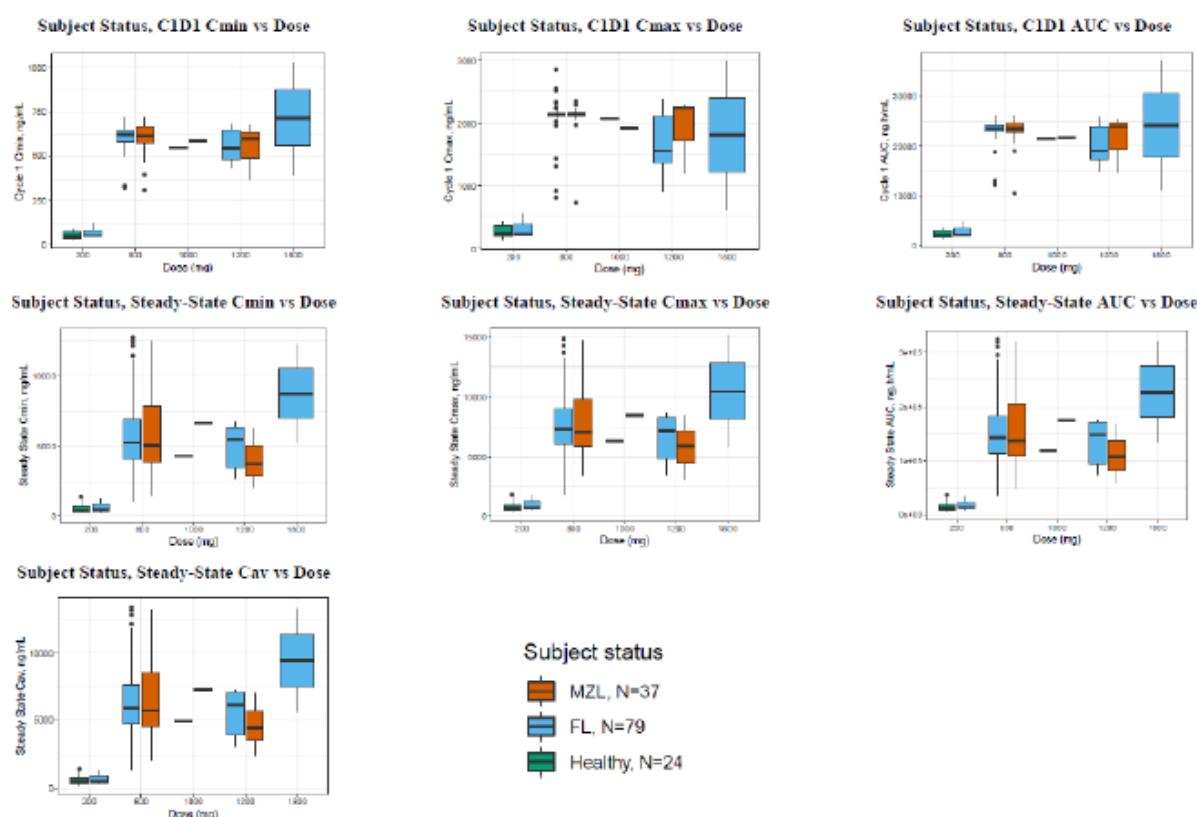
Source: the PBPK report (R_TGT/1/B)

Additional comments:

The multiple-dose PK data from the 800-mg umbralisib cohort (n=3) in Study TGR-1202-101 were used to build and optimize the umbralisib PBPK model during the model development. (b) (4) drug product was given under the fed condition in this study. Figures 15 - 16 and Table 45 show that the model could reasonably well recover umbralisib plasma concentrations in cancer patients, and the estimated exposures (C_{max} and AUC_{0-24h}) were mostly within 25% of the values observed or estimated from population PK (PopPK) analysis.

It should be noted that the applicant developed the PBPK model of umbralisib to predict DDI in cancer patients. However, all simulations were performed using the default sim-Healthy Volunteer population model. To apply the simulation results, there are two underlying assumptions. One is that umbralisib PK in healthy subjects is similar to that in cancer patients. This assumption may be supported by umbralisib PK at 200-mg dose in healthy subjects (TRG-1202-PK101) and cancer patients (TGR-1202-101) as shown in Figure 17 below. The second assumption is that there is no difference in enzyme abundance or activity of CYP3A and CYP2Cs between healthy subjects and cancer patients. This is the case for sim-Healthy Volunteer population and sim-Cancer population models. However, there are evidences that CYP enzyme abundance or activity may be altered in cancer patients (Coutant DE 2015; Schwenger H 2018). Therefore, the simulation results should be interpreted with caution.

Figure 17: PK parameters following oral administration of a single dose of 200-mg umbralisib under the fasted condition
(b) (4)



Source: Figure 4-4, the population PK analysis (TGTX-PMX-UMBRAISIB-1100-001)

2. Can PBPK analyses predict the effects of umbralisib on the pharmacokinetics of CYP substrates?

No, the PBPK analyses are inadequate to predict the complex inhibitory and induction effects on CYP3A, and the effects of umbralisib on the PK of the substrates of CYP2C8 (repaglinide), CYP2C9 (tolbutamide) and CYP2C19 (S-mephenytoin) due to the uncertainties about in vitro to in vivo extrapolation.

(b) (4)

(b) (4)

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Source: the reviewer's analysis

Conclusions

The effects of umbralisib on CYP3A, CYP2C8, CYP2C9 and CYP2C19 cannot be confidently predicted using the PBPK modeling approach. The potential of drug-drug interactions of umbralisib with substrates of these enzymes cannot be ruled out.

References

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4. Schwenger H et al. Harnessing Meta-analysis to Refine an Oncology Patient Population for Physiology-Based Pharmacokinetic Modeling of Drugs. *Clin Pharm Ther* 2018; 103 (2): 271-280

19.5. Grouped Preferred Terms Used in Safety Analyses Conducted by FDA

The FDA's Assessment:

The following table presents the FDA grouped preferred terms used for the safety analyses with this application.

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain	
Anemia	All PTs containing "anemia", RBC count decreased, hemoglobin decreased	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter, Cardiac flutter	
Bruising	All PTs containing "bruise," "contusion," or "ecchymosis"	Petechiae, Purpura, Increased tendency to bruise
Cardiac arrhythmias	High-level group term, "Cardiac arrhythmias"	
Cardiac failure	All PTs containing "cardiac failure", Congestive cardiomyopathy, Cardiomyopathy, Left ventricular failure, Cor pulmonale, Cardiopulmonary failure	
Chest pain	Chest discomfort, Chest pain, Angina pectoris	Noncardiac chest pain
Colitis	Colitis, Colitis microscopic, Colitis ulcerative, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic	Enteritis, Enterocolitis viral
Cough	All PTs containing "Cough"	
Cytomegalovirus infection	Cytomegalovirus infection, Cytomegalovirus viremia	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency	Post procedural diarrhea
Diarrhea or colitis	All terms under FDA's grouping of "Diarrhea" and "Colitis"	
Dizziness	All PTs containing "Dizziness" or "Vertigo"	
Dyspnea	All PTs containing "Dyspnea"	
Edema	Edema, Generalized edema, Face edema, Swelling face, Peripheral swelling, Swelling, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion	Edema blister, Localized sites of edema or swelling (e.g., Localized edema, Lip edema, Nasal edema, Periorbital edema, Eye

FDA Grouped PT	Included in Grouping	Not Included
		swelling, breast edema, testicular edema)
Fatigue	Asthenia, Fatigue, Lethargy	
Febrile neutropenia	Febrile neutropenia, Febrile bone marrow aplasia, Neutropenic infection, Neutropenic sepsis* * Note: Neutropenic sepsis is counted under both the “febrile neutropenia” and “sepsis” PTs	
Gastroenteritis	Gastroenteritis and specific types (e.g. viral), Enterocolitis viral	Gastroenteritis radiation, Gastritis
Gastrointestinal hemorrhage	All PTs containing “Gastrointestinal hemorrhage”, Gastric hemorrhage, Gastric ulcer hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage	
Headache	All PTs containing “headache”, Migraine	
Hemorrhage	All PTs containing “hemorrhage” or “hemorrhagic”, all PTs contained in FDA’s “Gastrointestinal hemorrhage” grouping, Menorrhagia, Hemarthrosis, Hemoptysis, Hematuria, Epistaxis	Petechiae, Purpura, FDA’s grouping for “Bruising”
Hemorrhage intracranial	Includes but is not limited to: Hemorrhage intracranial, Subdural hematoma, Subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	
Hepatitis	All PTs containing “hepatitis”, Hepatocellular injury, Hepatotoxicity, Drug-induced liver injury, Liver injury	FDA’s “Transaminase elevation” grouping, PTs containing “Hepatic failure”, Hepatic encephalopathy
Herpesvirus infection	High-level group term, “Herpes viral infection”	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hypertension	Hypertension, Essential hypertension, Blood pressure increased, Blood pressure systolic increased	
Hypotension	Hypotension, Diastolic hypotension, Orthostatic hypotension, Blood pressure decreased	
Leukocytosis ^a	Leukocytosis, Hyperleukocytosis, White blood cell count increase	
Lower respiratory tract infection	All PTs containing “bronchitis” or “lower respiratory tract infection”, Bronchiolitis, Lung infection	Bronchiectasis
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Noncardiac chest pain, Musculoskeletal pain, Musculoskeletal discomfort,	Arthralgia, Musculoskeletal stiffness

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FDA Grouped PT	Included in Grouping	Not Included
	Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain	
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion	Angina pectoris
Nausea	Nausea, Retching	Procedural nausea
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma, Lip squamous cell carcinoma	
Pneumonia	All PTs containing “pneumonia”, including within another word (e.g. bronchopneumonia), Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation	Lung infection
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease, Respiratory tract inflammation	
Rash	All PTs containing “rash”, all PTs containing “dermatitis” except as noted, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Skin reaction, Skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis	All PTs containing “Eczema”, Dermatitis atopic, Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes dermatitis, Acarodermatitis, Vaccination site rash, Photodermatosis
Renal insufficiency	All PTs containing “renal failure” or “nephropathy”, Acute kidney injury, Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal impairment, Hypercreatinemia, Chronic kidney disease	
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection, influenza, Haemophilus infection, Human metapneumovirus, Influenza like illness, Sinobronchitis	Upper respiratory tract infection, Lower respiratory tract infection
Sepsis	All PTs containing “Bacteremia” or “Sepsis”, including within another word (e.g. urosepsis) Septic shock * Note: Neutropenic sepsis is counted under both the “febrile neutropenia” and “sepsis” PTs	
Supraventricular tachycardia	High-level term, “Supraventricular arrhythmias”	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Immune thrombocytopenic purpura

FDA Grouped PT	Included in Grouping	Not Included
Thrombosis or thromboembolism	All PTs containing “thrombosis” except as noted, Peripheral embolism, Pulmonary embolism	Superficial thrombosis, Embolic cerebral infarction
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA’s “Hepatitis” grouping, PTs containing “hepatic failure”, Hepatic function abnormal
Upper respiratory tract infection	All PTs containing “upper respiratory tract infection,” “sinusitis,” “laryngitis,” “tonsillitis,” or “pharyngitis,” including within another word (e.g. nasopharyngitis), all PTs containing “rhinitis” except as noted, Rhinovirus infection, Human rhinovirus test positive, alpha hemolytic streptococcal infection	Rhinitis allergic
Urinary tract infection	All PTs containing “cystitis” or “urinary tract infection”, Pyelonephritis, Kidney infection	
Ventricular arrhythmia	High-level term, “Ventricular arrhythmias and cardiac arrest”	
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis	

^a Grouping for other lab-related AEs is similar, e.g., hyperglycemia = hyperglycemia + blood glucose increased, hypokalemia = hypokalemia + blood potassium decreased, lymphopenia = lymphopenia + lymphocyte count decreased

NDA 213176 (Original 1 & 2)/Umbralisib				
Assessment Aid Signatures				
DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Simon Williams, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: Simon Williams -S Digitally signed by Simon Williams -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Simon Williams -S, 0.9.2342.19200300.100.1.1 2001572753 Date: 2021.01.30 10 25 46 -05'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
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Clinical Pharmacology Reviewer	Edwin Chow, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
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Clinical Pharmacology TBPK Reviewer	Ying-Hong Wang, PhD	OCP/DPM	Sections: 6,19.4	Select one: ☒ Authored ☐ Approved
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Pharmacometrics Reviewer	Ruojing Li, PhD	OCP/DPM	Sections: 4, 19.4	Select one: ☒ Authored ☐ Approved
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Clinical Reviewer	Maryam Sarraf Yazdy, MD	OOD/DHMII	Sections: 2, 3, 4, 7, 8, 9, 10, 12, 13, 19	Select one: ☒ Authored ☐ Approved
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OOD: Office of Oncologic Diseases				
DHOT: Division of Hematology, Oncology, Toxicology				
OCP: Office of Clinical Pharmacology				
DPM: Division of Pharmacometrics				
DTPM: Division of Translational and Precision Medicine				
DCPI: Division of Cancer Pharmacology I				
OB: Office of Biostatistics				
DBIX: Division of Biometrics IX				
DHMII: Division of Hematologic Malignancies II				

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02/05/2021 09:06:45 AM

My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.

NDA Multi-disciplinary Review and Evaluation

Disclaimer: In this document, the sections labeled as “The Applicant’s Position” are completed by the Applicant, which do not necessarily reflect the positions of the FDA.

Application Type	New Drug Application
Application Number(s)	213176 – Original 2
Priority or Standard	Standard
Submit Date(s)	June 15, 2020
Received Date(s)	June 15, 2020
PDUFA Goal Date	June 15, 2021
Division/Office	Division of Hematologic Malignancies II
Review Completion Date	February 4, 2021
Established Name	Umbralisib (TGR-1202)
(Proposed) Trade Name	UKONIQ
Pharmacologic Class	Kinase inhibitor
Code name	Phosphatidylinositol 3-kinase inhibitor
Applicant	TG Therapeutics, Inc.
Formulation(s)	Tablets (200 mg)
Dosing Regimen	800 mg orally once daily continuously
Applicant Proposed Indication(s)/Population(s)	Treatment of adult patients with follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies.
Recommendation on Regulatory Action	Accelerated Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of adult patients with: Relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

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UKONIQ (umbralisib)

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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

%CfB	percent change from baseline
ABL1	Abelson murine leukemia viral oncogene homolog 1
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ARA	acid-reducing agent
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma/serum concentration-time curve
AUC ₀₋₄₈	area under the plasma concentration-time curve from time zero to 48 hours post-dose
AUC _{0-inf}	area under the plasma concentration-time curve from time zero to infinity
AUC _{0-t}	area under the plasma/serum concentration-time curve from time zero to the time of the last quantifiable concentration
C _{max}	maximum concentration
CD20	cluster of differentiation 20
CFR	Code of Federal Regulations
CI	confidence interval
CK1ε	casein kinase 1 epsilon
CMC	chemistry, manufacturing, and controls
C _{min,ss}	minimum plasma concentration at steady state
CNS	central nervous system
CR	complete response
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CV%	percentage coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DMF	drug master file
DOR	duration of response
DP	drug product
DS	drug substance
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate

NDA Multi-disciplinary Review and Evaluation: NDA 213176
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E-R	exposure-response
FDA	Food and Drug Administration
FL	follicular lymphoma
hERG	human ether-à-go-go-related gene
IC ₅₀	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IDB	integrated database
IND	Investigational New Drug
iNHL	indolent non-Hodgkin lymphoma
IRC	Independent Review Committee
ITT	intent-to-treat
MATE	multidrug and toxic compound extrusion transporter
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NDA	new drug application
NHL	non-Hodgkin lymphoma
OAT	organic anion transporter
OATP	organic anion transport protein
OCT	organic cation transporter
ORR	objective response rate
PBPK	physiologically-based PK
PD	progressive disease
PET-CT	positron emission tomography-CT
PFS	progression-free survival
P-gp	P-glycoprotein
PI3K	phosphoinositide 3-kinase
PI3K α , β , γ , δ	phosphoinositide 3-kinase alpha, beta, gamma, and delta isoforms
PK	pharmacokinetic(s)
PP	per protocol
PPK	population pharmacokinetics
PR	partial response
PT	preferred term
QD	once daily
QTc	corrected QT interval
QTcF	corrected QT interval by Fredericia
R ²	lenalidomide in combination with rituximab
SAE	serious adverse event

SAP	statistical analysis plan
SLL	small lymphocytic lymphoma
SOC	system organ class
SPD	sum of the products of longest diameters
T _{max}	time to maximum concentration
TEAE	treatment-emergent adverse event
TTR	time to response
US	United States

1 Executive Summary

1.1. Product Introduction

Umbralisib is a phosphoinositide-3-kinase-delta (PI3K δ) inhibitor in development for the treatment of patients with hematologic malignancies. While both the gamma and the delta isoforms of PI3K are restricted to cells of hematopoietic origin, the delta isoform has the highest expression on leukocytes. Umbralisib also inhibits Casein Kinase 1 epsilon (CK1 ϵ) which regulates the non-canonical Wnt/planar cell polarity pathway. This pathway is involved in lymphoid malignancy pathogenesis via regulation of cell survival, proliferation, chemotaxis, and migration. Regulation of the Wnt/ β -catenin pathway also modulates T-cell transcription factor-1, which affects the development of regulatory T cells (Tregs). The Applicant purports that this support of regulatory T-cells is the mechanism by which T-reg clones are supported, and the development of immune-related toxicity may be potentially mitigated.

On 15 June 2020, TG Therapeutics submitted Part 2 of their rolling NDA 213176 submission under 21 CFR 314.50 and Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act, seeking accelerated approval of umbralisib at the recommended dose of 800 mg by mouth daily for the following indication:

- Treatment of adult patients with follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The review team recommends accelerated approval of umbralisib for:

- Treatment of adult patients with relapsed or refractory follicular lymphoma (FL) who have received at least three prior lines of systemic therapy.

The recommended dose is 800 mg orally once daily.

This recommendation is based on efficacy findings from a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, single-arm, multi-cohort trial which included 131 patients with relapsed or refractory FL following at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The trial excluded patients with Grade 3b FL, large cell transformation, prior allogeneic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Patients received umbralisib 800 mg orally once daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) based on modified 2007 International Working Group criteria. Secondary endpoints included duration of response and progression-free survival.

For efficacy, the Applicant provided data for 117 patients with FL. The median age was 65 years (range: 29 to 87 years), 38% were female, 80% were White, 4% were Black, 73% had Stage III-IV disease, 38% had bulky disease and 97% had a baseline ECOG performance status of 0 to 1. The median number of prior systemic therapies was 3 (range 1 to 10) and 57% of the patients had received three or more regimens and 36% were refractory to their last therapy. The median follow-up time was 20.1 months (range: 13.5 to 29.6 months). The overall response rate per IRC was 42.7% (95% confidence interval [CI]: 33.6, 52.2), with 3.4% achieving a complete response. The median duration of response was 11.1 months (95% CI: 8.3, 16.4).

The review team has recommended accelerated approval of umbralisib for the treatment of adult patients with relapsed or refractory FL who have received at least three prior lines of systemic therapy. This contrasts with the UTX-TGR-205 eligibility criteria and the Applicant's proposed indication for those who have received at least two prior systemic therapies. The ORR of 42.7% with a lower bound of the confidence interval of 33.6% from a single-arm trial provides evidence of uncertainty regarding the clinical benefit of umbralisib in these patients. Further, to support accelerated approval, the efficacy data is considered in the context of available therapy for patients with FL in the 3rd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide (Table 4). In the 3rd line setting and beyond, consistent with the patient population enrolled in Study UTX-TGR-205, the overall response rates for these approved and available therapies, including single-agent and combinations, range from 57% to 80% with associated durability (Table 6). Thus, in the context of available therapy, there is residual uncertainty regarding the benefit of umbralisib in patients with relapsed or refractory FL who have received at least 2 prior systemic therapies. Based on the ORR of 42.7%, the lower bound of the confidence interval, and the higher response rates of available therapies in the intended patient population, the recommended indication is based on the characteristics of the FL patient population enrolled in UTX-TGR-205, specifically the

median of 3 prior lines of therapy, for which the data support the determination that umbralisib has clinically meaningful activity and a favorable benefit-risk evaluation. Therefore, the recommend indication is for adult patients with relapsed or refractory FL who have received at least three prior lines of systemic therapy.

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Umbralisib is a specific and orally bioavailable dual kinase inhibitor of phosphoinositide-3-kinase-delta (PI3Kδ) and casein kinase 1 epsilon (CK1ε).

Efficacy:

Efficacy of umbralisib in adult patients with relapsed or refractory (R/R) follicular lymphoma (FL) is based on the results from a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, single-arm, multi-cohort trial which included 131 patients with FL. Patients received umbralisib 800 mg twice daily continuously until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) based on modified 2007 International Working Group criteria. Among the 117 patients evaluable for efficacy, the median follow-up time was 20.1 months (range: 13.5 to 29.6 months). The overall response rate per IRC was 42.7% (95% CI: 33.6, 52.2), with 3.4% achieving a complete response. The median duration of response was 11.1 months (95% CI: 8.3, 16.4).

Safety:

The safety profile of umbralisib was supported by analysis of the 131 patients with follicular lymphoma from Study UTX-TGR-205 and a combined safety database of 371 patients with hematologic malignancies [marginal zone lymphoma (22%), follicular lymphoma (40%), diffuse large B-cell lymphoma or mantle cell lymphoma (20%), and other hematologic malignancies (18%)] who received single-agent umbralisib therapy.

In 131 patients with relapsed or refractory FL, the median duration of treatment was 7.3 months (range 1 day to 22.5 months) and the most common adverse events (≥20% of patients) were diarrhea-colitis, nausea, fatigue, musculoskeletal pain, vomiting, upper respiratory tract infection and abdominal pain. Treatment-emergent laboratory abnormalities of any grade occurring in ≥ 20% of patients were increased creatinine (75%), neutropenia (32%), anemia (28%), increased ALT/AST (27%) and thrombocytopenia (24%). Serious adverse events occurred in 22% of patients and no fatal adverse events occurred. Dose discontinuations due to an adverse event was reported in 12% of patients, most often due to diarrhea-colitis.

The primary safety issues identified with umbralisib include serious, including fatal, infections and cutaneous reactions, and serious diarrhea or colitis, hepatotoxicity, and neutropenia. In the 371 patients with hematologic malignancies, 51% of patients experienced a grade 3 or 4 toxicity, the most common including neutropenia (17%), diarrhea-colitis (8%), and increased AST/ALT (6%). Fifteen percent of patients discontinued umbralisib due to an adverse event, most often due to diarrhea-colitis and increased AST/ALT.

Benefit-Risk:

Umbralisib has an overall favorable benefit-risk in patients with relapsed or refractory follicular lymphoma; however, the benefit-risk determination was considered in the context of available therapy to support an accelerated approval.

The eligibility criteria for Study UTX-TGR-205 required patients with relapsed or refractory FL to have received at least two prior systemic therapies. The patients with FL enrolled had a median number of 3 prior therapies, 36% were refractory to their last therapy, and 31% were refractory to rituximab. The ORR of 42.7% (95% CI: 33.6%, 52.2%) warrants additional consideration in the context of available therapy in the 3rd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 3rd line setting and beyond, the ORRs for these therapies, including single-agent and combinations, ranges from 57% to 80% with associated durability. Taking into consideration the ORR of 42.7% with a lower bound of the confidence interval of 33.6%, and available therapies in a comparable treatment setting, the review team determined that the residual uncertainty regarding the benefit of umbralisib in these patients warrants restriction of the indication to patients with relapsed or refractory FL who have received 3 prior lines of systemic therapy, reflective of the patient population enrolled in Study UTX-TGR-205 and for which the data support the determination that umbralisib has clinically meaningful activity and a favorable benefit-risk evaluation.

Therefore, the benefit-risk of umbralisib is deemed favorable to support accelerated approval under 21 CFR 314.510 Subpart H for the following indication:

- Treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least three prior lines of systemic therapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Analysis of Condition</u>	- Follicular Lymphoma (FL) is considered incurable, and relapse is nearly universal. - With successive treatment regimens for relapsed or refractory disease, response rates and response duration tend to diminish. Patients with symptoms continue to receive treatment repeatedly until fatal resistant disease occurs. - Relapsed and refractory follicular lymphoma is a heterogenous disease and may have an indolent course. - Early relapse from first treatment, refractory disease and transformed lymphoma are associated with a poor prognosis.	Relapsed and refractory follicular lymphoma is a serious and life-threatening disease.
<u>Current Treatment Options</u>	- Treatment options for relapsed and refractory FL include chemotherapy, immunochemotherapy, and anti-CD20 monoclonal antibodies. - Numerous patients with relapsed or refractory FL cannot tolerant intensive chemotherapy due to age or comorbidities. - Approved chemoimmunotherapy and immunotherapy combinations have response rates of 55%-80% in the 3rd line setting and beyond, including 57%-79% in the 3rd and 4th line setting, which includes patients with rituximab refractory disease.	New treatments are needed for patients with relapsed or refractory FL, including chemotherapy-free treatments. Treatment options should be considered in the context of prior therapies and patient comorbidities

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<u>Benefit</u>	• Umbralisib was administered at 800 mg orally once daily • Study UTX-TGR-205 was an open-label, multi-center, single-arm, multi-cohort trial which included 131 patients with relapsed or refractory FL. • Overall response rate per independent review committee was 42.7% (95% CI: 33.6%, 52.2%) with a median duration of response of 11.1 months based on data from 117 patients with FL who were evaluable for efficacy.	Based on ORR with durability, umbralisib has clinically meaningful activity in patients with relapsed or refractory FL who have received at least 3 prior systemic therapies.
<u>Risk and Risk Management</u>	• Of 131 patients with follicular lymphoma treated with umbralisib 800 mg daily: ○ The median duration of treatment was 7.3 months (range 1, 22.5 months) ○ The most common adverse events (≥20% of patients) were diarrhea-colitis, nausea, fatigue, musculoskeletal pain, vomiting, upper respiratory tract infection and abdominal pain. ○ Laboratory abnormalities of any grade occurring in ≥ 20% of patients were increase in creatinine (75%), neutropenia (32%), anemia (28%), increase in ALT/AST (27%) and thrombocytopenia (24%). ○ Serious adverse events occurred in 22% of patients and no fatal adverse events occurred. ○ Dose discontinuations due to any adverse events were reported in 12% of patients with FL, most often due to diarrhea-colitis.	The safety profile of umbralisib is acceptable in the intended patient population. The USPI includes warnings and precautions for infections, neutropenia, diarrhea or colitis, hepatotoxicity, and severe cutaneous reactions.

1.4. Patient Experience Data

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

☐	The patient experience data that was submitted as part of the application, include:		Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as	[e.g., Section 6.1 Study endpoints]
	☐	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	[e.g., Section 2.1 Analysis of Condition]
	☐	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 was not submitted in the application, but was considered in this review.		

- Patients experience data was not submitted as part of this application.

X

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X

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2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma (NHL) and the most common (70%) indolent non-Hodgkin lymphoma (iNHL), with an estimated 15,000 new United States (US) cases annually (Freedman 2018; National Cancer Institute Published 2019). Its prevalence is strongly associated with age, with a median age at diagnosis of 63 years and an incidence of 2.8 per 100,000 person-years for people under 65 years of age and 14.7 per 100,000 person-years for people 65 years and over (Carbone et al. 2019). The majority of patients with FL has advanced-stage disease at diagnosis. Based on Surveillance, Epidemiology, and End Results statistics from 2009 to 2015, 88.4% of patients survive 5 years or more after diagnosis. Transformed follicular center B cells comprise mainly centrocytes with variable amounts of centroblasts, the frequency of which corresponds to the grade and the aggressiveness of the disease (grade 1, 2, or 3, depending on centroblast percentage) (Ma 2017). Approximately 85% of patients with FL have a translocation of chromosomes 14 and 18, resulting in the overexpression of BCL-2, which blocks apoptosis, and in additional gene mutations altering normal T-cell function within the malignant microenvironment that contribute to the pathobiology of the disease (Ghielmini 2010) and to a high degree of mutational heterogeneity in FL both from patient to patient and intra patient tumor diversity (Carbone et al. 2019).

The underlying biology of FL contributes to its disseminated presentation, varied prognosis, recurrent relapse, and progressive risk of transformation to high grade lymphoma. Even though patients are initially asymptomatic, a majority have advanced-stage disease at diagnosis, with 70% displaying bone marrow involvement (Freedman 2018). Asymptomatic patients are typically managed with observation until they meet the GELF criteria, which provide guidance on whether FL symptoms warrant treatment (Brice et al. 1997). FLIPI indices attempt to stratify patients into risk categories predictive of overall survival; however, the strongest determinant of survival is progression-free survival (PFS) at 2 years following first-line treatment with chemoimmunotherapy (Freedman 2018, Maurer et al. 2016). The introduction of rituximab has been a driving factor behind the improvement in FL survival rates (National Cancer Institute Published 2019).

Despite these therapeutic advances, FL remains incurable, with patients experiencing multiple relapses until ultimately succumbing to the disease. Furthermore, response rates progressively

diminish at each subsequent line of therapy, and the risk of developing transformed disease increases over time, with an incidence rate of 28% after 10 years (Montoto et al. 2007). FL patients who experience disease transformation have a substantially shorter median survival of 1.2 years from transformation.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

Currently, no standard-of-care treatment exists for FL following 2 prior therapies. In the relapsed or refractory setting, treatments vary depending on the clinical presentation, age, prior therapies, and overall health. Consensus guidelines (NCCN 2020) offer a variety of options for first-line therapy of FL with chemo-immunotherapy regimens including bendamustine+rituximab or rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), with milder regimens suggested for patients who are elderly or infirm, including rituximab monotherapy. Second-line and subsequent therapeutic options include repeat chemo-immunotherapy, lenalidomide+rituximab, ibrutinib, radioimmunotherapy, phosphoinositide 3-kinase (PI3K) inhibitors, or rituximab monotherapy. Treatment options are limited for patients who have received 2 or more prior therapies, with no Food and Drug Administration (FDA)-approved options specifically for this patient population.

A summary of FDA approved treatment options in the relapsed or refractory FL setting is shown in Table 1.

Table 1: Summary of FDA Approved Treatment Options in the Relapsed or Refractory FL Setting

Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Obinutuzumab (GAZYVA)	Treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen in	November 2017/ Full approval	1000 mg IV infusion on Days 1, 8, and 15 of Cycle 1, 1000 mg on Day 1 of Cycles 2-6 or Cycles 2-	Median PFS in obinutuzumab + bendamustine= not reached vs. bendamustine= 13.8 months HR=0.48 (95% CI: 0.34, 0.68)	Hepatitis B reactivation, PML, infusion reactions, hypersensitivity reactions including serum sickness, TLS, infections,

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Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Admini- stration	Efficacy Information	Important Safety and Tolerability Issues
	combination with bendamustine followed by obinutuzumab monotherapy		8, and then 1000 mg every 2 months for up to years		neutropenia, thrombocytopenia, immunization
Lenalidomide (REVLIMID®) in combination with a rituximab product	Treatment of adult patients with previously treated FL, in combination with a rituximab product	May 2019/ Full approval	20 mg PO QD on Days 1-21 of repeated 28-day cycles for up to 12 cycles	AUGMENT study: Median PFS (MZL and FL) + rituximab= 39.4 months (95% CI: 22.9, NE); vs. + placebo= 14.1 months (95% CI: 11.4, 0.62); HR=0.46 (95% CI: 0.34, 0.62) ORR in FL + rituximab=80% (95% CI: 73%, 86%) vs. + placebo=55% (95% CI:47%, 64%) MAGNIFY study: ORR=59% (95% CI: 51, 66)	Embryo-fetal toxicity, hematologic toxicity, venous and arterial thrombo-embolism, Hepato-toxicity, severe cutaneous reactions, TLS, impaired stem cell mobilization, hypersensitivity, second primary malignancies, tumor flare, serious and fatal cardiac adverse reactions
Idelalisib (ZYDELIG®)	Treatment of patients with relapsed FL in patients who received at least 2 prior systemic therapies	January 2018/ Full approval	150 mg PO BID	ORR=54% (95% CI:42%, 66%); CR=8%; PR=46%	Fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, infections, and intestinal perforation; severe

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Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Admini- stration	Efficacy Information	Important Safety and Tolerability Issues
					cutaneous reactions; anaphylaxis; neutropenia; embryo-fetal toxicity
Duvelisib (COPIKTRA®)	Treatment of adult patients with relapsed or refractory FL after at least 2 prior systemic therapies	September 2018/ Accelerated Approval based on ORR	25 mg PO BID; modify dosage for toxicity	OR=42% (95% CI: 31%, 54%); CR=1%; PR=41%	Fatal and serious toxicities: infections, diarrhea or colitis, cutaneous reactions, pneumonitis; hepato-toxicity; neutropenia; embryo-fetal toxicity
Copanlisib (ALIQOPA®)	Treatment of adult patients with relapsed FL who have received at least 2 prior systemic therapies	September 2017/ Accelerated Approval based on ORR	60 mg as 1-hour IV infusion on Days 1, 8, and 15 of a 28-day cycle on an intermittent schedule (3 weeks on and 1 week off); modify dosage for toxicity	ORR=59% (95% CI: 49%, 68%); CR=14%; PR=44%	Infections, hyper-glycemia, hyper-tension, NIP, neutropenia, severe cutaneous reactions, embryo-fetal toxicity

Abbreviations: BID, twice daily; CI, confidence interval; CR, complete response; FDA, Food and Drug Administration; FL, follicular lymphoma; HR, hazard ratio; IV, intravenous; MZL, marginal zone lymphoma; NE, not evaluable; NIP, non-infectious pneumonitis; ORR, overall response rate; PFS, progression-free survival, PO, oral; PML, progressive multifocal leukoencephalopathy; PR, partial response; QD, once daily; TLS, tumor lysis syndrome vs, versus.

Source: Drugs@FDA

While advances in treatment options have produced increases in overall survival, FL remains an incurable, life-threatening disease plagued by recurrent remissions. Furthermore, responses shorten with each subsequent line of therapy, highlighting the need for additional treatment options.

For relapsed/refractory FL, after 2 lines of systemic therapies, there are no fully approved treatment options; however, PI3K inhibitors idelalisib, copanlisib, and duvelisib have been granted accelerated approval with each carrying toxicities and dosing considerations which have limited their use. This paucity of therapeutic options represents a high unmet medical need for this serious and life-threatening condition.

FL is considered incurable and most patients eventually relapse or progress (Rivas-Delgado et al. 2019). Additionally, the response duration shortens after each relapse even in patients treated with rituximab combinations as the first-line option. Limited non-chemotherapeutic options exist for patients with relapsed or refractory disease following an anti-cluster of differentiation 20 (CD20) monoclonal antibody and an alkylating agent. Therefore, new treatments with alternative mechanisms are needed. There remains an unmet need for new drugs that will provide clinically meaningful efficacy with differentiated toxicity profiles.

The FDA's Assessment:

The FDA disagrees with the assertion that there are no FDA approved therapies for patients with FL who have received at least 2 prior therapies. Rituximab, bendamustine, bendamustine plus obinutuzumab, and lenalidomide plus a rituximab-product all have regular approval for patients with relapsed or refractory FL, which is inclusive of those patients with FL who have received at least 2 prior therapies. In addition, Table 1 above incorrectly indicates "Regular approval" for Idelalisib. In 2014, The FDA granted accelerated approval to Idelalisib for treatment of patients with relapsed follicular B-cell NHL who have received at least two prior systemic therapies. Furthermore, the table does not reflect the other approved therapies for patients with FL. The table below provides additional information:

Table 2: Additional Summary Information of FDA Approved Treatment Options in the Relapsed or Refractory FL Setting

Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Rituximab	Single Agent: Relapsed or refractory, low grade or follicular,	1997 Full approval	Dosing for FL: 375 mg/m ²	ORR 36% - 57%	infusion reactions, fever, lymphopenia, chills, infection

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Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Admini- stration	Efficacy Information	Important Safety and Tolerability Issues
	CD20-positive B-cell NHL as a single agent. Combination: Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to a rituximab product in combination with chemotherapy, as single-agent maintenance therapy. Previously untreated diffuse large B-cell, CD20-positive NHL in combination with (cyclophosphamide, doxorubicin,		See the Package Insert for details		and asthenia, hepatitis B reactivation

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Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Admini- stration	Efficacy Information	Important Safety and Tolerability Issues
	vincristine, and prednisone) (CHOP) or other anthracycline- based chemotherapy regimens.				
Obinutuzumab (GAZYVA)	Treatment of patients with FL who relapsed after, or are refractory to, a rituximab- containing regimen in combination with bendamustine followed by obinutuzumab monotherapy	November 2017/ Full approval	1000 mg IV infusion on Days 1, 8, and 15 of Cycle 1, 1000 mg on Day 1 of Cycles 2-6 or Cycles 2- 8, and then 1000 mg every 2 months for up to years	Median PFS in obinutuzumab + bendamustine= not reached vs. bendamustine= 13.8 months HR=0.48 (95% CI: 0.34, 0.68)	Hepatitis B reactivation, PML, infusion reactions, hypersensitivity reactions including serum sickness, TLS, infections, neutropenia, thrombocytope nia, immunization
⁹⁰ Y- ibritumomab tiuxetan	Treatment of patients with relapsed or refractory, low-grade or follicular B- cell NHL, and previously untreated follicular NHL who achieve partial or complete response to first-line chemotherapy	2002/ Full approval	See the Package Insert for details	ORR 74%	Infusion reaction, cytopenias, cutaneous and mucocutaneous reactions, MDS and leukemia

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Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues
Bendamustine	Indolent B-cell NHL that has progressed during or within six months of treatment with rituximab or a rituximab-containing regimen	2008/ Full approval	Dosing for FL: 120 mg/m ² See the Package Insert for details	ORR 74% CR 13%	Myelosuppression, Infections, Tumor lysis syndrome, secondary malignancies, skin reactions
Rituximab and hyaluronidase	Treatment of adult patients with FL: - Relapsed or refractory FL as a single agent - Previously untreated FL in combination with chemotherapy and as single-agent maintenance therapy - Nonprogressing FL as a single-agent after first-line CVP chemotherapy	2017/ Full approval	1,400 mg/hyaluronidase 23,400 units (fixed dose) SubQ See the Package Insert for details	ORR 84% (previously untreated FL in combination with chemotherapy)	
Lenalidomide (REVLIMID®) in	Treatment of adult patients	May 2019/ Full approval	20 mg PO QD on Days	AUGMENT study: Median PFS (MZL)	Embryo-fetal toxicity,

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Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Admini- stration	Efficacy Information	Important Safety and Tolerability Issues
combination with a rituximab product	with previously treated FL, in combination with a rituximab product		1-21 of repeated 28-day cycles for up to 12 cycles	and FL) + rituximab= 39.4 months (95% CI: 22.9, NE); vs. + placebo= 14.1 months (95% CI: 11.4, 0.62); HR=0.46 (95% CI: 0.34, 0.62) ORR in FL + rituximab=80% (95% CI: 73%, 86%) vs. + placebo=55% (95% CI:47%, 64%) MAGNIFY study: ORR=59% (95% CI: 51, 66)	hematologic toxicity, venous and arterial thrombo- embolism, Hepato-toxicity, severe cutaneous reactions, TLS, impaired stem cell mobilization, hyp ersensitivity, second primary malignancies, tumor flare, serious and fatal cardiac adverse reactions
Idelalisib (ZYDELIG®)	Treatment of patients with relapsed FL in patients who received at least 2 prior systemic therapies	January 2018/ Accelerated Approval based on ORR	150 mg PO BID	ORR=54% (95% CI:42%, 66%); CR=8%; PR=46%	Fatal and serious toxicities: hepatic, severe diarrhea, colitis, pneumonitis, infections, and intestinal perforation; severe cutaneous reactions; anaphylaxis; neutropenia; embryo-fetal toxicity

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Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Admini- stration	Efficacy Information	Important Safety and Tolerability Issues
Duvelisib (COPIKTRA®)	Treatment of adult patients with relapsed or refractory FL after at least 2 prior systemic therapies	September 2018/ Accelerated Approval based on ORR	25 mg PO BID; modify dosage for toxicity	OR=42% (95% CI: 31%, 54%); CR=1%; PR=41%	Fatal and serious toxicities: infections, diarrhea or colitis, cutaneous reactions, pneumonitis; hepato-toxicity; neutropenia; embryo-fetal toxicity
Copanlisib (ALIQOPA®)	Treatment of adult patients with relapsed FL who have received at least 2 prior systemic therapies	September 2017/ Accelerated Approval based on ORR	60 mg as 1-hour IV infusion on Days 1, 8, and 15 of a 28-day cycle on an intermittent schedule (3 weeks on and 1 week off); modify dosage for toxicity	ORR=59% (95% CI: 49%, 68%); CR=14%; PR=44%	Infections, hyper-glycemia, hyper-tension, NIP, neutropenia, severe cutaneous reactions, embryo-fetal toxicity
Tazemetostat (TAZVERIK™)	- Treatment of adult patients with relapsed or refractory follicular lymphoma whose tumors are positive for an EZH2 mutation as detected by an FDA-approved test	June 2020/ Accelerated Approval based on ORR	800 mg PO BID	EZH2 Mutant Follicular Lymphoma ORR= 69% (53%, 82%); CR=12%; PR=57% EZH2 Wild-Type Follicular Lymphoma ORR= 34% (22%, 48%) ;	

Product (s) Name	Relevant Indication	Year of Approval/ Type of Approval	Dosing/ Admini- stration	Efficacy Information	Important Safety and Tolerability Issues
	and who have received at least 2 prior systemic therapies - Treatment of adult patients with relapsed or refractory follicular lymphoma who have no satisfactory alternative treatment options			CR=4%; PR=30%	
Abbreviations: BID, twice daily; CI, confidence interval; CR, complete response; FL, follicular lymphoma; IV, intravenous, NHL, non-Hodgkin lymphoma, ORR, overall response rate; PR, partial response; QD, daily					

Table 3: Agents and Combination Regimens Commonly Used for Patients with Relapsed and Refractory Follicular Lymphoma

Drug or Regimen
Bendamustine ± rituximab
Bendamustine + obinutuzumab
Chlorambucil ± rituximab
Cyclophosphamide ± rituximab
Lenalidomide ± rituximab
Obinutuzumab
Obinutuzumab or Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone (R-CHOP or G-CHOP)
Rituximab or obinutuzumab + cyclophosphamide + vincristine + prednisone (CVP)
Copanlisib, Duvelisib, or Idelalisib
Tazemetostat

Source NCCN Guidelines B-Cell Lymphomas v1.2020

Radiation therapy, radioimmunotherapy, HSCT, CAR-T cell therapies and observation are other considerations.

In summary, overall response rates to available therapies, including those under accelerated approval, in patients with previously treated follicular lymphoma range from 36% to 80%. A summary and comparison with a description of the study populations of FDA approved therapies for relapsed and refractory follicular lymphoma are displayed in Table 4 and Table 5 below.

Table 4: Summary of Efficacy from Trials Supporting FDA Approved Therapies for Patients with Relapsed or Refractory Follicular Lymphoma (Regular Approval)

Therapy Number of Patients	Monotherapy			Combination Therapy		
	Rituximab N = 147 (control arm AUGMENT)	Rituximab N = 296	Bendamustine N = 166 (control arm GADOLIN)	Bendamustine + Obinutuzumab (GADOLIN) N = 155	Lenalidomide + Rituximab	
					MAGNIFY N = 177	AUGMENT N = 147
Population	1 prior	R/R low grade NHL or FL (3 studies)	≥ 1 prior Rituximab refractory	≥ 1 prior Rituximab refractory	1 prior	1 prior
ORR 95% CI	55% (47,64)	36*-57% *retreatment	75% (67, 81)	78% (72,84)	59% (51, 66)	80% (72,86)
CR	20%	6-14%	19%	16%	15% CRu 20%	35%
Median DOR	15 months (11, 25)	6.9-15 months	11.6 months	NR	NE 80% ≥ 12 months	36 months (25, NE)
Abbreviations: CI, confidence interval; CR, complete response; CRu, complete response unconfirmed; DOR, duration of response; FL, follicular lymphoma; NHL, Non-Hodgkin lymphoma; ORR, overall response rate; R/R, relapsed or refractory Source: FDA review of USPIs for Rituximab, Obinutuzumab, Lenalidomide						

Table 5: Summary of Efficacy from Trials Supporting FDA Approved Therapies for Relapsed and Refractory Follicular Lymphoma (Accelerated Approval)

	Tazemetostat		Copanlisib N = 104	Duvelisib N = 83	Idelalisib N = 72
	Tazemetostat EZH2 WT N = 54	Tazemetostat EZH2 MT N = 45			
Population	≥ 2 prior therapies	≥ 2 prior therapies	≥ 2 prior therapies	≥ 1 prior, Rituximab refractory Exclude 3b, prior transplant	≥ 2 prior, Refractory to rituximab and alkylator
Median Prior Treatments (Range)	3 (1-8)	2 (1,11)	3 (2,8)	3 (1,10)	4 (2, 12)
Rituximab Refractory	59%	49%	57%	100%	100%
ORR 95% CI	35% (23, 49)	69% (53, 82)	59% (49, 68)	42% (31, 54)	54% (42,66)
CR	4%	13%	14%	1%	8%
Median DOR	13 (5.6, NE) 37% ≥ 12 months	11 (7.2 NE) 23% ≥ 12 months	12.2 (0+, 23)	NE 17% ≥ 12 months	NE (0,+ 14.8+)
Abbreviations: CI, confidence interval; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, overall response rate Source: FDA review of USPI for Copanlisib, Duvelisib, and Idelalisib					

To further evaluate the data for available therapies in patients with relapsed or refractory follicular lymphoma, the FDA performed a subanalysis evaluating the response rate in patients with at least 2 or 3 prior therapies and is summarized in the table below.

Table 6: FDA Subanalysis of Efficacy from Trials Supporting FDA Approved Therapies for Relapsed or Refractory Follicular Lymphoma After at Least 2 or 3 Prior Therapies (Regular Approval)

	MAGNIFY (2019) Rituximab + Lenalidomide		AUGMENT (2019) Rituximab + Lenalidomide		GADOLIN (2016) Bendamustine + Obinutuzumab vs. Bendamustine	
	N = 115	N = 74	N = 67	N = 44	N = 173 N = 79 BO vs. 94 B	N = 66 N = 30 BO vs 36 B
Population	≥2 3 rd Line +	≥ 3 4 th Line +	≥2 3 rd Line +	≥ 3 4 th Line +	≥2 3 rd Line +	≥ 3 4 th Line +
Prior Therapy Median (Range)	3 (2,10)	4 (3,10)	3 (2,12)	3 (3,12)	2 (2,10)	3 (3,10)
Rituximab Refractory	47%	45%	0	0	100%	
ORR 95% CI	57% (48, 66)	59% (47, 70)	81% (69, 89)	80% (64, 90)	BO = 75% B = 79% (63, 84) (69, 86)	BO = 70% B = 75% (50, 85) (57, 87)
CR	13%	11%	34%	32%	BO = 20% B = 20%	BO = 27% B = 19%
Median DOR - months 95% CI	5.1 (2.3, 8.5)	NR (8.8, -)	NR (19.6, -)	NR (19.3, -)	NR (19.5, -) BO 13 (8.9, 16.8) B	26.4 (20.4, -) BO 13.2 (7, -) B
Abbreviations: B, bendamustine; BO, bendamustine plus obinutuzumab; CI, confidence interval; CR, complete response; DOR, duration of response; NR, not reached; ORR, overall response rate Source: FDA analysis from efficacy datasets						

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Umbralisib is a new molecular entity and is not currently marketed in any country. New Drug Application (NDA) 213176 is submitted for accelerated approval of single agent umbralisib for

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the treatment of adult patients with FL who have received at least (b) (4) prior systemic therapies.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

3.2. Summary of Presubmission/Submission Regulatory Activity
The Applicant's Position:

Date	Event Summary
04 March 2020	Orphan Drug Designation granted to umbralisib for treatment of FL (#19-7268)
14 January 2020	Type B meeting – Other meeting to discuss adding a second indication for FL in NDA 213176
10 January 2020	Presubmission of Part 1 of 2 of NDA 213176
20 December 2019	FDA Granted Rolling Review of NDA 213176
16 September 2019	Type B meeting – Breakthrough Therapy to discuss the format and content of NDA 213176
10 June 2019	Type B meeting – Breakthrough Therapy meeting to discuss the overall development plan of single agent umbralisib in MZL intended to support consideration for an accelerated approval opportunity
13 August 2018	Type B meeting – CMC to discuss the CMC umbralisib development program
18 April 2018	Type C meeting– Guidance to discuss the nonclinical and clinical pharmacology program for umbralisib
03 January 2018	Type B meeting – End-of-Phase 1 meeting to discuss the ongoing study UTX-TGR-205
23 September 2015	IND (b) (4) was activated and opened in the United States
28 December 2012	IND 116762 was activated and opened in the United States
05 April 2012	IND (b) (4) was activated and opened in the United States

Abbreviations: CMC, Chemistry, Manufacturing, and Controls; FDA, Food and Drug Administration; FL, follicular lymphoma; IND, Investigational New Drug; MZL, marginal zone lymphoma.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

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

4.1. Office of Scientific Investigations (OSI)

Clinical site inspections were requested for two clinical sites in the U.S. with the highest accrual for Study UTX-TGR-205, along with inspection of the Applicant, TG Therapeutics. The clinical sites included 1) Site HOB - MD Anderson (Felipe Samaniego, MD; Houston, TX), which enrolled 24 patients and 2) Site CLA - Levine Cancer Institute (Nilanjan Ghosh, MD; Charlotte, NC), which enrolled 19 patients. Based on the clinical site inspections, the study data from the clinical sites were considered reliable. Additionally, the Applicant was inspected concerning its oversight of Study UTX-TGR-205. Based on the inspection, the Applicant's oversight of the clinical trial and the quality of conducting the study were determined to be adequate. The audited study data submitted to the Agency was deemed acceptable in support of the NDA application, in compliance with Good Clinical Practice.

4.2. Product Quality

Umbralisib tosylate is a small chiral BCS class II molecule that is produced as a single enantiomer that is manufactured by Alembic Pharmaceuticals Limited, India, as a single enantiomer in a linear, two-stage synthesis. The drug product is presented as a 200 mg immediate-release tablet for oral administration. It is a green film-coated, oval-shaped tablet, debossed with "L474" on one side and plain on the other.

The recommended starting dose for the drug product is 800 mg orally, once daily until disease progression or unacceptable toxicity.

Based on the information provided by the Applicant, the Office of Product Quality (OPQ) has determined that the data is adequately supportive and the potential risks to patient safety, product efficacy, and product quality are mitigated appropriately. Therefore, OPQ recommends approval of umbralisib and grants a (b) (4) month retest for the drug substance and a 36-month shelf-life for the drug product when stored in HDPE bottles at 20°C and 25°C (68°F to 77°F).

4.3. Clinical Microbiology

The data to support the microbiology assessment were adequate and there were no issues from a microbiology standpoint.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Umbralisib (also known as RP-5264, TGR-1202, (b) (4) and RP-5307) is a small molecule inhibitor of phosphoinositide-3-kinase delta (PI3K δ) and casein kinase 1 epsilon (CK1 ϵ). The targets mediate tumor-progressive signaling in a variety of hematologic malignancies.

Umbralisib binds to human PI3K δ and CK1 ϵ with dissociation constants (K_d) of 6.2 nM and 180 nM, respectively. A screen of 442 kinases incubated with 1 μ M of umbralisib showed that the phosphorylated Abelson murine leukemia viral oncogene homolog 1 containing the mutation F317I (ABL1 (F317I)-phosphorylated) kinase was inhibited at levels comparable to CK1 ϵ . In vitro growth-inhibitory activity was assessed in a panel of 13 human leukemia and lymphoma cell lines. Growth inhibitory (GI₅₀) values ranged from 0.6 to 66 μ M after the cells were treated for 72 or 96 hours with umbralisib. The test article also inhibited cytokine-mediated adhesion and migration in vitro.

The in vivo antitumor activity of umbralisib was evaluated in a MOLT-4 xenograft model. MOLT-4 tumor-bearing mice were dosed orally with umbralisib at 150 mg/kg/day for 25 days, with the measurement of tumor growth continuing until 41 days after dosing initiation. The test article dosing group had tumors growing at a slower rate than the control group tumors.

Safety pharmacology studies assessed the effects of umbralisib on cardiovascular, central nervous system (CNS), and respiratory function. Umbralisib had no toxicologically-significant effects on cardiovascular function in a cardiovascular study in dogs, and had no effects on neurobehavioral function or temperature in mice. Respiratory function was affected by umbralisib with decreases in tidal volume as much as 24%, respiration rate as much as 38%, and minute volume as much as 46% observed in respiratory studies conducted in mice administered a single umbralisib dose of 50 to 500 mg/kg.

The oral bioavailability of umbralisib in mice and dogs were 47% and 34% respectively for the 2 species. A mass balance study in male mice demonstrated that 89% and 5% of umbralisib is excreted in feces and urine, respectively. Umbralisib metabolism was evaluated in vitro with liver microsomes. After 60 minutes of incubation with mouse, dog, and human liver microsomes, 75%, 77%, and 86% respectively of umbralisib remained.

The repeat-dose studies in mice and dogs referenced above were conducted to assess the general toxicity of umbralisib. The drug was administered once daily for 26 weeks in mice and 39 weeks in dogs, with the doses and durations informed by the experience of the 13-week repeat-dose studies in both species. The studies were conducted using the oral route of administration, which is consistent with the intended clinical route of administration. There were several unscheduled deaths in the mouse study, while dose reductions and dosing holidays were applied to the dog study. Drug-related findings included decreased white blood cells (WBCs) and differentials, increased liver weights and alkaline phosphatase (ALP) levels, and lymphoid depletion.

In the 26-week mouse study, umbralisib was administered by oral gavage at 30, 100, and 300 mg/kg/day with 4 weeks of recovery. Umbralisib-induced mortality was observed in the study with half of all observed mortalities and unscheduled euthanasia's occurring in the 300 mg/kg dose group. The exact causes of death in these animals were undetermined. In the surviving animals, toxicities included reduced lymphocyte levels, increased liver weights and ALP levels, and inflammatory findings. In the 39-week dog study, dogs were initially dosed orally with umbralisib at 10, 30, or 100 mg/kg/day, but doses were reduced to 8, 20, and 50 mg/kg/day due to notable weight loss as the study proceeded. The high-dose group (100/50 mg/kg/day) also had a dosing holiday due to continued weight loss. Reduced RBCs, hemoglobin, hematocrit, and reticulocyte levels were observed in all umbralisib-dosed conditions. Microscopic findings were limited to decreased cellularity in the lymph nodes and the thymus. Additional findings of decreased weight and the presence of debris in the lumen, and tubular degeneration and atrophy in the testes were noted in the 13-week repeat-dose study in dogs.

A combined male and female fertility study was conducted in mice with umbralisib administered once daily at doses of 50, 150, or 300 mg/kg/day, starting 28 days prior to pairing and through mating in males and starting 14 days prior to pairing through Gestation Day (GD) 7 in females. Umbralisib-related findings included reduced testis and epididymis weights, and reduced sperm count and motility in the mid- and high-dose groups. Findings in female mice included increased post-implantation loss and increased resorption. Exposure at 150 mg/kg/day is approximately 1.3 times the recommended human clinical dose based on the toxicokinetic (AUC) values.

In an embryo-fetal development study, daily oral administration of umbralisib at 100, 200, or 400 mg/kg/day to pregnant mice on GD 6-15 resulted in increased litter losses, visceral findings and fetal skeletal abnormalities in all dose groups. Malformations noted were increased frequency of cleft palates in the mid- and high-dose groups and low incidence nasopharyngeal fistula (one fetus) at high dose. The 100, 200, and 400 mg/kg groups had exposures that were 0.9, 1.4, and 2.4 times the exposures at the recommended clinical dose based on AUC. In an embryo-fetal development study in female rabbits, daily administration of umbralisib at 30,

100, or 300 mg/kg/day on GD 6-19 resulted in maternal toxicity characterized by a 50% reduction in food intake and an 8% reduction in body weight by the end of the dosing period. Fetal weights were lower in the high-dose group. Elevated fetal abnormalities were noted in the mid- and high-dose groups compared to the concurrent controls, although the levels were considered within the normal range for this strain of rabbit. The 30, 100, or 300 mg/kg/day doses resulted in exposures that were 0.03, 0.08, and 0.03 times the exposures at the recommended clinical dose based on AUC. There was high inter-animal variability in the toxicokinetic values in this study within each dose group, reduced exposures at high dose, and lack of dose-dependence in exposures observed in rabbits.

Umbralisib was not mutagenic in the in vitro bacterial reverse mutation test or clastogenic in either the in vitro chromosomal aberrations assay or in the in vivo bone marrow micronucleus assay in mice. No carcinogenicity studies have been conducted or are warranted to support the marketing of umbralisib for the current indications.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of umbralisib for the proposed indications.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

The following NDAs and Drug Master Files (DMFs) are referenced in this application:

Investigational New Drug (IND) (b) (4), IND 116762, IND (b) (4), DMF (b) (4), DMF (b) (4), and DMF (b) (4).

5.3. Pharmacology

Primary pharmacology

The FDA's Assessment:

In vitro and in vivo pharmacology studies conducted with umbralisib assessed the mechanism of action and the pharmacological activity. The binding affinity for CK1 ϵ and PI3K was determined with a competitive binding assay based on phage display (Study # TGT027-01-S-00001). Umbralisib was incubated with CK1 ϵ and PI3K variants α , β , δ , and γ for an hour at room temperature prior to an assessment of binding affinity (K_d). The resulting K_d s were 180 nM for CK1 ϵ and 6.2 for PI3K δ . The K_d s for the other PI3K variants were in the μ M range.

Inhibitory activity of umbralisib

Umbralisib K_d (nM)					
Kinase	CK1 ϵ	PI3K α	PI3K β	PI3K δ	PI3K γ

	180	>10000	>10000	6.2	1400

The selectivity of umbralisib was determined by evaluating its binding to a panel of 442 kinases that included PI3K variants and CK1 ϵ (Study # INO006-01-P-00001). Using the same platform that determined the K_d for umbralisib, the test article was incubated with the panel of kinases at 1 μ M for an hour at room temperature prior an assessment of binding inhibition normalized to control conditions. Beyond the intended targets, phosphorylated Abelson murine leukemia viral oncogene homolog 1 containing the mutation F317I (ABL1 (F317I)-phosphorylated) was the only kinase in the panel that was inhibited by the test article at levels beyond the 65% threshold. With an inhibition level of 72%, ABL1 was inhibited at levels comparable to CK1 ϵ , which had an inhibition level of 73% in the same assay.

The in vitro inhibitory effect of umbralisib on malignant cell proliferation was evaluated with a panel of 13 leukemia and lymphoma cell lines (RPMI-8226, U266B1, MM1.S, MM1.R, DLBCL, Toledo, Daudi, Raji, CCRF-CEM, MOLT-4, U937, THP-1, and Jurkat. Study # IVT-5264-LCA-01). Umbralisib was incubated with the cell lines for 72 or 96 hours at 37°C. Growth was determined with a 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay and normalized to untreated conditions. Growth inhibitory (GI₅₀) values ranged from 14.9 μ M (Daudi, a Burkitt's lymphoma cell line) to 0.58 μ M (Toledo, a DLBCL/non-Hodgkin's lymphoma cell line).

In vitro proliferation inhibitory activity of umbralisib

Cell line	Disease origin	GI ₅₀ (μ M)
RPMI-8226	Myeloma	65.56
U266B1		0.61
MM1.S		3.16
MM1.R		2.59
DLBCL	DLBCL	3.14
Toledo		0.58
Daudi	Burkitt's lymphoma	14.90
Raji		4.66
CCRF-CEM	ALL	6.15

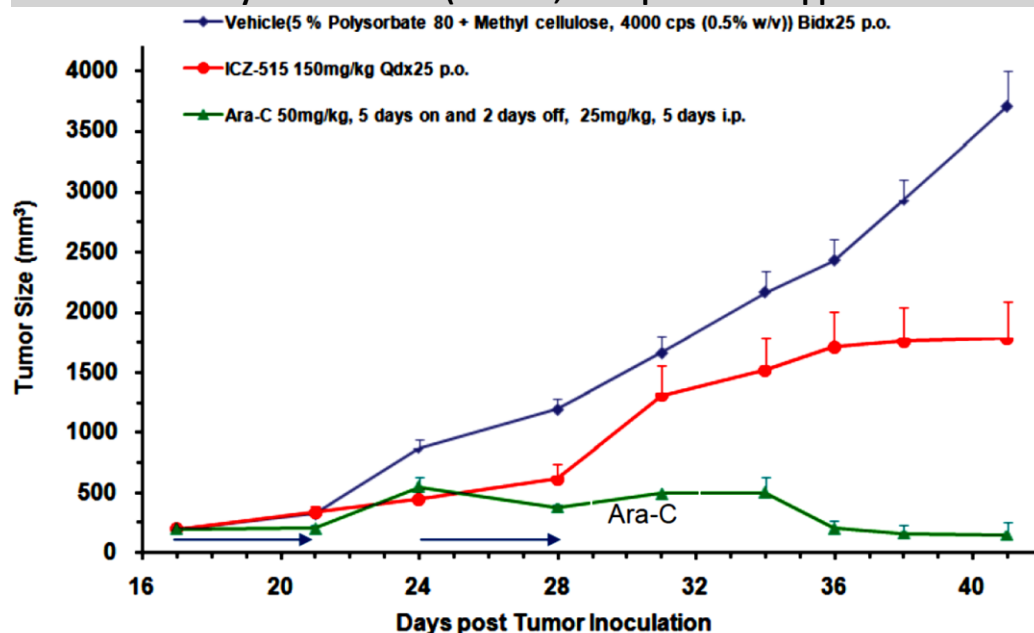
Cell line	Disease origin	GI ₅₀ (μM)
MOLT-4		1.33
U937	Histiocytic lymphoma	3.64
THP-1	AML	1.94
Jurkat	ALL	1.87

To determine if umbralisib inhibits cell adhesion (Study # VT-5264-VCAD-29), Daudi cells were treated with the test article at 1 μM for an hour prior to a brief plating on VCAM- and CXCL12- or CCL19-coated plates with centrifugation at room temperature. The plates were washed and the remaining cells were fixed and stained prior to plate reading for absorbance at 570 nm. Umbralisib inhibited CXCL12-mediated adhesion by 50% and CCL19-mediated adhesion by 70%.

Umbralisib inhibition of cell migration was also evaluated with Daudi cells (Study # IVT-5264-VCMIG-28). The cells were added to VCAM-coated migration chamber inserts which were then added to chambers containing CXCL12, CXCL13, or CCL19, with umbralisib at 1 μM for 5 hours at room temperature. Cells that migrated to the underside of the migration chamber insert were stained prior to plate reading for absorbance at 570 nm. Umbralisib inhibited CXCL12- and CCL19-mediated migration by 70% and CXCL13-mediated migration by 80%.

Umbralisib's in vivo antitumor activity was evaluated in a Molt-4 xenograft model (Study # Incozen-CP-P006). The Molt-4 cell line was established subcutaneously in female NOD/SCID mice prior to oral dosing with umbralisib at 150 mg/kg for 25 days. Tumors were measured 3 times per week and the mice were weighed weekly. The tumor volumes were determined and normalized to the untreated condition. A group of mice were dosed with Ara-C as a dosing control with known antitumor effects on the model. The animals were euthanized on day 41. Umbralisib-dosed animals had reduced tumor growth rates compared to untreated animals.

Antitumor activity of umbralisib (ICZ-515; excerpted from Applicant's submission)



Secondary Pharmacology

The Applicant's Position:

Umbralisib demonstrated selectivity against a panel of 442 kinases in a KINOMEScan™ competition binding assay. At a fixed concentration of 1 μ M, umbralisib inhibited ligand binding of only 3 kinases at greater than the 65% inhibition cutoff: PI3K δ (100% inhibition), casein kinase 1 epsilon (CK1 ϵ) (73% inhibition), and phosphorylated Abelson murine leukemia viral oncogene homolog 1 (ABL1)(F317I)-phosphorylated (72% inhibition).

The FDA's Assessment:

The FDA agrees with the Applicant that umbralisib at a concentration of 1 μ M inhibited 3 out of 442 kinases at levels greater than 65%. One of the 3 kinases, ABL1(F317I), is not an intended target and was inhibited at levels comparable to CK1 ϵ at the concentration tested.

Safety Pharmacology

The Applicant's Position:

In a cell-based human ether-à-go-go-related gene (hERG) assay, the IC₅₀ for umbralisib was found to exceed 100 μ M (highest tested concentration), a concentration which is beyond the relevant human concentrations of umbralisib in the circulation. In electrocardiogram (ECG) evaluations in dogs, oral doses of umbralisib up to 250 mg/kg (equivalent to 5,000 mg/m² or 9,722 mg in a 70 kg human) did not result in any changes in cardiovascular parameters. In a

central nervous system (CNS) evaluation in mice, after a single dose of umbralisib at doses up to 300 mg/kg (equivalent to 900 mg/m² or 1707 mg in a 70 kg human), there were no changes in functional observational battery observations. In mice, after a single dose of umbralisib at doses up to 500 mg/kg (equivalent to 1,500 mg/m² or 2917 mg in a 70 kg human), there were dose-dependent decreases in tidal volume, respiration rate, and minute volume, which were considered minimal and non-adverse.

The FDA's Assessment:

The FDA agrees with the Applicant's summary for safety pharmacology. Additional details regarding the safety pharmacology assessments are provided below.

A. Central Nervous System

CD-1 mice that were part of the 26-week GLP toxicology study were subjected to a CNS functional observation battery (FOB). The animals were dosed with umbralisib daily with 30, 100, or 300 mg/kg. Overall, umbralisib had no significant effects on neurobehavioral function at doses up to 300 mg/kg.

B. Respiratory

In a study evaluating the effects on respiratory function (Study # 037274), CD-1 mice were administered a single oral dose of umbralisib (50, 150, or 500 mg/kg) or vehicle (0.5% methylcellulose and 10% PS80 in water). Respiratory measurements including tidal volume, respiratory rate, and derived minute volume, were taken at 0.25 through 8 hours after dosing. Compared to control conditions, umbralisib caused a 24% decrease in tidal volume at the high dose by the end of the testing period and transient decreases in respiratory rate (lowest of 36% and 38% at 1 hour for the 50 and 150 mg/kg groups, and 24% at 1.75 hours for the 500 mg/kg) and tidal volume at all doses tested (lowest of 11% at 2.25 hours for the 50 mg/kg group, and 15% at 4.25 hours for the 150 mg/kg group). Minute volumes in the umbralisib-treated conditions were at their relative lowest between 1 and 2 hours after dosing, with maximum differences of 43% and 47% for the 50 and 150 mg/kg groups at 1 hour, and 39% for the 500 mg/kg group at 1.75 hours.

C. Cardiovascular

An in vitro hERG channel inhibition study (Study # CYP0358-R10) with hERG-expressing cells incubated with umbralisib at concentrations up to 100 µM showed that the test article had an IC₅₀ greater than the highest dose tested. In vivo cardiovascular assessments were conducted as part of a 13-week repeat dose general toxicology study in dogs. ECG examinations showed that umbralisib at doses 30, 100, or 250 mg/kg did not result in any umbralisib-related effects on CV system parameters.

5.4. ADME/PK

The Applicant's Position:

After a single oral dose, umbralisib absorption was faster in mice, with a time to maximum concentration (T_{max}) of 0.5 hours, compared to 2, 7, and 3 hours in rats, dogs, and monkeys, respectively. The absolute oral bioavailability, ranked from highest to lowest, was >100% in rats, 51.4% in dogs, 46.8% in mice, and 30.3% in monkeys. Following repeat oral administration to mice and dogs, the systemic exposures generally increased in a less-than-dose proportional manner over a dose range of 30 to 750 mg/kg/day in mice and 30 to 500 mg/kg/day in dogs. Little to no drug accumulation occurred in mice or rats, but 2- to 13-fold drug accumulation was apparent in dogs. No consistent sex-related effects were apparent in any animal species tested. Plasma protein binding of umbralisib ranged from 99.7% to 99.8% in animals and humans. In mice, umbralisib was widely distributed, with the highest concentrations in the gastrointestinal, metabolic/excretory, fatty, secretory, and endocrine tissues and the lowest concentration in brain, demonstrating penetration of umbralisib occurred in richly perfused organs, while passage to the CNS was limited. There was no meaningful ocular distribution. Fecal elimination was the primary excretion pathway.

The FDA's Assessment:

The FDA generally agrees with the Applicant's statement. See the review below for additional details regarding the PK studies.

Type of Study	Major Findings
Absorption	
Single dose Bioavailability study of ICZ-515 in Beagle Dogs (DMPK-ICZ-515-PK-04&25)	Beagle dogs were given single oral and IV doses of 1 mg/kg and 30 mg/kg. • Oral bioavailability was 33.52% (different from the levels stated by the Applicant above). • T_{max} was 0.7.0 hours. • $T_{1/2}$ was 37.13 hours.
Pharmacokinetic Study of RP5307 (PTSA salt of RP5264) after Single Oral and Intravenous Administration to Balb/C Mice (DMPK-5307-PK-13)	Male balb/C mice were given single oral and IV doses of 20 and 1 mg/kg, respectively. • Oral bioavailability was >47%. • T_{max} was 0.5 hours. • $T_{1/2}$ was 2.4 hours.
Distribution	

Type of Study	Major Findings					
Mass Balance in Male CD-1 Mice and Tissue Distribution by Quantitative Whole Body Autoradiography in Male C57BL/6 Mice Following a Single Oral Administration of [14C]TGR-1202 (C18008)	Tissue	Mean mouse tissue Concentration (µg/g or µg/mL) of umbralisib Over Time				
		1 hr	2 hrs	24 hrs		
	Plasma	10.7	14.6	2.29		
	Heart	48.0	51.0	2.92		
	Liver	122	144	31.1		
	Spleen	21.6	32.9	1.99		
	Lung	22.0	25.8	1.78		
	Kidney	46.9	76.5	5.63		
	Brain	10.3	19.8	0		
	Stomach	626	372	6.14		
	Small Intestine	1304	699	39.0		
	Testicle	7.55	21.1	1.80		
	Fat	108	182	9.24		
	Muscle	15.4	27.0	1.05		
	Thymus	20.1	29.6	1.57		
	Skin	11.7	16.3	2.61		
Metabolism						
In Vitro Intrinsic clearance of RP5264 in Mouse, Rat, Dog, Monkey and Human Liver Microsomes (DMPK-5264-MS-02)	Time (minutes)	Umbralisib metabolic stability in liver microsomes (%)				
		Mouse	Rat	Dog	Monkey	Human
	0	100	100	100	100	100
	15	96.87	70.14	94.31	98.48	97.95
	30	84.70	57.96	90.10	90.95	95.85
	45	77.36	52.44	82.73	82.41	92.03
	60	74.47	42.67	76.94	76.83	85.83
Excretion						
Mass Balance in Male CD-1 Mice and Tissue Distribution by Quantitative Whole Body Autoradiography in Male C57BL/6 Mice Following a Single Oral Administration of [14C]TGR-1202 (C18008)	[14C]Umbralisib Recovery %					
	Urine	Feces	Cage Rinse/Wash			
	4.21	88.79	0.7			
TK data from general toxicology studies A 26-week Study of TGR-1202 by Oral Gavage in Mice with a 28-day Recovery Period (20150163)	Mice: - Higher exposures in females compared to males - Higher exposures on day 182 compared to day 1					

Type of Study	Major Findings																																																																					
A 39-week Study of TGR-1202 by Oral Capsule in Dogs with a 28-day Recovery Period (20150164)	• T_{max} increases at high dose in males, indicating potential for saturation of absorption at high doses • Less than dose-proportional increases in exposures, particularly at higher doses, also suggesting saturation of absorption																																																																					
	Dogs: • Variable exposures between males and females • T_{max} increases at high doses, indicating potential for saturation of absorption at high doses																																																																					
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TK data from reproductive toxicology studies TGR-1202: An Embryo Fetal Development Study in Mice via Oral Gavage GD46XG TGR-1202: An Oral (Gavage) Embryo Fetal Development Study in Rabbits WR05CP TGR-1202: Study of Fertility and Early Embryonic Development in the CD-1 Mouse by Oral Gavage Administration YC15PK	<table><tr><th colspan="4">Umbralisib Exposure in Oral Embryo-fetal Developmental Toxicity Study in Rats on GD15</th></tr><tr><th>Dose (mg/kg)</th><th>100</th><th>200</th><th>400</th></tr><tr><td>AUC₀₋₂₄ (ng.h/mL)</td><td>129000</td><td>194000</td><td>339000</td></tr><tr><td>Relative Exposure (multiples of 141000*)</td><td>0.92X</td><td>1.38X</td><td>2.40X</td></tr></table> <table><tr><th colspan="4">Umbralisib Exposure in Oral Embryo-fetal Developmental Toxicity Study in Rabbits on GD19</th></tr><tr><th>Dose (mg/kg)</th><th>30</th><th>70</th><th>150</th></tr><tr><td>AUC₀₋₂₄ (ng.h/mL)</td><td>4220</td><td>10500</td><td>3780</td></tr><tr><td>Relative Exposure (multiples of 141000*)</td><td>0.03X</td><td>0.08X</td><td>0.03X</td></tr></table> <table><tr><th colspan="4">Umbralisib Exposure in Male Oral Fertility and Early Embryonic Development Study in Male Mice on Day 63</th></tr><tr><th>Dose (mg/kg)</th><th>50</th><th>150</th><th>300</th></tr><tr><td>AUC₀₋₂₄ (ng.h/mL)</td><td>102000</td><td>184000</td><td>262000</td></tr><tr><td>Relative Exposure (multiples of 141000*)</td><td>0.72X</td><td>1.31X</td><td>1.85X</td></tr></table> * In patients, umbralisib steady-state AUC₀₋₂₄ is 141 µg (141000 ng) *h/mL following administration of the approved recommended dosage of 800 mg/day.	Umbralisib Exposure in Oral Embryo-fetal Developmental Toxicity Study in Rats on GD15				Dose (mg/kg)	100	200	400	AUC ₀₋₂₄ (ng.h/mL)	129000	194000	339000	Relative Exposure (multiples of 141000*)	0.92X	1.38X	2.40X	Umbralisib Exposure in Oral Embryo-fetal Developmental Toxicity Study in Rabbits on GD19				Dose (mg/kg)	30	70	150	AUC ₀₋₂₄ (ng.h/mL)	4220	10500	3780	Relative Exposure (multiples of 141000*)	0.03X	0.08X	0.03X	Umbralisib Exposure in Male Oral Fertility and Early Embryonic Development Study in Male Mice on Day 63				Dose (mg/kg)	50	150	300	AUC ₀₋₂₄ (ng.h/mL)	102000	184000	262000	Relative Exposure (multiples of 141000*)	0.72X	1.31X	1.85X
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5.5. Toxicology

5.5.1. General Toxicology

The Applicant's Position:

Umbralisib was well tolerated after a single dose, with a maximum tolerated dose (MTD) of <1000 mg/kg/day in mice and >2000 mg/kg/day in rats. The tolerability, potential toxicities, target organs, and toxicokinetics of umbralisib were evaluated in repeat-dose toxicity studies up to 26 weeks in mice and 39 weeks in dogs. Umbralisib was generally well tolerated through acute, subchronic, and chronic dosing; test article-related mortality occurred at ≥ 100 mg/kg/day in mice (equivalent to 300 mg/m² or 584 mg in a 70 kg human), and adverse clinical findings necessitating dose reductions occurred at ≥ 10 mg/kg/day in dogs (equivalent to 200 mg/m² or 389 mg/kg in a 70 kg human) when administered chronically.

The liver was identified as the main target organ in mice and the gastrointestinal tract in dogs. Increased liver weights were observed in all studies in mice for the high-dose groups, but these findings did not correlate with increases in liver enzymes, and liver histopathology findings were minimal to mild. Another major finding was damage to the non-glandular stomach mucosa after subchronic and chronic administration, but the clinical relevance of these findings in humans cannot be determined, as humans do not have a non-glandular stomach. Other findings in mice included decreases in leukocytes and lymphocytes and increases in cholesterol that were considered minimal, non-adverse, or related to the pharmacologic action of umbralisib. All findings in mice were reversible upon treatment cessation. None of these findings were observed in dogs upon treatment with umbralisib. In dogs, diarrhea, body weight reductions, and decreased food consumption were noted in all studies and increased in severity and frequency in a dose-dependent manner. Dogs with body weight loss and decreased food consumption were offered canned food to increase appetite and food consumption. Dose holidays and dose reductions were necessitated during chronic administration due to low body condition scores. There were no gross pathology or histopathology findings that correlated to the clinical signs. Clinical pathology showed minor changes in metabolic parameters that were considered secondary to the clinical findings. There were no other adverse findings upon umbralisib treatment in dogs.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment; see additional information provided below for the 26-week and 39-week repeat-dose toxicity studies in mice and dogs, respectively.

Study title/Study number: A 26-week Study of TGR-1202 by Oral Gavage in Mice with a 28-day Recovery Period/20150163

Key Study Findings

- There were 20 unscheduled deaths, with all but 1 occurring in the umbralisib-dosed groups and half occurring in the high-dose group. While umbralisib induced mortality occurred in a dose-dependent manner, the deaths were due to undetermined causes.
- Principle hematology findings included reduced lymphocyte levels in mid-dose and high-dose male and female animals.
- Hepatotoxicity: Liver weights, ALP levels, and microscopic signals (minimal necrosis, inflammation, and hypertrophy) were increased in umbralisib-dosed animals.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (control), 30, 100, or 300 mg/kg/day (umbralisib batch # TGR1202/II/A422/10). Administered once daily.

Route of administration: Oral gavage

Formulation/Vehicle: 0.5% (w/v) methylcellulose and 10% (v/v) Tween 80 in deionized water

Species/Strain: CD-1 mice

Number/Sex/Group: Terminal: 20
Recovery: 6

Age: 7 to 8 weeks

Deviation from study protocol affecting interpretation of results: None that affected the overall interpretation of the study findings nor compromised the integrity of the study.

Observations and Results: changes from control

Parameters	Major findings
Mortality	There were 20 unscheduled deaths during the study. Control: One control group female mouse was found dead on day 177. LD: A total of 5 animals died or were euthanized with 3 of the 5 animals dying due to housing-related incidents unrelated to umbralisib. The other 2 were females euthanized on day 72. These animals exhibited ulcerative dermatitis, which was determined as the cause of death. MD: A total of 4 animals died. Two of the 4 animals died due to housing-related incidents unrelated to umbralisib. The other 2 were females found dead on days 50 and 164. These animals had no macroscopic findings and microscopic findings, including inflammatory signals in the liver and lymph nodes, were not considered causal to their deaths by the Applicant's pathologist. HD: 10 animals died prematurely. One animal died due to housing-related incidents unrelated to umbralisib. Two animals, a male and a

NDA Multi-disciplinary Review and Evaluation: NDA 213176
UKONIQ (umbralisib)

Parameters	Major findings																																											
	female, exhibited ulcerative dermatitis while another 2 males contracted urogenital infections that resulted in septicemias. Five females found dead on days ranging from 42 to 164 had deaths that could not be ascribed to a specific cause; none had macroscopic observations. Cortical adrenal hyperplasia was the most common organ microscopic signal in these animals.																																											
Clinical Signs	Clinical signals were generally unremarkable. Notable clinical observations <table><tr><th rowspan="3">Observations</th><th colspan="4">Dose (mg/kg/day)</th></tr><tr><th>0</th><th>30</th><th>100</th><th>300</th></tr><tr><th colspan="4">Number of animals affected (M/F)</th></tr><tr><td>Abnormal gait</td><td>0/0</td><td>0/0</td><td>0/0</td><td>2/0</td></tr><tr><td>Hunched posture</td><td>1/1</td><td>1/0</td><td>0/0</td><td>3/0</td></tr><tr><td>Fur staining, yellow</td><td>1/0</td><td>4/0</td><td>4/0</td><td>3/0</td></tr><tr><td>Fur, ungroomed</td><td>1/0</td><td>0/0</td><td>2/1</td><td>3/0</td></tr><tr><td>Decreased activity</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/2</td></tr><tr><td>Cold to touch</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/2</td></tr></table>	Observations	Dose (mg/kg/day)				0	30	100	300	Number of animals affected (M/F)				Abnormal gait	0/0	0/0	0/0	2/0	Hunched posture	1/1	1/0	0/0	3/0	Fur staining, yellow	1/0	4/0	4/0	3/0	Fur, ungroomed	1/0	0/0	2/1	3/0	Decreased activity	0/0	0/0	0/0	0/2	Cold to touch	0/0	0/0	0/0	0/2
Observations	Dose (mg/kg/day)																																											
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Fur, ungroomed	1/0	0/0	2/1	3/0																																								
Decreased activity	0/0	0/0	0/0	0/2																																								
Cold to touch	0/0	0/0	0/0	0/2																																								
Neurobehavioral Observations	A functional observational battery was conducted on the first dosing day. There were generally no umbralisib-related differences that were outside of the reasonable range for the strain. There was a notably elevated left pinna reflex in all umbralisib-dosed male and female groups.																																											
Body Weights/food consumption	Unremarkable																																											
Ophthalmoscopy	Unremarkable																																											
Respiratory Rate	Unremarkable																																											
Hematology	Hematology changes by the end of the dosing period included significantly lower lymphocyte levels in MD and HD males with notably reduced levels in females at all doses. At the MD and HD, reduced levels were noted in WBC, basophil, leukocyte, hemoglobin, and hematocrit levels. These values reversed by the end of the recovery period.																																											

Hematology values at the end of the dosing period									
Value	Unit (% of control)	Control		30 mg/kg/day		100 mg/kg/day		300 mg/kg/day	
		M	F	M	F	M	F	M	F
White blood cells (WBC)	10 ³ /μL	5.9	6.2	5.6 (-4.6)	4.7 (-24.3)	4.6 (-22.3)	4.4 (-29.4)	4.4 (-24.4)	3.9 (-38.3)
Lymphocytes (LYMPH)		4.3	5.1	4.3 (1.5)	3.7 (-28.6)	2.9 (-32.9)	3.4 (-34.5)	3.1 (-27.8)	2.7 (-47.7)
Eosinophils (EOS)		0.17	0.16	0.13 (-25.6)	0.13 (-18.9)	0.14 (-18.4)	0.07 (-55.6)	0.11 (-34.3)	0.09 (-44.9)
Basophils (BASO)		0.016	0.03	0.018 (9.4)	0.02 (-37.5)	0.011 (-29.7)	0.01 (-58.3)	0.009 (-45.3)	0.02 (-47.6)
Red blood cells (RBC)	10 ⁶ /μL	9.2	9.2	8.9 (-3.0)	8.9 (-2.8)	9.1 (-4.4)	9.0 (-2.2)	8.9 (-3.3)	8.9 (-3.0)

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Parameters	Major findings																																																													
Clinical Chemistry	In males, increases in ALP, creatinine, cholesterol, and albumin levels were observed in all umbralisib-dosed groups. In females, increases in MD and HD females were observed in urea nitrogen, creatinine, triglycerides, and albumin. These normalized by the end of the recovery period.																																																													
Clinical chemistry parameters at the end of the dosing period																																																														
Value	Unit (% of control)	Control		30 mg/kg/day		100 mg/kg/day		300 mg/kg/day																																																						
		M	F	M	F	M	F	M	F																																																					
Alkaline phosphatase (ALP)	U/L	34.5	67.0	41.3 (19.8)	48.8 (-27.2)	43.5 (26.1)	62.9 (-6.1)	56.0 (62.3)	63.9 (-4.7)																																																					
Urea nitrogen (UREAN)	mg/dL	20.5	15.4	17.7 (-13.8)	14.7 (-4.6)	22.6 (10.2)	16.9 (9.7)	22.3 (8.9)	22.9 (48.4)																																																					
Creatinine (CREAT)	mg/dL	0.11	0.10	0.14 (31.3)	0.10 (0.0)	0.15 (36.4)	0.15 (50.0)	0.19 (71.7)	0.21 (114.3)																																																					
Cholesterol (CHOL)	mg/dL	169	118	202 (19.5)	134 (13.5)	217 (28.2)	136 (15.1)	229 (35.5)	170 (43.9)																																																					
Triglycerides (TRIG)	mg/dL	148	93.1	155 (4.6)	104.6 (12.4)	191 (29.1)	144.7 (55.4)	244 (65.1)	186.7 (100.6)																																																					
Albumin (ALB)	g/dL	2.9	1.6	3.2 (11.9)	1.6 (-2.7)	5.2 (9.7)	1.7 (1.5)	5.2 (9.2)	1.7 (0.5)																																																					
Gross Pathology		Unremarkable																																																												
Organ Weights		Increases (20-51%) in liver weights relative to brain weights were observed in MD and HD males and females. These changes reversed by the end of the recovery period.																																																												
Histopathology		Microscopic findings were noted in the liver and spleen, principally in males where increased liver hypertrophy was noted at all doses. These findings were not observed following the recovery period. Selected liver and spleen parameters at the end of the dosing period <table><tr><th rowspan="3">Observations</th><th colspan="4">Dose (mg/kg/day)</th></tr><tr><th>0</th><th>30</th><th>100</th><th>300</th></tr><tr><th colspan="4">Number of animals affected (M/F)</th></tr><tr><td>Number examined</td><td>20/19</td><td>17/18</td><td>18/18</td><td>17/14</td></tr><tr><td>Liver necrosis: minimal</td><td>1/2</td><td>1/4</td><td>1/1</td><td>6/1</td></tr><tr><td>Liver hypertrophy: Minimal</td><td>0/0</td><td>5/1</td><td>7/1</td><td>9/1</td></tr><tr><td>Mild</td><td>0/0</td><td>4/0</td><td>7/1</td><td>5/0</td></tr><tr><td>Liver inflammation: Minimal</td><td>1/4</td><td>8/9</td><td>7/5</td><td>2/7</td></tr><tr><td>Spleen hematopoiesis: Minimal</td><td>0/0</td><td>0/0</td><td>3/0</td><td>1/0</td></tr><tr><td>Mild</td><td>0/1</td><td>0/0</td><td>1/0</td><td>1/1</td></tr><tr><td>Moderate</td><td>1/0</td><td>0/0</td><td>0/0</td><td>1/0</td></tr></table>								Observations	Dose (mg/kg/day)				0	30	100	300	Number of animals affected (M/F)				Number examined	20/19	17/18	18/18	17/14	Liver necrosis: minimal	1/2	1/4	1/1	6/1	Liver hypertrophy: Minimal	0/0	5/1	7/1	9/1	Mild	0/0	4/0	7/1	5/0	Liver inflammation: Minimal	1/4	8/9	7/5	2/7	Spleen hematopoiesis: Minimal	0/0	0/0	3/0	1/0	Mild	0/1	0/0	1/0	1/1	Moderate	1/0	0/0	0/0	1/0
Observations	Dose (mg/kg/day)																																																													
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Moderate	1/0	0/0	0/0	1/0																																																										
Toxicokinetics		Toxicokinetic parameters for the end of the dosing period																																																												

Parameters	Major findings				
	Dose (mg/kg/day)	C _{max} (ng/mL)		AUC _{0-t} (ng.h/mL)	
		M	F	M	F
	30	8290	7520	55400 (0.39X*)	67700 (0.48X*)
	100	20600	22000	140000 (0.99X*)	281000 (2.0X*)
	300	30500	41000	334000 (2.4X*)	553000 (3.9X*)
*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC ₀₋₂₄ was 141 µg (141000ng)*h/mL)					

LD: low dose; MD: mid dose; HD: high dose

Study title/Study number: A 39-week Study of TGR-1202 by Oral Capsule in Dogs with a 28-day Recovery Period/20150164

Key Study Findings

- Due to weight loss and thin appearance, most notably in the mid- and high-dose animals, all umbralisib-dosed groups had dose modifications. High-dose animals received 2 dose modifications, a dosing holiday, and early euthanization on day 183 (week 26).
- Hematology signals included reduced RBC, hemoglobin, hematocrit, and reticulocytes in all umbralisib-dosed conditions.
- Microscopic findings included decreased cellularity in the lymph nodes and thymus.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 0 (control), 10, 30, or 100 mg/kg/day (umbralisib batch # TGR1202/II/A422/10). Administered once daily. LD, MD, and HD groups were reduced to 8, 20, and 50 mg/kg/day, respectively, on day 127 (week 18). HD recovery group dogs were dosed with 20 mg/kg/day from day 183 (week 26) to day 273 (week 39).

Route of administration: Oral capsule

Formulation/Vehicle: Empty capsule

Species/Strain: Beagle dogs

Number/Sex/Group: Terminal: 4
Recovery: Control: 2; HD: 3

Age: 6 months

Deviation from study protocol affecting interpretation of results:	None that affected the overall interpretation of study findings nor compromised the integrity of the study.

Observations and Results: changes from control

Parameters	Major findings																											
Mortality	HD terminal study animals were euthanized early on day 183 (week 26) due to poor condition (principally thin appearance and liquid feces).																											
Clinical Signs	MD and HD animals were determined to be thin or extremely thin during dosing day 95 (week 13) and were given canned food to encourage weight gain by increased food consumption. Food consumption increased but weight gain remained at lower levels than controls. MD and HD animals also had liquid feces. HD animals were given dosing holidays from day 12 and all dose levels were reduced. Clinical signals reversed by the end of the dosing holiday and recovery period.																											
Body Weights	Described in the clinical signs section. Body weight by day 126 (week 18) <table><tr><th>Condition (mg/kg/day)</th><th colspan="2">Control</th><th colspan="2">10/8</th><th colspan="2">30/20</th><th colspan="2">100/50/20</th></tr><tr><td>Sex</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr><tr><td>Body weight (Kg)</td><td>9.4</td><td>9.0</td><td>9.1</td><td>8.8</td><td>8.9</td><td>8.0</td><td>8.6</td><td>7.6</td></tr></table>	Condition (mg/kg/day)	Control		10/8		30/20		100/50/20		Sex	M	F	M	F	M	F	M	F	Body weight (Kg)	9.4	9.0	9.1	8.8	8.9	8.0	8.6	7.6
Condition (mg/kg/day)	Control		10/8		30/20		100/50/20																					
Sex	M	F	M	F	M	F	M	F																				
Body weight (Kg)	9.4	9.0	9.1	8.8	8.9	8.0	8.6	7.6																				
Food consumption	Increased in HD groups and unremarkable in the LD and MD groups due to feeding of umbralisib-dosed groups with canned food.																											
Ophthalmoscopy	Unremarkable																											
ECG	Unremarkable																											
Respiratory Rate	Unremarkable																											
Hematology	Hematology changes by week 39 included lower basophil (BASO), RBC, hemoglobin, and hematocrit levels in MD and HD males and HD females. These signals demonstrated reversibility by the end of the recovery period.																											
Hematology values by day 274 (week 39)																												
Value	Unit (% of control)	Control		10/8 mg/kg/day		30/20 mg/kg/day		100/50 mg/kg/day																				
		M	F	M	F	M	F	M	F																			
RBC	10 ⁶ /μL	7.1	6.5	6.2 (-12.8)	6.0 (-7.6)	6.0 (-15.2)	6.0 (-7.2)	6.4 (-8.7)	6.3 (-3.2)																			
HGB	g/dL	15.6	14.9	14.0 (-10.5)	13.5 (-9.5)	13.3 (-14.7)	14.1 (-5.4)	14.5 (-7.2)	13.5 (-9.6)																			
HCT	%	46.5	44.1	41.3 (-11.3)	40.2 (-8.8)	39.7 (-14.6)	41.4 (-6.1)	42.5 (-8.7)	39.7 (-10.1)																			
Clinical Chemistry	Clinical chemistry signals were mild, variable, and reversible. Increased ALT, decreased albumin, and decreased total protein levels were noted in the HD group by the end of the treatment period.																											

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Clinical chemistry parameters by day 274 (week 39)																																												
Value	Unit (% of control)	Control		10 mg/kg/day		30 mg/kg/day		100 mg/kg/day																																				
		M	F	M	F	M	F	M	F																																			
Alanine aminotransferase (ALT)	U/L	33.3	22.0	44.0 (32.0)	22.5 (2.3)	33.0 (-1.0)	26.0 (18.2)	48.0 (44.0)	35.5 (61.4)																																			
Cholesterol (CHOL)	mg/dL	137	188	155 (13.0)	180 (-4.1)	151 (3.6)	183 (-2.7)	130 (-5.1)	198 (5.6)																																			
Total protein (TPROT)	g/dL	5.5	5.3	5.2 (-5.8)	5.1 (-3.6)	4.8 (-11.7)	5.0 (-6.9)	4.8 (-12.2)	4.8 (-9.7)																																			
Triglyceride (TRIG)	mg/dL	27.5	32.7	25.8 (-6.4)	34.5 (5.6)	28.5 (3.6)	32.5 (-0.5)	29.5 (7.3)	32.5 (-0.5)																																			
Albumin (ALB)	g/dL	3.3	3.4	3.1 (-7.3)	3.3 (-1.2)	2.9 (-11.8)	3.2 (-6.4)	2.8 (-15.6)	2.9 (-13.9)																																			
Gross Pathology			Unremarkable																																									
Organ Weights			Dose-dependent decreases in thymus weight (absolute and % of body or brain weight) were noted at the terminal sacrifice. This finding reversed by the end of the recovery period. Thymus weights by terminal euthanasia day (183/274) <table><tr><td>Group (mg/kg)</td><td colspan="2">10/8</td><td colspan="2">30/20</td><td colspan="2">100/50/20</td></tr><tr><td>Weight % of control</td><td>M</td><td>F</td><td>M</td><td>F</td><td>M</td><td>F</td></tr><tr><td>Absolute</td><td>2.8</td><td>-6.7</td><td>-17.6</td><td>-28.1</td><td>-46.6</td><td>-44.8</td></tr><tr><td>% Body weight</td><td>5.3</td><td>-3.8</td><td>-16.4</td><td>-18.5</td><td>-37.1</td><td>-21.2</td></tr><tr><td>% Brain weight</td><td>3.0</td><td>-8.8</td><td>-24.9</td><td>-29.8</td><td>-45.9</td><td>-47.9</td></tr></table>							Group (mg/kg)	10/8		30/20		100/50/20		Weight % of control	M	F	M	F	M	F	Absolute	2.8	-6.7	-17.6	-28.1	-46.6	-44.8	% Body weight	5.3	-3.8	-16.4	-18.5	-37.1	-21.2	% Brain weight	3.0	-8.8	-24.9	-29.8	-45.9	-47.9
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% Brain weight	3.0	-8.8	-24.9	-29.8	-45.9	-47.9																																						

Histopathology	Decreased cellularity observed in the lymph nodes and thymus was determined to be attributable to the administration of umbralisib . These findings were not observed following the recovery period.				
	Selected microscopic parameters at the end of the dosing period				
	Observations	Dose (mg/kg/day)			
		0	30	100	300
		Number of animals affected (M/F)			
	Number examined	4/4	4/4	4/4	4/4
	GALT decreased cellularity:				
	Minimal	0/0	1/1	3/4	1/0
	Mild	0/0	0/0	0/0	1/1
	Moderate	0/0	0/0	0/0	2/3
	Mandibular lymph node decreased cellularity:				
	Minimal	0/0	1/1	0/3	0/0
	Mild	0/0	1/1	4/1	4/4
	Mesenteric lymph node decreased cellularity:				
	Minimal	0/0	3/1	1/3	1/0
Mild	0/0	0/0	1/1	2/3	
Moderate	0/0	0/0	0/0	0/1	
Thymus decreased cellularity:					
Minimal	1/1	0/1	1/0	0/0	
Mild	1/0	0/0	2/0	1/2	
Moderate	1/0	2/0	0/0	0/1	
Marked	0/0	0/0	0/0	2/0	
Adrenal gland cytoplasmic zona fasciculata vacuolation:					
Minimal	2/3	2/2	1/2	1/0	
Mild	0/0	0/2	0/0	3/3	
Adrenal gland cortex atrophy:					
Moderate	0/0	0/0	0/0	0/1	
Toxicokinetics	Toxicokinetic parameters for day 91 (week 13)				
	Dose (mg/kg/day)	C _{max} (ng/mL)		AUC ₀₋₂₄ (ng.h/mL)	
		M	F	M	F
	10	3530	2500	61500 (0.44X*)	38800 (0.28X*)
	30	8750	8410	185000 (1.3X*)	177000 (1.3X*)
	100	13900	12800	293000 (2.1X*)	280000 (2.0X*)
	*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC ₀₋₂₄ was 141 µg (141000ng)*h/mL)				

LD: low dose; MD: mid dose; HD: high dose

Additional toxicology studies

Below is a summary of the 13 week toxicology study in dogs, titled "TGR-1202: 13-Week Oral Toxicity Study in Dogs with a 30-Day Dose-Free Recovery" (Study 034717):

Beagle dogs (3/sex/group) were administered umbralisib orally at doses of 0, 30, 100, or 250 mg/kg/day for 13 weeks. There were no test article-related mortalities. Treatment with umbralisib resulted in:

- GI toxicities as presented with soft, mucoid, and/or liquid feces, and emesis.
- Hematological changes included reductions in RBC parameters (hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration).
- Notable but reversible changes in clinical chemistry parameters were most evident in the HD group, with reductions in total protein, albumin, globins, electrolytes, cholesterol, and triglycerides. These changes may be the secondary effect of the clinical changes (weight loss, emesis, reduced food intake).
- Lower thymus and spleen weights with microscopic observations of thymic atrophy and lymphoid depletion of lymph nodes
- Lowered weights in the testes and epididymides. MD and HD males displayed testicular changes that included degeneration, multinucleated giant cells, vacuolation, and sloughed cells in the tubular lumen within the seminiferous epithelium.

5.5.2. Genetic Toxicology

The Applicant's Position:

Umbralisib was negative for mutagenic potential in an in vitro Ames assay at concentrations up to 5000 µg/plate and in an in vitro micronucleus assay. In vivo mutagenicity was also assessed in vivo after dosing CD-1 mice with 2 oral gavage doses of umbralisib up to 1000 mg/kg administered once daily. No increases in the scored micronuclei of reticulocytes in treated mice compared to control mice were detected under the study conditions.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment. Additional details regarding the studies are provided in the review below.

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: Bacterial Reverse Mutation Assay/ AF33EJ.502ICH. ^{(b) (4)}

Key Study Finding:

- Umbralisib did not increase the number of revertant colonies in tester strains with or without metabolic activation.
- Precipitate was observed at ≥1000 µg per plate and toxicity resulting in a reduction in revertant count was observed at 5000 µg per plate.

GLP compliance: Yes.

Test system: Salmonella typhimurium strains TA98, TA100, TA1535, and TA1537, and Escherichia Coli strain WP2 uvrA in the presence or absence of rat liver S9 extract (at concentrations up to 5000 µg/plate).

Study is valid: Yes.

In Vitro Assays in Mammalian Cells

Study title/number: In Vitro Mammalian Cell Micronucleus Assay in TK6 Cells/
AF33EJ.361ICH. (b) (4)

Key Study Finding:

- Umbralisib did not induce chromosome aberrations in TK6 cells with or without metabolic activation.

GLP compliance: Yes.

Test system: The TK6 human lymphocytic cell line +/- S9 activation. Drug concentrations of umbralisib were 15 to 75 µg/mL for 4 hours of incubation in both the S9-activated and non-activated conditions, and 5 to 50 µg/mL for 27 hours of incubation in the non-activated condition.

Study is valid: Yes.

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: In Vivo Mammalian Micronucleus Assay in Mice with Flow Cytometric Analysis in Peripheral Blood Reticulocytes/AF33EJ.123M021FLPBICH. (b) (4)

Key Study Finding:

- Umbralisib did not increase the frequency of micronucleated polychromatic erythrocytes in mice after oral administration.

GLP compliance: Yes.

Test system: CD-1 mice were administered 2 oral doses of umbralisib 24 hours apart at doses ranging from 75 mg/kg to 1000 mg/kg. Necropsies were conducted 48 hours after the second dose.

Study is valid: Yes.

5.5.3. Carcinogenicity

The Applicant's Position:

In accordance with the International Council for Harmonisation (ICH) guideline ICH S9 (2009),

no carcinogenicity studies have been conducted because umbralisib is intended for use in patients with advanced cancer.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

The potential for umbralisib exposure to impact male and female fertility parameters and pregnancy parameters was evaluated in mice at doses up to 300 mg/kg/day. In male mice, umbralisib administration at 300 mg/kg/day (equivalent to 900 mg/m² or 1707 mg in a 70-kg human) for 4 weeks resulted in reduced testis weights accompanied by reduced sperm count and motility. The magnitude of these changes was small and did not impact overall male reproductive health.

The potential for umbralisib exposure to impact maternal health, pregnancy parameters, and embryonic development was evaluated in embryo-fetal development studies in mice and rabbits. In mice, doses ≥ 200 mg/kg (equivalent to ≥ 600 mg/m² or ≥ 1138 mg in a 70 kg human) administered during the period of organogenesis resulted in no effects on maternal health but impacted pregnancy parameters (resorptions and post-implantation losses) and the developing fetus (increased incidence of cleft palate, nasopharyngeal fistula, and minor skeletal abnormalities). Treatment-related findings included an increase in the number of litters that exhibited 100% resorptions and post implantation resorption; and external (cleft palate), visceral (nasopharyngeal fistula), and skeletal fetal abnormalities. In rabbits, doses of 300 mg/kg (equivalent to 3600 mg/m² or 6774 mg in a 70 kg human) administered during the period of organogenesis resulted in maternal toxicity of reduced body weights and food consumption with no other reported findings on pregnancy and fetal development in rabbits.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's assessment. The FDA's review of the fertility and early embryonic development study in mice and embryo-fetal development studies in mice and rabbits is provided below.

Fertility and Early Embryonic Development

Study title/ number: TGR-1202: Study of Fertility and Early Embryonic Development in the CD-1 Mouse by Oral Gavage Administration/YC15PK

- There were notable reductions in testis and epididymis weights in all umbralisib-dosed groups, reduced sperm counts in the 150 and 300 mg/kg/day groups, and reduced

sperm motility in the 300 mg/kg/day group. These reductions were within historic ranges.

- Increased resorption and post-implantation loss were observed in the mid-dose group.
- While the fertility index is comparable to, or is higher than, the values in the concurrent control group, the low number of pregnancies in the concurrent control group makes it difficult to make a conclusion on the fertility index for umbralisib-treated animals
- The doses of 50, 150, and 300 mg/kg/day doses resulted in exposures that were 0.7, 1.3, and 1.9 times the clinical exposure at the recommended dose of 800 mg/day.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes.

Methods

Dose and frequency of dosing:

0, 150, 300 mg/kg/day

Males: From 4 weeks (28 days) prior to mating, through mating until sacrifice.

Females: From 2 weeks (14 days) prior to mating through gestation day (GD) 7. Sacrificed on GD 13.

Route of administration:

Oral gavage.

Formulation/Vehicle:

10 % (v/v) polysorbate 80 in 0.5 % (w/v) methylcellulose (400 cp), in deionized water

Species/Strain:

Mice/CD-1

Number/Sex/Group:

22

Satellite groups:

4 spare animals/sex

Study design:

Mice were paired 1:1 for 14 days or until evidence of mating (presence of a copulatory plug or sperm in the vaginal smear).

Deviation from study protocol

affecting interpretation of results:

No

Observations and Results

Parameters	Major findings
Mortality	Two males, both from the 300 mg/kg/day group, died prior to the scheduled euthanasia day. One mouse was found dead on dosing day 62. This animal had no apparent clinical or macroscopic findings. Another mouse was moribund and euthanized on dosing day 33. This animal had decreased activity, was cold to the touch, had irregular breathing, a distended abdomen, and partially closed eyelids. The animal's body weight had decreased and there were macroscopic findings observed in the GI tract that included distention, gas, and a yellow fluid. The causes of death were undetermined in these animals.
Clinical signs	Unremarkable

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UKONIQ (umbralisib)

Body weights	Unremarkable																																																																										
Food consumption	Unremarkable																																																																										
Estrous cycle	Unremarkable																																																																										
Organ weights	Umbralisib-related reductions in testicular weight were noted. Significant and dose-dependent absolute right and left testis weight reductions were noted in all umbralisib treatment groups, and reductions in relative right and left testis weights were noted in the 300 mg/kg/day group. There were also notable weight reductions in the right and left epididymis in all umbralisib treatment groups. The historical control data for CD-1 mice from (b) (4) showed that the reductions in testes and epididymis weights were within normal ranges.																																																																										
Necropsy findings	Unremarkable																																																																										
Mating, fertility, and sperm analysis	There were 2 males in each of the 50 mg/kg/day and 150 mg/kg/day groups who did not successfully mate after 14 days of pairing. These were removed from the study pairings and replaced with males from within each group who had successfully mated. Umbralisib-associated changes included reduced sperm motility in the 300 mg/kg/day group and reduced sperm counts in the 150 and 300 mg/kg/day groups. <table><tr><th>Dose (mg/kg/day)</th><th>0</th><th>50</th><th>150</th><th>300</th></tr><tr><td>No evaluated:</td><td></td><td></td><td></td><td></td></tr><tr><td>Male</td><td>22</td><td>20</td><td>20</td><td>22</td></tr><tr><td>Female</td><td>22</td><td>22</td><td>22</td><td>22</td></tr><tr><td>Females confirmed pregnant</td><td>18</td><td>20</td><td>19</td><td>21</td></tr><tr><td>Fertility index (%):</td><td></td><td></td><td></td><td></td></tr><tr><td>Male</td><td>81.8*</td><td>90.0</td><td>85.0</td><td>95.5</td></tr><tr><td>Female</td><td>81.8**</td><td>90.9</td><td>86.4</td><td>95.5</td></tr><tr><td>Mean no of live conceptus</td><td>11.6</td><td>11.9</td><td>12.0</td><td>11.3</td></tr><tr><td>Resorptions (mean %)</td><td>0.4</td><td>0.3</td><td>1.1</td><td>0.3</td></tr><tr><td>Post-implantation loss (%)</td><td>3.5</td><td>2.4</td><td>10.2</td><td>2.9</td></tr><tr><td>Sperm motility (%)</td><td>98.0</td><td>98.3</td><td>98.8</td><td>94.6</td></tr><tr><td>Sperm count (millions/g)</td><td>372.0</td><td>388.8</td><td>352.3</td><td>316.3</td></tr><tr><td>Normal sperm morphology (%)</td><td>60.1</td><td>56.9</td><td>59.3</td><td>57.2</td></tr></table> *Value is below the mean value in the historical control (HC; (b) (4)). HC data shows a mean value of 92.5% (range of 76% to 100%). HC data from (b) (4) is not available. ** Value is below the mean value in the HC (b) (4). HC data shows a mean value of 91.3% (range of 76% to 100%)					Dose (mg/kg/day)	0	50	150	300	No evaluated:					Male	22	20	20	22	Female	22	22	22	22	Females confirmed pregnant	18	20	19	21	Fertility index (%):					Male	81.8*	90.0	85.0	95.5	Female	81.8**	90.9	86.4	95.5	Mean no of live conceptus	11.6	11.9	12.0	11.3	Resorptions (mean %)	0.4	0.3	1.1	0.3	Post-implantation loss (%)	3.5	2.4	10.2	2.9	Sperm motility (%)	98.0	98.3	98.8	94.6	Sperm count (millions/g)	372.0	388.8	352.3	316.3	Normal sperm morphology (%)	60.1	56.9	59.3	57.2
Dose (mg/kg/day)	0	50	150	300																																																																							
No evaluated:																																																																											
Male	22	20	20	22																																																																							
Female	22	22	22	22																																																																							
Females confirmed pregnant	18	20	19	21																																																																							
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Toxicokinetics (Day 63)	<table><tr><th>Dose (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th>AUC₀₋₂₄ (ng.h/mL)</th></tr><tr><td>50</td><td>13351.39</td><td>102000 (0.7X*)</td></tr><tr><td>150</td><td>20774.27</td><td>184000 (1.3X*)</td></tr><tr><td>300</td><td>25368.70</td><td>262000 (1.86X*)</td></tr></table> *Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC was 141 µg (141000ng)*h/mL)			Dose (mg/kg/day)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng.h/mL)	50	13351.39	102000 (0.7X*)	150	20774.27	184000 (1.3X*)	300	25368.70	262000 (1.86X*)																																																												
Dose (mg/kg/day)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng.h/mL)																																																																									
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300	25368.70	262000 (1.86X*)																																																																									

Embryo-Fetal Development

Study title/ number: An Embryo Fetal Development Study in Mice via Oral Gavage/GD46XG

Key Study Findings

- Adverse findings were observed at all dose levels but were most evident at mid-dose and high-dose.
- Increased litter losses were observed at all dose levels.
- Increased skeletal abnormalities were noted in all umbralisib-dosed groups.
- Increased cleft palate rates were noted in 200 and 400 mg/kg/day groups.
- The 100, 200, and 400 mg/kg/day groups had exposures that were 0.9, 1.4, and 2.4 times the exposures at the recommended clinical dose of 800 mg/day.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing:

0, 100, 200, or 400 mg/kg/day from GD6 to GD15

Route of administration:

Oral gavage

Formulation/Vehicle:

Polysorbate 80 (PS80, 10% v/v) and methylcellulose (0.5% w/v) in deionized water

Species/Strain:

Mice/Crl:CD-1

Number/Sex/Group:

Main study: 22 females/group

Toxicology study: Control: 6 females/group

Umbralisib: 18 females/group

Satellite groups:

Four mated females were retained for possible replacement.

Study design:

Pregnant mice received umbralisib daily during GD 6 through 15. Euthanization/caesarean section/necropsy were performed on GD17.

Deviation from study protocol

No

affecting interpretation of results:

Observations and Results

Parameters	Major findings
Mortality	One HD female was found dead on GD12. Overall, the necropsy was unremarkable which led to the cause of death being undetermined and considered not test article

	related. The animal was bearing 13 fetuses that were all resorbed.				
Clinical Signs	No umbralisib-related clinical signs were noted.				
Body Weights (adjusted for uterine weight)	Changes in the body weights were not considered test article-related due to the lack of dose-dependency.				
Macroscopic observations	Unremarkable				
Necropsy findings Cesarean Section Data	Drug-related findings included non-viable fetuses, total resorptions, and post-implantation losses.				
	Dose (mg/kg/day) Number tested	Control 22	100 22	200 22	400 22
	No of Pregnancy (%)	14 (63.6*)	15 (68.2)	15 (68.2)	20 (90.9)
	No of pregnant animals with 100% non-viable fetuses	0	1	2	2
	Mean total resorptions	1.1	0.4	1.8	2.1
	Mean pre-implantation losses (%)	5.4	15.3	13.7	5.7
	Mean post-implantation losses (%)	8.1	10.2	17.2	16.5
	Total live pups/litter	11.8	11.7	10.9	12.3
	* Below the values for the historical control (HC; (b) (4)). HC has a mean value of 91.3% and a range of 76.0% to 100%. HC data from (b) (4) is not available.				
	Fetal observations	Treatment with umbralisib resulted in malformations. Increased folded retinas and/or skeletal abnormalities were noted in all umbralisib-dosed groups. Increased cleft palate rates were noted in the MD and HD groups. An incident of nasopharyngeal fistula formation was noted in the HD group.			
		Incidences (fetuses/litters)			
No examined		81/14	81/14	69/13	110/18
Dose (mg/kg)		Control	100	200	400
Folded retina		1/1	4/2	0/0	2/2
Lung fusions/absent lobes		0/0	0/0	7/3	1/1
Kidney: dilated pelvis		4/3	1/1	8/6	5/5
Rib and vertebra supernumerary		34/12	58/13	50/13	95/18
Incomplete sternebrae		4/3	6/5	13/7	20/12
Incomplete vertebrae		38/13	51/13	44/16	82/19

	Increased ossification	11/3	26/8	15/3	10/6
	Cleft palate	1/1	1/1	3/2	15/6
	Nasopharyngeal fistula	0/0	0/0	0/0	1/1
Toxicokinetics (GD15); mean values	Dose (mg/kg)	C_{max} (ng/mL)		AUC₀₋₂₄ (ng.h/mL)	
	100	10607		129000 (0.9X*)	
	200	14154		194000 (1.4X*)	
	400	361000		339000 (2.4X*)	

LD: low dose; MD: mid dose; HD: high dose

*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC was 141 µg (141000ng)*h/mL)

Study title/ number: An Oral (Gavage) Embryo-Fetal Development Study in Rabbits/TGR-1202

Key Study Findings

- Umbralisib administered at the highest dose of 300 mg/kg/day resulted in maternal toxicity characterized by a 50% reduction in food intake and an 8% reduction in body weight by the end of the dosing period. Both findings reversed by the end of the dosing-free period prior to euthanasia.
- Fetal weights at the high-dose were significantly lower than controls.
- Increased fetal skeletal abnormalities compared to the concurrent controls were noted principally in the 100 mg/kg/day (0.08 time the patient exposure) and 300 mg/kg/day dosing groups. These findings were considered within the common range for the strain of rabbits.

Conducting laboratory and location:

(b) (4)

GLP compliance:

Yes

Methods

Dose and frequency of dosing: 0, 30, 100, or 300 mg/kg/day from GD6 to GD19
Route of administration: Oral gavage
Formulation/Vehicle: 10% (v/v) PS80 and 0.5% methylcellulose (w/v) in purified water.
Species/Strain: Rabbits/NZW
Number/Sex/Group: Main study: 22
Toxicokinetic study: 3
Satellite groups: Four female mated rabbits were used for possible replacement prior to and including GD6.

Study design:	Pregnant rabbits were given daily oral doses of umbralisib from GD6 through GD19. Euthanization/cesarean section/necropsy was performed on GD29.																			
Deviation from study protocol affecting interpretation of results:	No																			
Observations and Results																				
Parameters	Major findings																			
Mortality	There were 7 unscheduled deaths. Four HD animals were euthanized, one each on GD 21, 22, 23, and 28. They displayed red vaginal discharge, decreased fecal pellets, perigenital/perianal staining, and inappetence. At necropsy there were no notable macroscopic findings and all animals were pregnant. Their deaths were attributed to umbralisib. Three animals were found dead. A control group female was found dead on GD13 and 2 LD animals were found dead on GD6. All 3 animals presented with lung damage consistent with gavage errors.																			
Clinical Signs	MD and HD groups showed decreased defecation.																			
Body Weights/food consumption	HD animals had significantly reduced food consumption and body weights compared to the control group. These findings were reversible. <table><tr><td>Dose (mg/kg)</td><td>Control</td><td>30</td><td>100</td><td>300</td></tr><tr><td>Body weight (kg) on GD20 (% change from control)</td><td>3.49</td><td>3.44 (-1%)</td><td>3.50 (0%)</td><td>3.21 (-8%)</td></tr><tr><td>Food consumption (g) on GD18-19 (% change from control)</td><td>157</td><td>149 (-5%)</td><td>149 (-5%)</td><td>81 (-48%)</td></tr></table>					Dose (mg/kg)	Control	30	100	300	Body weight (kg) on GD20 (% change from control)	3.49	3.44 (-1%)	3.50 (0%)	3.21 (-8%)	Food consumption (g) on GD18-19 (% change from control)	157	149 (-5%)	149 (-5%)	81 (-48%)
Dose (mg/kg)	Control	30	100	300																
Body weight (kg) on GD20 (% change from control)	3.49	3.44 (-1%)	3.50 (0%)	3.21 (-8%)																
Food consumption (g) on GD18-19 (% change from control)	157	149 (-5%)	149 (-5%)	81 (-48%)																
Macroscopic observations	Unremarkable																			
Necropsy findings Cesarean Section Data	Unremarkable																			
Fetal observations	MD and HD fetal weights were notably lower than those in control animals. <table><tr><td>Dose (mg/kg)</td><td>Control</td><td>30</td><td>100</td><td>300</td></tr></table>					Dose (mg/kg)	Control	30	100	300										
Dose (mg/kg)	Control	30	100	300																

	Fetal weight (g) (% change from control)	41.2	40.5 (-2%)	38.0 (-8%)	37.8 (-8%)
	Fetal abnormalities were noted in all umbralisib-dosed groups.				
		Incidences (fetuses/litters)			
	No examined	171/20	184/21	220/21	157/18
	Dose (mg/kg)	Control	30	100	300
	Lung: Absent lobe	7/4	8/3	18/11	9/6
	Rib: Interrupted ossification	6/5	11/9	11/6	8/6
	Sternebrae: Wide	0/0	0/0	1/1	2/2
	Ossification deficiency: Cranial	0/0	4/3	4/2	8/4
	Ossification deficiency: Appendicular skeleton	10/7	10/5	18/12	52/16
	Increased ossification: Cranial	0/0	0/0	3/1	11/2
Toxicokinetics (GD19); mean values	Dose (mg/kg)	C _{max} (ng/mL)		AUC ₀₋₂₄ (ng.h/mL)	
	30	725		4220 (0.03X*)	
	100	1010		10500 (0.08X*)	
	300	406		3780 (0.03X*)	

LD: low dose; MD: mid dose; HD: high dose

*Fold exposure compared to the recommended clinical dose of 800 mg/day (mean steady-state AUC was 141 µg (141000ng)*h/mL)

5.5.5. Other Toxicology Studies

The Applicant's Position:

No other toxicology studies have been conducted.

The FDA's Assessment:

The FDA concurs with the Applicant.

X

X

Simon Williams, PhD
Primary Reviewer

Brenda Gehrke, PhD
Supervisor

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

Umbralisib is a small molecule inhibitor of phosphoinositide-3-kinase delta (PI3K δ) and casein kinase 1 epsilon (CK1 ϵ). The Applicant is seeking approval of umbralisib for the treatment of patients with follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies. The proposed dosing regimen is 800 mg QD taken orally with food.

The Clinical Pharmacology section of the NDA is supported by single and multiple dose pharmacokinetics (PK) characterization, population PK and exposure-response analyses, QT assessment, human mass balance, relative bioavailability, and in vivo food effect studies, in vitro metabolic and transport studies, and physiologically-based pharmacokinetic (PBPK) modeling.

The clinical pharmacology review focused on the appropriateness of the proposed dosing regimen and dose recommendations for patients with hepatic impairment, and drug-drug interactions.

Recommendations:

The Office of Clinical Pharmacology has reviewed the information submitted in NDA213176 (b) (4). This NDA is approvable from a clinical pharmacology perspective. The key review issues with specific recommendations/comments are summarized below in the table below.

Table 7: Key Clinical Pharmacology Review Issues by FDA

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary evidence of effectiveness comes from pivotal study UTX-TGR-205. The proposed dosing regimen is supported by the overall efficacy of umbralisib with an objective response rate (ORR) of 42.7% (95% CI: 33.6, 52.2) in patients with relapsed or refractory follicular lymphoma.
General dosing instructions	The proposed umbralisib dosing regimen of 800 mg given orally with food is acceptable for approval from a clinical pharmacology perspective: Favorable anti-tumor activity: This dosing regimen demonstrated an ORR of 42.7% in patients with FL. Across the dose range of 400 to 1200 mg QD, $\geq$ 800 mg QD dosage appeared to show > 50% ORR and increased in percent change from baseline (%CfB) of target lesion dimensions in more than 50% of the FL

Review Issue	Recommendations and Comments
	population, whereas, at lower dosage (<800 mg), there may be reduced activity. Positive exposure-response relationships for safety: Higher exposure resulted in higher incidence of adverse events, particularly for diarrhea and elevated ALT and AST levels.
Dosing in patient subgroups (intrinsic and extrinsic factors)	- No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin $\leq$ upper limit of normal [ULN] with AST > ULN or total bilirubin >1 to 1.5 $\times$ ULN with any AST). There is no data available for patients with moderate or severe hepatic impairment (>1.5 $\times$ULN and any AST). - No dose adjustment is recommended for patients with mild or moderate renal impairment (CLcr 30-89 mL/min). There is no data available for patients with severe renal impairment (CLcr 15-29 mL/min). - Based on PopPK analyses, no dose adjustment is required based on age (18 to 87 years old), sex, race (White and Black), and body weight (44 to 165 kg).
Drug-drug interactions	- No clinically significant differences in umbralisib pharmacokinetics were observed when used concomitantly with omeprazole, a proton pump inhibitor. - The available data do not support the Applicant's claim that co-administration of umbralisib is not expected to significantly impact the PK of P-gp sensitive substrates. - The available data do not support the Applicant's claim that co-administration of umbralisib is not expected to significantly impact the PK of cytochrome (CYP) sensitive substrates. - The available data do not support the Applicant's claim that co-administration of strong CYP3A inhibitors is not expected to significantly impact the PK of umbralisib. - There is no data to evaluate the effect of CYP2C9 modulators on the PK of umbralisib.
Labeling	Overall, the proposed labeling recommendations are acceptable contingent upon the Applicant's agreement with the FDA revisions to the label. Clinical pharmacology labeling recommendations are detailed in Section 2.1, 8.6, 8.7, 12.2, and 12.3.

Postmarketing Requirements and Commitments

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	Umbralisib dose in patients with moderate to severe hepatic impairment	Hepatic metabolism plays a major role in the elimination of umbralisib. The recommended dose of umbralisib in patients with moderate and severe hepatic impairment (based on NCI-ODWG criteria) has not been established. The clinical study will determine whether dose adjustment is needed in this specific population.	Conduct a clinical pharmacokinetic trial to determine an appropriate safe dose of umbralisib in patients with moderate to severe hepatic impairment (based on NCI criteria).
PMR	The effect of strong CYP3A and moderate CYP2C9 inhibitors on the exposure of umbralisib	CYP3A and CYP2C9 plays a role in the elimination of umbralisib. The recommended dose of umbralisib when used concomitantly with a strong CYP3A or moderate CYP2C9 inhibitor has not been established. The clinical study will determine whether dose adjustment is needed in these patients.	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP3A and CYP2C9 inhibitors on the single dose pharmacokinetics of umbralisib to determine appropriate dosing recommendations.
PMR	The effect of umbralisib on the exposure of CYP and P-gp substrates	In vitro, umbralisib has the potential to inhibit CYP2C8, CYP2C9, CYP2C19, and CYP3A4 and P-gp. However, repeated dosing of umbralisib on the PK of CYP and P-gp sensitive substrates in clinical trials is not fully characterized. The clinical study will evaluate the effect of repeated dosing of umbralisib on these CYP and P-gp sensitive substrates and address the potential for excessive drug toxicity.	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of umbralisib on the single dose pharmacokinetics of sensitive CYP2C8, CYP2C9, CYP2C19, and CYP3A and P-gp substrates to address the potential for excessive drug toxicity.

PMR or PMC	Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
PMR	The effect of umbralisib on QT interval	The effect of umbralisib on the QT interval is not fully characterized as umbralisib exposure observed in TGR-1202-102 for QT assessment is 37% lower than the expected maximum therapeutic exposure (C _{max,ss}). Additional ECG data are needed to assess the risk of QTc prolongation with umbralisib.	The QT study can be conducted as a dedicated study or as a sub-study of ongoing trials to characterize QTc prolongation risk with umbralisib at steady-state maximal concentrations.
PMC	The effect of strong CYP3A ^{(b) (4)} inducers on the exposure of umbralisib	CYP3A ^{(b) (4)} plays a role in the elimination of umbralisib. The recommended dose of umbralisib when used concomitantly with a strong CYP3A ^{(b) (4)} inducer has not been established. The clinical study will determine whether dose adjustment is needed in these patients.	Conduct a clinical pharmacokinetic trial to evaluate the effect of repeat doses of CYP3A ^{(b) (4)} inducers on the single dose pharmacokinetics of umbralisib to determine appropriate dosing recommendations.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The Applicant's Position:

The clinical pharmacology of umbralisib has been well characterized. The data in the application to support the use of umbralisib 800 mg once daily (QD) in subjects with FL comprise in vitro experiments using human biomaterials; clinical pharmacology studies with umbralisib in healthy subjects and subjects with cancer including single and repeat-dosing pharmacokinetic (PK) studies, biopharmaceutic studies (food effect), intrinsic factors (sex), extrinsic factors

(drug-drug interactions [DDIs]); and population PK analyses.

The FDA's Assessment:

The FDA does not agree that the clinical pharmacology of umbralisib has been well characterized. The PK of umbralisib in patients with moderate to severe hepatic impairment, potential drug interactions of umbralisib as a perpetrator of CYP enzymes (CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and P-gp and a victim (CYP3A and CYP2C9 inhibitors and inducers), and the effect of umbralisib on the QT interval are not well characterized. Additional studies are needed (see Postmarketing Requirements and Commitments, Section 13).

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

The Applicant's Position:

During the course of the development of umbralisib, absorption, distribution, metabolism, excretion, and DDI properties were comprehensively evaluated. The appropriateness of umbralisib for the FL indication was evaluated in the exposure-response (E-R) analyses for efficacy and safety across five dose levels: 400, 600, 800, 1000, and 1200 mg. The pooled population pharmacokinetics (PPK)/E-R analyses robustly evaluated biologically inter-dependent endpoints of efficacy and safety. Overall, the dose-response results demonstrate an acceptable balance between benefits and risk at the recommended dose of 800 mg and justify the use of this dose regimen in subjects with FL.

The FDA's Assessment:

The FDA agrees with the Applicant's position that the recommended dosing regimen of 800 mg QD with food for patients with FL is reasonable. The Applicant compared the key efficacy and safety endpoints for a wide dose range of 400 to 1200 mg QD and identified that (1) for the 800 mg QD dose regimen, $\geq 50\%$ of the FL population showed an ORR greater than 50% and an increased in %CfB of target lesion dimensions; (2) < 800 mg, there may be reduced activity in the FL population. At doses > 800 mg, there may be an increased risk of any grade and Grade ≥ 3 elevated ALT/AST. After evaluating the benefit and risks based on the dose/exposure-response relationships for efficacy and safety, the proposed 800 mg QD for the treatment of FL populations is reasonable.

6.2.2.2. Therapeutic Individualization

The Applicant's Position:

No therapeutic individualization is needed in the proposed indication based on demographic factors (age, sex, race, body weight), DDIs (use of acid-reducing agent [ARA], concomitant use of strong 3A4 inhibitor, P-glycoprotein [P-gp] substrates), or in special populations of mild hepatic impairment or mild and moderate renal impairment. The impact of umbralisib on moderate and severe hepatic impairment and severe renal impairment have not been investigated.

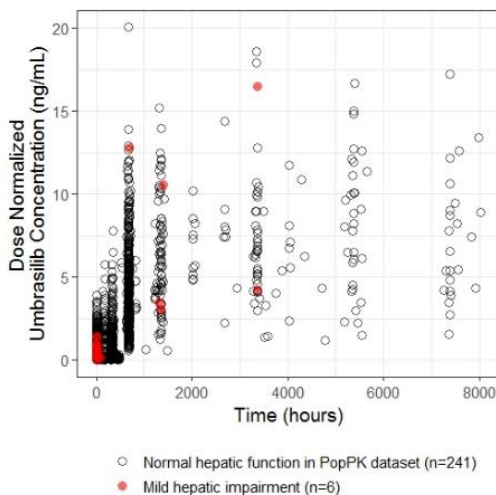
The FDA's Assessment:

Based on the population PK (PPK) analysis, FDA agrees with the Applicant that no dose adjustment is needed for demographic factors (age, sex, race and body weight) and patients with mild to moderate renal impairment. However, the FDA does not agree with the Applicant's position regarding the dose recommendations for concomitant use of strong CYP3A4 inhibitors based on the PPK analysis.

In the Applicant's evaluation of the impact of concomitant strong CYP3A4 inhibitors, the frequency and dosing time of the co-administered strong CYP3A4 inhibitors were not available. In addition, in a pooled PK analysis (Study TGR-1202-101 and Study UTX-TGR-205) of 10 patients who were co-administered strong CYP3A4 inhibitors, only 4 patients had intense PK data available, while 6 patients had sparse PK of 1-3 PK samples. Based on the limited PK data and information on the administration time of concomitant strong CYP3A4 inhibitors, the Applicant's current conclusion that no dose adjustment would be needed for concomitant administration of strong CYP3A4 inhibitors is not acceptable.

The FDA agrees with the Applicant that no dose adjustment is needed for patients with mild hepatic impairment. In the Applicant's PPK evaluation of the impact of mild hepatic impairment, PK data were only available for 6 patients with mild hepatic impairment (classified by NCI-ODWG criteria). Out of the 6 patients, 4 patients had only one PK datapoint. The available data were insufficient to use the PPK approach to assess the effect of mild hepatic impairment on the PK of umbralisib; however, the observed dose-normalized umbralisib concentrations from patients with mild hepatic impairment were within the range of those from patients with normal hepatic function (Figure 1), supporting no dose adjustment in patients with mild hepatic impairment. There are no data for patients with moderate or severe hepatic impairment.

Figure 1: Comparison of umbralisib observed concentrations between patients with normal hepatic function and mild hepatic impairment



Source: Reviewer's analysis

6.2.2.3. Outstanding Issues

The Applicant's Position:

None.

The FDA's Assessment:

The FDA disagrees with the Applicant's position that there are no outstanding issues. The PK characterization of umbralisib in patients with hepatic impairment, potential drug interactions of umbralisib as a perpetrator of CYP enzymes (CYP2C8, CYP2C9, CYP2C19, and CYP3A4) and P-gp and a victim (CYP3A and CYP2C9 inhibitors and inducers), and the effect of umbralisib on the QT interval are not well characterized. Refer to the Postmarketing Requirements and Commitments, Section 13.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The Applicant's Position:

Based on comprehensive clinical pharmacology evaluations of umbralisib, the following characteristics of umbralisib are observed.

Absorption and Pharmacokinetics:

- From Study TGR-1202-101, the observed median T_{max} at 800 mg was 2.1 and 3.9 hours on Days 1 and 29 of dosing, respectively.
- Linear PK was observed over a dose range of 200 to 1000 mg by non compartmental analysis and 200 to 1800 mg by PPK analysis, although the number of subjects at 1800 mg was limited (n=2)
- Following repeat dosing at 800 mg, the observed accumulation ratio for area under the plasma/serum concentration-time curve (AUC) and maximum concentration (C_{max}) were 5.2- and 2.8-fold, respectively; the PPK model-estimated median steady state accumulation ratio for AUC was 6.4-fold (95% confidence interval [CI]: 3.7, 10.9). Ninety percent of the AUC at steady state was achieved after 35.5 doses (95% CI: 20, 70) of 800 mg QD.
- The PPK model-estimated relative oral bioavailability of drug product (DP) containing (b) (4) drug substance (DS) was 193% compared to DP containing (b) (4) DS.

Distribution:

- The geometric mean (percentage coefficient of variation [CV%]) apparent volume of distribution at steady state in healthy subjects was 1900 L/h (38%). This value is about 30 times greater than the volume of total body water in humans (Davies and Morris 1993), suggesting wide tissue distribution of umbralisib. This observation is expected for a Biopharmaceutics Classification System Class 2 compound, such as umbralisib.
- Umbralisib plasma protein binding was high in humans at concentrations of 2 (99.7%) and 5 (99.8%) $\mu\text{mol/L}$. The PPK model-estimated C_{max} at steady state and minimum plasma concentration at steady state ($C_{min,ss}$) were 11 and 8 $\mu\text{mol/L}$ (6.3 and 4.7 $\mu\text{g/mL}$), respectively.

Elimination:

Metabolism:

- In plasma, umbralisib was minimally metabolized. In a radiolabeled mass balance study, unchanged umbralisib was the predominant radioactive component found in plasma (79.2% of total radioactivity area under the plasma concentration-time curve from time zero to 48 hours post-dose [AUC_{0-48}]) with 2 minor metabolites identified. Each plasma metabolite represented <5% of total radioactive AUC_{0-48} .
- The proposed metabolites were formed by O-de-alkylation, mono-oxidation, methylation, oxidative defluorination, hydrogenation, glucuronidation, or

combinations thereof.

Excretion:

- Hepatobiliary elimination was the major excretion pathway for umbralisib, with fecal excretion accounting for 81% and urine excretion accounting for 3% of the total radioactive dose administered orally.
- In Study TGR-1202-904, the geometric mean (CV%) umbralisib apparent clearance was 8.72 (31%) L, with an apparent terminal phase half-life of 151 (33%) hours.

The FDA's Assessment:

The FDA generally agrees with the Applicant's assessment on general pharmacology and pharmacokinetic characteristics of umbralisib.

The FDA disagrees with the Applicant's position that umbralisib is minimally metabolized. Based on data from the human mass balance study (TGR-1202-902), the majority of radioactivities in feces and urine were observed to be metabolites. Thus, umbralisib is mainly eliminated through metabolic pathways.

Differences in PK exposure was observed between healthy subjects and patients. Based on the PPK analysis, healthy subjects (n = 24) appeared to have 30% lower relative bioavailability (F) in Study 1102 compared to subjects with hematological malignancies in Study 101 (n=83). Central volume of distribution (Vc/F) in healthy subjects (n=24) appeared to be 79.5% lower than those in patients (n = 223) with hematological malignancies. The impact of food effect and formulations (b) (4) on relative bioavailability was taken into account in the PPK analysis and could not fully explain the exposure difference observed between Study 101 and Study 205. The rationale for the difference is currently unknown.

The general overview of umbralisib ADME and clinical PK information as assessed by FDA are presented in the table below.

Table 8: Highlights of Clinical Pharmacology for umbralisib

Physiochemical properties

Chemical structure and molecular weight	Chemical Structure of umbralisib (Source: NDA213176, Module 3.2.S.1.2. Figure 1) Molecular weight of umbralisib tosylate: 743.75 g/mol (571.56 g/mol salt form) Log P: 4.84 Log D: 4.79 at pH 7.4 Umbralisib is a weak base with pKa of 2.71 and exhibits pH dependent solubility characteristics (Table 9). Table 9: Aqueous Solubility of umbralisib tosylate at 25°C. <table border="1"> <tr> <td data-bbox="427 1266 760 1455">Solubility - Aqueous (25°C)</td><td data-bbox="760 1266 1370 1455"> 0.032 mg/ml @ pH 1.2 0.018 mg/ml @ pH 2.2 0.002 mg/ml @ pH 4.5 0.003 mg/ml @ pH 7.4 0.003 mg/ml @ pH 10.2 </td></tr> </table> (Source: NDA213176, Module 3.2.S.1.3. General Properties, Table 1)	Solubility - Aqueous (25°C)	0.032 mg/ml @ pH 1.2 0.018 mg/ml @ pH 2.2 0.002 mg/ml @ pH 4.5 0.003 mg/ml @ pH 7.4 0.003 mg/ml @ pH 10.2
Solubility - Aqueous (25°C)	0.032 mg/ml @ pH 1.2 0.018 mg/ml @ pH 2.2 0.002 mg/ml @ pH 4.5 0.003 mg/ml @ pH 7.4 0.003 mg/ml @ pH 10.2		
Pharmacology			

Mechanism of Action	Umbralisib is a small molecule inhibitor of phosphoinositide-3-kinase delta (PI3K δ) and casein kinase 1 epsilon (CK1 ϵ). The mechanism of action (MOA) involves competitive binding of umbralisib to PI3K δ and CK1 ϵ , inhibiting cell proliferation and inducing apoptosis of lymphoma and leukemic cell lines and primary tumor cells.
Active Moieties	Umbralisib was observed to be the major active species in plasma (79.2%).
QT/QTc Prolongation	Umbralisib exhibits no large mean increases in the QTc interval (i.e., >20 msec). However, the effect of umbralisib on the QT interval is not fully characterized as umbralisib exposure observed in TGR-1202-102 for QTc assessment is 37% lower than that reported by the PPK model. The effect of food and formulation differences in clinical trials and bioanalytical assays were not considered factors for this PK differences.
General Information	
Bioanalysis	Two validated PK assays were used to measure umbralisib concentrations in human plasma (MET126) and serum (MET193). A cross-validation study of plasma and serum (MET126 Addendum 1) indicated 12.5% bias between the methods, which is not a significant factor. The majority of PK data were obtained from plasma PK samples (91.6%). A summary of the method validation reports is included in Appendix 19.4.1.
Healthy Volunteers vs. Patients	Based on population PK analysis, F and Vc/F in healthy subjects were 30% and 79.5% lower when compared to those in patients with hematological malignancies. The reason for this difference is currently unknown.
Drug exposure at steady state following the therapeutic dosing regimen	In adult patients with hematological malignancies who received umbralisib 800 mg QD with food, geometric steady-state (CV%) C _{max} and AUC _{tau} of umbralisib were 7.3 (39%) μ g/mL and 141 (46%) μ g*h/mL, respectively, based on the PPK model. Noncompartmental pooled PK analysis was not conducted as there were a limited number of patients (n=3) with intense PK sampling available in Phase 1 portion of Study TGR-1202-101.
Minimal effective dose or exposure	Not determined.

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Maximal tolerated dose or exposure	In Study TGR-1202-101, the MTD of umbralisib as a single-agent treatment in patients with hematological malignancies was not reached at doses up to 1800 mg due to PK saturation in absorption.
Dose Proportionality	Umbralisib (b) (4) appears to show dose-proportionality for both C_{max} and AUC in the dose range of 200 to 1000 mg following a single dose and at steady state.
Accumulation	The median accumulation ratios (R_{acc}) following umbralisib 800 mg QD with food was approximately 6.4-fold for AUC_{tau} and 3.8-fold for C_{max} based on PPK analysis.
Variability	Based on PPK analysis, the inter-subject variability (CV%) of apparent clearance (CL/F) and central volume of distribution (V_c/F) were 51.9% and 185%, respectively.
Absorption	
Bioavailability	Absolute bioavailability study was not conducted.
T_{max}	The median time to reach peak plasma concentration (T_{max}) of umbralisib following 800 mg QD with food was about 3.9 hours.

Relative Bioavailability (b) (4)	Study TGR-1202-PK102 was an open-label, randomized, 2-way crossover study in 26 healthy subjects to evaluate the PK of umbralisib with (b) (4) tablets. The results showed that the exposure of umbralisib was increased 60% and 2.2-fold for AUC and C _{max} , respectively, following a single dose of 200 mg (b) (4) tablet and a single dose of 200 mg (b) (4) tablet in healthy subjects under fasting condition (Table 10).		
	Table 10: Statistical analysis (test/reference) of umbralisib PK parameters between (b) (4) (reference) and (b) (4) (test) tablets		
	AUC_{0-inf} (GMR, 90% CI)	C_{max} (GMR, 90% CI)	T_{max} (hours) (range)
	1.60 (1.47-1.76)	2.24 (2.02-2.47)	(b) (4) 3.0 (2.0-6.0) (b) (4) 3.0 (2.0-4.0)

Food effect (Fed/fasted)	There were two studies (TGR-1202-PK101 and TGR-1202-908) evaluating the effect of food on the PK of umbralisib with two different formulations (b) (4).		
	Study TGR-1202-PK101 was an open-label, single-dose, randomized, crossover study to determine whether high-fat, high calorie food has an effect on the PK of umbralisib in 24 healthy subjects who received a single dose of 200 mg (b) (4) tablet. Results showed that the exposure of umbralisib was increased 67% and 2.7-fold for AUC and C _{max} , respectively, with food following a single dose of 200 mg (b) (4) tablet in healthy subjects (Table 11).		
	Table 11: Statistical analysis (test/reference) of umbralisib PK parameters (umbralisib (b) (4) tablets) under fasted (reference) and fed (test) condition		
	AUC _{0-inf} (GMR, 90% CI)	C _{max} (GMR, 90% CI)	T _{max} (hours) (range)
	1.67 (1.42-1.98)	2.73 (1.77-4.83)	Fast 3.0 (2.0-4.0) Fed 4.0 (2.0-8.0)
	Study TGR-1202-908 was an open-label, single-dose, randomized, crossover study to determine whether high-fat, high calorie food (approximately 917 calories with 171 calories from protein, 232 calories from carbohydrate, and 502 calories from fat) has an effect on the PK of umbralisib in 24 healthy subjects who received a single dose of 200 mg (b) (4) tablet. Results showed that the exposure of umbralisib was increased 40% and 2.2-fold for AUC and C _{max} , respectively, with food following a single dose of 200 mg (b) (4) tablet in healthy subjects (Table 12).		
	Table 12: Statistical analysis (test/reference) of umbralisib PK parameters (umbralisib (b) (4) tablets) under fasted (reference) and fed (test) condition		
	AUC _{0-inf} (GMR, 90% CI)	C _{max} (GMR, 90% CI)	T _{max} (hours) (range)
	1.40 (1.21-1.62)	2.15 (1.84-2.51)	Fast 3.0 (1.5-6.0) Fed 4.0 (3.0-5.0)

Proton Pump Inhibitor (PPI) effect (omeprazole)	Study TGR-1202-904 was an open-label, single-dose, crossover study to determine whether repeated doses of omeprazole (40 mg QD for 4 consecutive days), a proton pump inhibitor (PPI), has an effect on the PK of umbralisib in 18 healthy subjects who received a single dose of 800 mg (b) (4) tablet under fed conditions. Results showed that there was no clinically meaningful PK changes on the exposure of umbralisib, following a single dose of 800 mg (b) (4) tablet in healthy subjects with food (Table 13).		
	Table 13: Statistical analysis (test/reference) of umbralisib PK parameters (umbralisib (b) (4) tablets) with (test) and without PPI (reference)		
	AUC _{0-inf} (GMR, 90% CI)	C _{max} (GMR, 90% CI)	T _{max} (hours) (range)
	1.20 (1.10-1.31)	0.92 (0.83-1.01)	Fast 4.0 (2.0-6.0) Fed 4.0 (2.0-6.0)
Distribution			
Volume of distribution	Based on the PPK analysis, the geometric mean apparent volume of distribution of the central compartment (V _c /F) of umbralisib was estimated to be 312 L in patients with hematological malignancies.		
Plasma protein binding	In vitro, protein binding of umbralisib was 99.7-99.8%.		
Blood to plasma ratio	The mean blood-to-plasma ratio was 0.61-0.64 for umbralisib.		
Elimination			
Half-life	Following a single 800 mg dose in healthy subjects, the mean apparent elimination half-life (t _{1/2}) of umbralisib was approximately 110 hours based on noncompartmental analysis. In patients with hematological malignancies who received 800 mg QD, the geometric mean effective t _{1/2} of umbralisib was approximately 91 hours (42% CV) based on PPK analysis.		

Clearance	Based on the PPK analysis, the geometric mean apparent clearance of umbralisib was estimated to be 15.5 L/h in patients with hematological malignancies.
Metabolism	
Primary metabolic pathway(s)	In vitro, umbralisib appears to be metabolized by CYP3A4 and CYP2C9 and to a lesser extent CYP1A2. The metabolic assay [low incubation time (1 hr) of umbralisib with human recombinant P450 enzymes] was not adequate to determine the exact enzyme contribution due to low hepatic extraction of umbralisib.
Inhibitor/Inducer	In vitro, • Umbralisib inhibits CYP2C8 (IC₅₀ value of 10.6 µmol/L), CYP2C9 (IC₅₀ value of 3.4 µmol/L), CYP2C19 (IC₅₀ value of 13.5 µmol/L), and CYP3A4 (IC₅₀ value of 3.9 to 4.6 µmol/L), but does not inhibit CYP1A2, CYP2B6, and CYP2D6. • Umbralisib induces CYP3A4. • Umbralisib is not a substrate to P-gp, BCRP, OAT1, OAT3, OCT2, OATP1B1, OATP1B3, MATE1, and MATE2-K. • Umbralisib inhibits P-gp (IC₅₀ value of 0.0653 µmol/L).
Excretion	
Primary excretion pathways (% dose) ±SD	In the human mass balance Study TGR-1202-902 with mean total radioactivity recovery of 57.0-86.8% over 600 hours period, the mean radioactivity recovery in feces and urine in 6 healthy subjects were 81.0% (16.9% unchanged umbralisib) and 3.2%, respectively.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The Applicant's Position:

Yes, at 800 mg QD, a 54% objective response rate (ORR) was observed among subjects with FL for whom PK data was available for E-R analysis, and 58% of subjects with FL achieved >50% decrease in target lesion dimensions. The model-predicted ORR rate was 56.1 (90% CI: 46.2, 65.1). The model-predicted percent change from baseline (%CfB) (90% CI) in target lesion dimensions was -47.3% (-56.9%, -38.4%). A significant ($p < 0.05$) relationship was observed between exposure and ORR, and between exposure and best %CfB in target lesion dimensions in subjects with FL. There were no significant ($p > 0.05$) exposure-efficacy relationships for duration of response (DOR), PFS, or time to response (TTR) in subjects with FL. The PPK model-predicted $C_{min,ss}$ (bound and unbound umbralisib) after 800 mg QD was at least 7-fold higher than the concentration achieving 90% of maximal inhibition of PI3K δ inhibition for the FL population.

The FDA's Assessment:

The FDA generally agrees with Applicant's position.

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

The Applicant's Position:

Yes, the proposed dose of 800 mg QD is effective and generally well tolerated with no dosing difference observed in PK for age, sex, race, body weight, use of ARA, concomitant use of strong 3A4 inhibitor, mild hepatic impairment, or mild and moderate renal impairment.

During umbralisib development, 800 mg under fed conditions was implemented as the clinical dose for Phase II and later studies. The appropriateness of umbralisib for the FL indication was evaluated in the PK-efficacy relationships across several dose/exposure levels, including the clinical dose of 800 mg. This assessment used the final population PK model for all efficacy and safety endpoints. The integrated view of absorption, distribution, metabolism, excretion, and DDI properties of umbralisib and the dose-exposure-response relationships showed consistent trends that support the proposed clinical dose of 800 mg for patients with FL.

E-R analysis indicated no positive E-R relationship between average steady-state concentration and adverse events of special interest (AESI), with the exception of diarrhea (any grade) and elevated alanine aminotransferase (ALT)/aspartate aminotransferase (AST) (any grade and Grade ≥ 3). Exposure-corrected QT interval (QTc) analyses indicated no cardiac safety-related risk at the recommended umbralisib dose of 800 mg or at a supratherapeutic dose of 1200 mg. Other additional covariate analyses supported no dose adjustment for subjects with hepatic or

renal impairment.

The FDA's Assessment:

The FDA agrees with the Applicant's proposed dosing regimen for the general patient population. However, the FDA disagrees with the Applicant's position that there is no risk of QTc prolongation with umbralisib. The Applicant's exposure-corrected QT interval (QTc) analyses were conducted using steady state exposure ($C_{max,ss}$) data in Study TGR-1202-102. The geometric mean C_{max} on Cycle 2 Day 1 was 4012 ng/mL (n=20), which was lower than the therapeutic exposure (7266 ng/mL) obtained from PPK analysis. The 1200 mg QD dose group in Study TGR-1202-102 did not provide higher exposure (4172 ng/mL) as compared to the 800 mg QD dose group. Thus, the Applicant's QT assessment was not adequate to extrapolate the risk of QTc prolongation to the higher exposure range. The FDA agrees that there were no large mean increases (i.e., 20 msec) with umbralisib treatment.

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

The Applicant's Position:

No. Based on the assessment of intrinsic factors, no dose adjustment or change in regimen is required based on demographics or in special populations.

Specific Populations: No clinically significant differences in the PK of umbralisib were observed based on age (<65 or ≥65 years old), sex, race (White or non-White), body weight (<78.5 or ≥78.5 kg), or mild and moderate renal impairment (estimated glomerular filtration rate [eGFR] 60 to <90 or 30 to <60 mL/min, respectively, estimated by Modification of Diet in Renal Disease equation). The effect of severe renal impairment (eGFR <30 mL/min) and dialysis on umbralisib PK is unknown.

Hepatic Impairment: Umbralisib is minimally metabolized in the liver. No significant difference in the PK of umbralisib was observed in patients with mild hepatic impairment (total bilirubin >1 to 1.5 × upper limit of normal and any AST/ALT, by National Cancer Institute - Organ Dysfunction Working Group criteria). The effect of moderate and severe hepatic impairment on umbralisib PK is unknown.

The FDA's Assessment:

The FDA agrees with the Applicant that no dose adjustment is required based on age (18 to 87 years old), sex, race [83.8% (n=207) White and 5.7% (n=14) Black], body weight (44 to 165 kg) or mild to moderate renal impairment (CLcr 30 to 89 mL/min, estimated by the Cockcroft-Gault equation). In the Applicant's PPK evaluation of the impact of mild hepatic impairment, only 6 patients with mild hepatic impairment were included. Of the 6 patients, 4 patients had only 1 available PK sample for analysis. The available data were insufficient to use the PPK approach to assess the effect of mild hepatic impairment on the PK of umbralisib; however, the observed

dose-normalized umbralisib concentrations from patients with mild hepatic impairment were within the range of those with normal hepatic function (Figure 1), supporting no adjustment in patients with mild hepatic impairment.

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

The Applicant's Position:

The clinically relevant food-drug interactions and DDIs with concomitant medications are described in further detail below with their respective recommendation for management.

Food: Umbralisib is recommended to be taken with food as administration of a single dose with a high-fat meal in healthy subjects increased AUC and C_{max} of umbralisib by 61% and 115%, respectively, relative to fasting condition.

Effect of Other Drugs on Umbralisib:

ARA: Repeat dosing of omeprazole, an ARA, had no apparent impact on the exposure of a single dose of umbralisib. The area under the plasma/serum concentration-time curve from time zero to the time of the last quantifiable concentration (AUC_{0-t}) and area under the plasma concentration-time curve from time zero to infinity (AUC_{0-inf}) were both increased by 20% and the C_{max} decreased by 8% in the coadministration group, relative to the umbralisib alone group.

Cytochrome P450 (CYP)3A4 Inhibitors or Inducers: PPK analysis revealed that concomitant use of CYP3A4 inhibitors with umbralisib did not impact the PK of umbralisib. Use of strong CYP3A4 inducers (n=9) on the PK of umbralisib is unknown.

Transporter Systems: Umbralisib was not a substrate of organic anion transporter (OAT)1, OAT3, organic cation transporter (OCT)2, organic anion transport protein (OATP)1B1, OATP1B3, multidrug and toxic compound extrusion transporter (MATE)1, MATE2 K, P-gp, and breast cancer resistance protein. Thus, no impact on the PK of umbralisib is expected with concomitant use of these transporter substrates.

Effect of Umbralisib on Other Drugs:

P-gp Substrates: Umbralisib increased the absorption rate of fexofenadine (a sensitive P-gp substrate) producing a 42% higher C_{max} and a 1 hour decrease of T_{max} in the coadministration group relative to the fexofenadine alone group. However, the overall extent of fexofenadine exposure was unaffected, with the AUC_{0-t} and AUC_{0-inf} increased by 9% to 10%, respectively, in the coadministration group relative to the fexofenadine alone group. Therefore, co-administration of umbralisib is not expected to significantly impact the PK of P-gp substrates.

CYP3A4 Substrates: Simultaneous simulation using a physiologically-based PK (PBPK) model suggested umbralisib was a weak (≥ 1.25 - to ≤ 2 -fold changes in C_{max} and AUC ratios,

respectively) inhibitor. Specifically, multiple doses of umbralisib increased AUC and $C_{\max}$ of single dose midazolam 1.56- and 1.52-fold, respectively. These simulated exposure increases of midazolam suggested that umbralisib did not induce CYP3A4.

CYP2C8, CYP2C9, and CYP2C19 Substrates: Simulation using PBPK modeling suggested that multiple doses of umbralisib did not impact the exposures of single doses of repaglinide (CYP2C8 substrate), tolbutamide (CYP2C9 substrate), or S-mephenytoin (CYP2C19 substrate). Specifically, the predicted $C_{\max}$ and AUC ratios with and without simulated coadministration of the probe substrate for each CYP isozyme were <1.25-fold under simulated steady state conditions of umbralisib.

The FDA's Assessment:

The FDA agrees with the Applicant that umbralisib should be taken with food.

Effect of omeprazole on PK of umbralisib:

The FDA agrees with the Applicant that no dose adjustment is required for the use of omeprazole.

Effect of umbralisib on PK of P-gp substrates:

The FDA disagrees with the Applicant's position that co-administration of umbralisib is not expected to significantly impact the PK of P-gp substrates. In Study TGR-1202-901, the study design is only sufficient to examine the effect of intestinal P-gp inhibition as only a single oral dose of umbralisib (800 mg with food) and fexofenadine (180 mg) were administered to healthy subjects. However, in vitro data suggest that umbralisib inhibits P-gp with an IC_{50} value of 0.064 $\mu\text{mol/L}$. Umbralisib has a high accumulation ratio (6.4-fold), a long half-life (effective half-life of 91 hours), and a small fluctuation between $C_{\max}$ and $C_{\min}$ (0.008 to 0.011 $\mu\text{mol/mL}$) at steady state. Under a worst case scenario when steady state of umbralisib is reached, there is a high potential that systemic inhibition of P-gp (liver and kidney) may affect the PK of P-gp sensitive substrates. Thus, the current data do not support the claim that umbralisib does not affect the PK of P-gp sensitive substrates.

Effect of strong CYP3A inhibitors on PK of umbralisib:

The FDA disagrees with Applicant's position that co-administration of strong CYP3A inhibitors is not expected to significantly impact the PK of umbralisib. In the Applicant's evaluation of the impact of concomitant strong CYP3A4 inhibitors, the frequency and dosing time of the co-administered strong CYP3A4 inhibitors were not available. In addition, of the 10 patients who were co-administered strong CYP3A4 inhibitors, only 4 patients had intense PK, while 6 patients only had sparse PK data of 1-3 PK samples. Based on the limited PK data and information on the administration time of concomitant strong CYP3A4 inhibitors, the Applicant's current conclusion that no dose adjustment would be needed for concomitant administration of strong CYP3A4 inhibitors is not acceptable.

Effect of umbralisib on PK of CYP substrates:

The FDA disagrees with Applicant's position that co-administration of umbralisib is not expected to significantly impact CYP substrates. The effect of umbralisib on CYP3A, CYP2C8, CYP2C9 and CYP2C19 substrates could not be confidently predicted using the PBPK modeling approach due to uncertainties about the in vitro to in vivo extrapolation. The potential of drug-drug interactions of umbralisib with substrates of these enzymes cannot be ruled out.

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7 Sources of Clinical Data

7.1. Table of Clinical Studies

The Applicant's Position:

All studies pertinent to the evaluation of efficacy and safety are summarized in Table 14.

Table 14: Listing of Clinical Trials Relevant to this NDA

Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
UTX-TGR-205/ Phase IIb/ NCT02793583	Open-label, randomized Phase IIb study of single agent umbralisib and in combination with ublituximab with or without bendamustine in subjects with previously treated iNHL, MCL, or DLBCL	FL and SLL cohorts: <u>Stage 1:</u> Single agent umbralisib <u>Stage 2:</u> Arm A: U2 Arm B: single agent umbralisib Arm D: single agent ublituximab MZL cohort: <u>Stage 1:</u> Single agent umbralisib <u>Stage 2:</u> U2 MCL cohort: <u>Stage 1:</u> Single agent umbralisib <u>Stage 2:</u> U2 DLBCL cohort: <u>Stage 1:</u> Arm A: U2 Arm B: umbralisib Following futility analysis: <u>Stage 2:</u> Arm A: U2 Arm C: U2+bendamustine	Primary efficacy: ORR based on the IRC and Investigator assessments Secondary efficacy: CR, PFS, DOR and TTR Safety endpoints: TEAEs, laboratory parameters, vital signs, ECOG performance status	Median duration of exposure = 9.43 months (range: 0.2 to 23.0 months) for subjects with MZL. Median time of follow- up for all subjects with MZL from study treatment to data cutoff: 20.3 months (range: 15.0 to 28.7 months) Median duration of exposure = 7.33 months (range: 1.0 to 22.5 months) for subjects with FL. Median time of follow- up for all subjects with FL from study treatment to data cutoff: 20.1 months (range: 13.5 to 29.6 months).	Umbralisib: Total: 275 MZL: 69 FL: 131 MCL: 23 DLBCL: 30 SLL: 22 U2: Total: 147 MZL: 17 FL: 41 MCL: 23 DLBCL: 66	Subjects with previously treated NHL with histological subtypes: FL (Grades 1, 2, and 3A), SLL, MZL, MCL, or DLBCL	US (82) Poland (10) UK (6) South Korea (5) Spain (5) Italy (4) Israel (4) Australia (3) Slovakia (1)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
		<u>Ublituximab:</u> 900 mg on Days 1, 8, and 15 of Cycle 1, then on Day 1 of Cycles 2 through 6, and thereafter on Day 1 every 3 cycles from Cycle 9 through Cycle 24; IV <u>Umbralisib:</u> 800 mg QD with food during all cycles in the study, starting on Day 1 of Cycle 1; PO <u>Bendamustine:</u> 90 mg/m² on Days 1 and 2 of Cycles 1 through 6; IV					
TGR-1202-101 (HEMREF 31)/ Phase I/ NCT01767766	First-in-human, open-label, Phase I study of umbralisib administered as a single agent in subjects with relapsed or refractory hematologic malignancies	<u>Umbralisib</u> (b) (4): 50 mg QD increased to 100, 200, 400, 800, 1200, and 1800 mg QD until the MTD was identified; PO <u>Umbralisib</u> (b) (4): 200 mg QD with food increased to 400, 800, 1200, and 1800 mg QD with food until the MTD was identified; PO Dose expansion phase: <u>Umbralisib</u> 800, 1000, and 1200 mg QD with food; PO	Primary safety: MTD and PK Primary efficacy: ORR (PR, CR, or CR with incomplete marrow recovery [Cri] for CLL per Hallek definition) Secondary efficacy: DCR, DOR Exploratory: PD biomarker assessment	Overall mean (median) duration of exposure - 10.3 (4.4) months Mean exposure: CLL: 15.4 months DLBCL: 6.0 months FL: 14.1 months HL: 3.6 months MZL: 15.2 months Other: 4.6 months	Total: 90 CLL: 25 DLBCL: 16 FL: 19 HL: 11 MZL: 5 Other: 14	Subjects with histologically confirmed HL, B-cell NHL, PTCL, CLL, SLL, or other B-cell lymphoproliferative disorders whose disease had relapsed after, or was refractory to, at least 1 previous treatment regimen	US (7)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
TGR-1202-102 (REFMAL404)/ Phase I/ NCT02574663	Open-label, Phase I study of umbralisib administered as a single agent and in combination either with nab-paclitaxel plus gemcitabine, with FOLFOX (±bevacizumab) , or nivolumab in subjects with solid tumor malignancies	<u>Umbralisib</u> : 800 and 1200 mg QD; PO <u>Umbralisib+nab-paclitaxel+ gemcitabine (Cohort 1)</u> : Umbralisib (800 mg QD; PO) +nab-paclitaxel (125 mg/m ² Days 1, 8, and 15 of each cycle; IV) +gemcitabine (1000 mg/m ² Days 1, 8, and 15 of each cycle; IV) <u>Umbralisib+FOLFOX+ bevacizumab (Cohort C)</u> : Umbralisib (800 mg QD; PO) +FOLFOX (Days 1 and 15 of each cycle; IV) +bevacizumab (5 mg/kg prior to FOLFOX Days 1 and 15 of each cycle; IV) <u>Umbralisib+nivolumab (Cohort N)</u> : Umbralisib (800 mg QD; PO) +nivolumab (240 mg every 2 weeks; IV)	Primary safety : TEAEs, laboratory parameters, vital signs, ECGs, ECOG performance status Primary efficacy : ORR, DOR, and PFS Exploratory : PK parameters	Median duration of exposure to umbralisib monotherapy = 1.6 months (range: 0 to 9.5 months) Median duration of exposure to umbralisib/ other agents: umbralisib+ nab-paclitaxel+ gemcitabine = 2.8/3.0 months Umbralisib+FOLFOX+ bevacizumab = 2.0/2.5 months Umbralisib+nivolumab = 3.4/2.2 months	Total: 66 Single agent umbralisib: 32 Umbralisib in combination with other agents: 34	Subjects with histologically or cytologically confirmed solid tumor that was locally advanced, recurrent, or metastatic, for which curative resection was not currently possible and for which systemic treatment with one of the selected anticancer agents was a reasonable therapeutic option	US (5)
UTX-TGR-501/ Ongoing Safety and Efficacy Long-term Extension/ NCT03207256	Open-label, long-term safety and efficacy extension study for subjects who completed treatment in	<u>Umbralisib</u> : Parent Studies TGR-1202- 101 and UTX-TGR-103: 200, 400, 600, 800, or 1200 mg with food QD ; PO Parent Studies TGR-1202- 102 and TGR-GA-106: 200, 400, 600, or 800 mg with food QD; PO	Safety endpoints : TEAEs, laboratory parameters Efficacy endpoints : PFS and DOR	Of the 7 subjects who rolled over from Study TGR-1202-101, mean duration of exposure to umbralisib in this study = 11.7 months (range: 0.9 to 20.1 months) as of the cutoff date.	Total: 10 TGR-1202- 101: 7 TGR-1202- 102: 0 UTX-TGR-	Subjects must have completed at least 6 cycles of therapy on their current parent protocol and have at least stable disease at the time of entry	US (5)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
	parent studies TGR-1202-101 (single agent umbralisib), TGR-1202-102 (single agent umbralisib), TGR-GA-106 (on single agent umbralisib and have completed or discontinued obinutuzumab and chlorambucil therapy), or UTX-TGR-103 (on umbralisib and/or ublituximab only and have completed or discontinued concomitant ibrutinib or bendamustine therapy)	<u>Ublituximab</u> : Study UTX-TGR-103: 900 mg at the next planned dose, >12 weeks from the immediate prior dose in the previous study, then every 12 weeks; IV		Of the 3 subjects who rolled over from Study UTX-TGR-103, mean duration of exposure to umbralisib in this study = 10.9 months (range: 2.5 to 19.7 months) as of the cutoff date.	103: 3 TGR-GA- 106: 0		
TGR-1202-202/ Phase II/ NCT03364231	Open-label, Phase II study of single agent umbralisib in subjects with non-follicular	Umbralisib 800 mg with food QD; PO	Primary efficacy: ORR (CR+PR+VGPR+MR) and DOR Secondary: PFS, time to treatment failure,	Mean duration of exposure = 8.0 months for subjects with MZL and 4.5 months for subjects with WM.	Total: 18 MZL: 8 WM: 10	Subjects with non- follicular iNHL (MZL and WM) who either relapsed or were refractory	US (4)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
	iNHL that is relapsed or refractory following at least 1 prior standard therapy regimen		safety (TEAEs)			following at least 1 prior regimen of standard therapy.	
UTX-TGR-103/ Phase I/Ib/ NCT02006485	Open-label, Phase I/Ib study of U2, U2+ibrutinib, and U2+bendamustine in subjects with B-cell malignancies	Dose escalation in the 2 disease groups (NHL or CLL/SLL) was carried out separately. U2: 3-6 subjects were enrolled in each cohort (Cohorts 1, 2, 3, 3a, 4, 7, and 9) of each disease group U2+ibrutinib: Once a dose level in the U2 cohort was determined safe, the triplet cohort was initiated (Cohorts 5, 5a, 6, and 8) U2+bendamustine: 2 dose cohorts were planned with the triplet combination (Cohorts 11 and 11a), with 3-6 subjects per cohort. Only subjects with DLBCL or FL were included. Following confirmation of MTD in either NHL or CLL/SLL groups, additional subjects were enrolled	Efficacy endpoints: Lymphoma response (CR, PR, or stable disease) and disease progression according to the Revised Response Criteria for Malignant Lymphoma for NHL subjects and the International Workshop on Chronic Lymphocytic Leukemia Working Guidelines for CLL/SLL subjects. Safety endpoints: TEAEs, laboratory parameters, vital signs	Median duration of exposure to umbralisib = 3.0 months (17.3 months for subjects with MZL, 6.4 months for subjects with FL, and 1.7 months for subjects with DLBCL). Median duration of exposure to ublituximab = 2.5 months (10.3 months for subjects with MZL, 5.0 months for subjects with FL, and 1.1 months for subjects with DLBCL).	U2: Total: 46 MZL: 5 FL: 14 MCL: 2 DLBCL: 25	The NHL cohort included subject's refractory to or relapsed after at least 1 prior treatment regimen. The CLL/SLL cohort included subjects previously untreated or with relapsed or refractory disease. The U2+bendamustine cohorts were restricted to subjects with DLBCL or FL refractory to or relapsed after at least 1 prior	US (6)

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Trial Identity/ Phase/ NCT No.	Trial Design	Test Product(s); Dosage Regimen; Route of Administration	Study Endpoints	Treatment Duration/ Follow Up	No. of Subjects Treated	Study Population	Countries (No. of Centers)
		(Cohorts 7E, 9E, and 10E) <u>Ublituximab:</u> Protocol Version 4.1 or earlier: 600 or 900 mg IV infusion on Days 1, 8, and 15 of Cycles 1 and 2, then on Day 1 of Cycles 4, 6, 9, and 12, and every 3 to 6 months thereafter based on Investigator discretion <u>Protocol Version 5.0 or later:</u> 600 or 900 mg IV infusion on Days 1, 8, and 15 of Cycle 1, then on Day 1 of Cycles 2 to 6, 9, and 12, and every 3 to 6 months thereafter based on Investigator discretion <u>Umbralisib</u> (b) (4): 800 or 1200 mg QD; PO <u>Umbralisib</u> (b) (4): 400, 600 (NHL only), 800, or 1200 mg QD with food; PO <u>Ibrutinib:</u> 420 mg (CLL) or 560 mg (NHL) QD; PO <u>Bendamustine:</u> 90 mg/m² on Days 1 and 2 of Cycles 1-6; IV				treatment.	

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Abbreviations: CLL, chronic lymphocytic leukemia; CR, complete response; DLBCL, diffuse large B-cell lymphoma; DOR, duration of response; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; FOLFOX, 5-fluorouracil/leucovorin/oxaliplatin; HL, Hodgkin's lymphoma; iNHL, indolent NHL; IRC, Independent Review Committee; IV, intravenous;; MCL, mantle cell lymphoma; MR, minor response; MTD, maximum tolerated dose; MZL, marginal zone lymphoma; NCT, National Clinical Trial; NDA, new drug application; NHL, non-Hodgkin's lymphoma; ORR, overall response rate; PFS, progression-free survival; PK, pharmacokinetic(s); PO, oral; PR, partial response; PTCL, peripheral T-cell lymphoma; QD, once daily; SLL, small lymphocytic lymphoma; TEAE, treatment emergent adverse event; TTR, time to response; U2, ublituximab+umbralisib; UK, United Kingdom; US, United States; VGPR, very good partial response; WM, Waldenström's macroglobulinemia.

The FDA's Assessment:

The clinical review of efficacy was primarily based on an analysis of the single-arm cohort of study UTX-TGR-205, an open-label, multi-center, multi-cohort trial (NCT02793583) that included 117 patients with relapsed/refractory FL who were evaluable for efficacy.

The review of safety is primarily based on the pooled data from 371 patients with hematologic malignancies in three single-arm, open-label trials (Study TGR-1202-101, TGR-1202-202, and UTX-TGR-205) and one open-label extension trial (Study UTX-TGR-501). Of note, data from UTX-TGR-103, described in the table above, was not included in the NDA submission.

All major efficacy and safety analyses were reproduced or audited. Statistical analyses by the reviewers were performed using SAS/JMP 13.0 (SAS Institute, Inc., Cary, NC) and MedDRA-Based Adverse Event Diagnostics (MAED) 1.8 (Enterprise Performance and Lifecycle System Design).

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The efficacy of umbralisib in subjects with FL was evaluated in a Phase I study, TGR-1202-101, and the Phase II single-arm study, UTX-TGR-205. The pivotal study to characterize the efficacy of umbralisib in FL is the ongoing Phase IIb Study UTX-TGR-205; efficacy data of subjects with FL are summarized as of the cutoff date of 30 November 2019. Efficacy data from Study TGR-1202-101 are used as supportive information.

8.1.1. Study UTX-TGR-205

Trial Design

The Applicant's Description:

Basic Study Design

Study UTX-TGR-205 is an ongoing, Phase IIb, randomized study to evaluate the efficacy and safety of single agent umbralisib and umbralisib in combination with ublituximab with or without bendamustine in subjects with previously treated iNHL, mantle cell lymphoma (MCL), and diffuse large B-cell lymphoma (DLBCL). Subjects were enrolled into 1 of 4 cohorts (marginal zone lymphoma [MZL], FL and small lymphocytic lymphoma [SLL], MCL, or DLBCL) based on tumor type.

Trial Location

This study is being conducted at 83 sites in the US and 38 sites outside of the US (10 sites in Poland, 6 sites in the United Kingdom, 5 sites each in Spain and South Korea, 4 sites each in Israel and Italy, 3 sites in Australia, and 1 site in Slovakia).

Choice of Control Group

On the basis of the disease types and settings being studied, an open-label Phase II design without an active controlled standard of care arm was selected.

Diagnostic Criteria

Subjects were enrolled with histologically confirmed diagnosis of B-cell NHL with histological subtype FL of Grade 1, 2, or 3a based on criteria established by the World Health Organization 2008 classification of tumors of hematopoietic and lymphoid

tissues.

Key Inclusion/Exclusion Criteria

Male or female subjects ≥ 18 years of age with FL were required to be relapsed or refractory after ≥ 2 prior lines of systemic therapy. Subjects must have received an anti-CD20 monoclonal antibody and an alkylating agent and must have documented evidence for requiring treatment (1 or more of the following: bulky disease [>5 cm], high lactate dehydrogenase, B symptoms, threatened organ function, splenomegaly, cytopenias due to lymphoma, or effusions).

Subjects with FL also had to have measurable disease, defined as at least 1 measurable disease lesion >1.5 cm in at least 1 diameter by computed tomography (CT), positron emission tomography (PET)-CT, or magnetic resonance imaging (MRI) in an area of no prior radiation therapy, or in an area that was previously irradiated that has documented progression.

Subjects were excluded if they were receiving cancer therapy (i.e., chemotherapy, radiation therapy, immunotherapy, biologic therapy, hormonal therapy, surgery, and/or tumor embolization) or any investigational drug within 21 days of Day 1 of Cycle 1 or had prior exposure to drugs that specifically inhibit PI3K.

Dose Selection

Based on the results from a Phase I dose-escalation study of umbralisib (TGR-1202-101) and 2 Phase I PK studies in healthy volunteers (TGR-1202-PK101 and TGR 1202-PK102), a dose of 800 mg QD of umbralisib under fed condition was selected.

Study Treatments

Umbralisib 800 mg QD was taken orally with food during all cycles in the study. Umbralisib was to be continued daily until progressive disease (PD), unacceptable toxicity, or withdrawal from the study for other reasons.

Assignment to Study Treatment

In Stage 1, eligible FL subjects received single agent umbralisib.

Blinding

This was an open-label study.

Dose Modification

For adverse events (AEs) suspected to be related to umbralisib, management guidance and dose delays and/or modifications were provided in the protocol. Supportive care was to be considered for any subject who experiences Grade ≥ 2 cytopenias, or Grade ≥ 1 non-hematologic toxicities. If a subject experienced a treatment-related AE requiring dose modification during the course of therapy, then study drug administration was to be held, as necessary, until the AE resolves or stabilizes to an acceptable degree.

Administrative Structure

The best clinical response as well as disease progression was determined by an Independent Central Radiology Group, also referred to as an Independent Review Committee (IRC).

An independent Data Safety Monitoring Board was established to advise the Sponsor on safety for subjects enrolled in the study. Given that this was an open-label, non-comparator Phase II trial, the Sponsor evaluated preliminary efficacy and safety data periodically to guide continued development of ublituximab and umbralisib.

Procedures and Schedule

During the study period, all subjects were evaluated for response by CT, PET-CT, and/or MRI at the end of Cycle 3 and then within 14 days prior to Day 1 of Cycles 6, 9, and 12. After Cycle 12, response assessments occurred every 6 cycles or more frequently. Subjects remained on study drug until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to Investigator decision or other reasons. Subjects who discontinued from study drug for reasons other than disease progression were followed for progression.

Treatment Compliance

Study drug compliance was reviewed with the subject at the beginning of each new treatment cycle and as needed.

Subject Completion

Subjects continued on study treatment until the occurrence of definitive disease progression, unacceptable toxicity, or withdrawal from the study due to Investigator decision or other reasons. Subjects who discontinued from study treatment (either for toxicity or physician choice) and have not progressed were followed for progression.

The FDA's Assessment:

The FDA agrees with the Applicant's description.

Study Endpoints

The Applicant's Description:

The study endpoints ORR and PFS are all accepted and well-recognized for oncology trials. The primary efficacy outcome, ORR, was defined as the percentage of subjects who achieved complete response (CR) or partial response (PR), according to the Revised Criteria for Malignant Lymphoma (Cheson 2007). The primary analysis for ORR was based on the IRC assessments.

The FDA's Assessment:

The FDA agrees with the Applicant's position and has provided additional information below.

The determination of response and progression was based on the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma (Cheson et al., 2007) modified so that the six index lesions included both nodal and extranodal lesions as described in the Lugano classification (Cheson et al. 2014) rather than considering nodal and extranodal lesions separately. The best clinical response and disease progression were determined by the independent central radiology group (ICRG). The findings of the ICRG were considered primary for analyses of ORR, PFS, and other tumor control endpoints. Subjects who discontinued from study treatment (either for toxicity or physician choice) and had not progressed continued to be followed for progression.

In the absence of a control arm and due to the open-label single-arm design of the trial, it is difficult to interpret and is unlikely to provide evidence to support the time-to-event endpoints, PFS and OS. The major limitation is that the measurements in isolation are out of context and comparing them to historical controls is prone to bias. The durability of the ORR will be assessed using the duration of response.

Statistical Analysis Plan and Amendments

The Applicant's Description:

The Statistical Analysis Plan (SAP) was agreed upon and finalized prior to the conduct of any efficacy analysis.

Analysis Populations

The intent-to-treat (ITT) Population included all subjects who were enrolled in the FL cohort (Stage 1) and who received at least 1 dose of single agent umbralisib. The ITT

Population was used for the efficacy analyses of ORR, DOR, PFS, CR, and TTR. To be included in the ITT Population, an FL subject must have

- been enrolled in the FL/SLL cohort Stage 1 (last enrollment 16 October 2018) to receive single agent umbralisib, and indicated as FL, not SLL, at Screening
- received at least 1 dose of study drug
- had prior systemic therapy with an anti-CD20 antibody and an alkylating agent.

The Per Protocol (PP) Population included all ITT subjects without major protocol deviations related to efficacy parameters and who had at least 1 post-baseline response assessment.

Interim Analysis

This was an interim analysis based on Amendment 7, Version 5.1 of the study protocol as of the data cutoff date of 30 November 2019. Results from the following analyses were presented in the interim CSR:

- Efficacy assessments of single agent umbralisib in FL cohort (Stage 1)
- Safety assessments for single agent umbralisib and by disease type, if appropriate

Efficacy Analysis

The primary efficacy outcome was ORR defined as the percent of subjects who achieved CR or PR, according to the Revised Criteria for Malignant Lymphoma (Cheson 2007). The primary analysis for ORR was conducted in the ITT population based on the IRC assessments. The estimated response rate and the exact 2-sided 95% CI (Clopper-Pearson method) were presented. Waterfall plots of maximum percentage decrease in sum of the products of longest diameters (SPD) by IRC assessment was presented, also showing FL grades. Additionally, the Investigator assessments were summarized in supportive analyses, and agreement in best overall response between IRC and Investigator assessments was also summarized.

Subject follow-up time (months) was calculated as follows: (date of efficacy data cutoff - date of first dosing +1)/30.4375.

The DOR was defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of definitive disease progression or death from any cause. The DOR was calculated based on subjects who achieved a response. For subjects who responded but never progressed in the study, the DOR was censored at the time of

last tumor assessment using the same censoring algorithm as for PFS. The DOR was summarized by Kaplan-Meier method.

The TTR was defined as the interval from enrollment to the first documentation of CR or PR. The Kaplan-Meier estimate for TTR was presented for the ITT population only in subjects who achieved CR or PR.

PFS was defined as the time from the date of enrollment until the date of first documentation of definitive disease progression or date of death from any cause, whichever occurred first. The median duration of PFS and the proportion of subjects who were progression-free at 6, 12, and 18 months were estimated using the Kaplan-Meier method. For each estimate, a 95% CI was reported. Additional sensitivity analyses were also performed for PFS.

Efficacy endpoints were examined for subgroups of the ITT population. The same methodology as for the primary analysis of ORR, PFS, CR, and DOR was used. Forest plots were produced for ORR.

Safety Analysis

Study treatment exposure was summarized for the ITT and Safety populations. The number and percentage of subjects with treatment-emergent adverse events (TEAEs), Grade ≥ 3 TEAEs, drug-related (to umbralisib and to ublituximab) TEAEs, drug-related Grade ≥ 3 TEAEs, serious TEAEs, Grade ≥ 3 serious TEAEs, drug-related serious TEAEs, TEAEs resulting in discontinuation of study treatment (umbralisib or ublituximab), and TEAEs with fatal outcome were summarized by tumor type, system organ class (SOC), and preferred term (PT). The number and percentage of subjects with AESIs was also summarized by AESI category and PT. Laboratory data for hematology and serum chemistry tests, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status were also summarized with shift tables from baseline.

Planned Subgroup Analyses

Analyses using following subgroups were performed for efficacy endpoints ORR, CR, PFS, and DOR:

- Gender
- Age group (<65, ≥ 65 years)
- Race (Caucasian, Non-Caucasian)
- Geographical region (US, Non-US)

- Baseline ECOG Performance status score (0, ≥ 1)
- FL grade at Screening (1, 2, 3a)
- Relapse or refractory to last therapy (Relapse, Refractory)
- Bulky disease (>5 cm)
- Splenomegaly
- Number of prior lines of therapy (<3 , ≥ 3)
- Previously treated with lenalidomide (Yes, No)
- Previously treated with lenalidomide in combination with anti-CD20 antibody (Yes, No)
- Previously treated with lenalidomide in combination with rituximab (Yes, No)

Changes to the Planned Analyses

The following changes to the planned subgroup analyses were revised from Version 1.0 of the SAP:

- Number of prior lines of therapy (<3 , ≥ 3)

Reason for change: The study inclusion criteria required at least 2 prior therapies for subjects with FL. The new category (<3 , ≥ 3) was added; otherwise, the number of subjects in the <2 subgroup would be too small for subgroup analysis.
- Previously treated with lenalidomide in combination with rituximab (Yes, No) was added as a new subgroup.

The FDA's Assessment: The FDA agrees, in general, with the Applicant's position and has the following comments.

According to the sample size calculation provided in the SAP, 100 patients in the FL cohort would provide a 90% power at the 5% level of significance to rule out 35% ORR under the null against the alternative hypothesis that ORR is 51.5%. Using a confidence interval of the ORR derived using the Clopper-Pearson exact method, an estimated ORR of 45% (i.e., 45 subjects responding of 100 FL subjects evaluated) would achieve a 1-sided 97.5% lower bound of 35.0%.

Although there were no planned interim analysis in the SAP, updated efficacy data was submitted on 9/15/2020 during the review of this application. The updated efficacy

results will be presented in the FDA's assessment section.

Protocol Amendments

The Applicant's Description:

The study protocol was amended 7 times during the study. None of the implemented changes impacted the integrity of the trial or the interpretation of the results. Important modifications/amendments to the study protocol included the following:

- Amendment 3 (Version 2.0, 12 April 2017 and Version 2.0 UK 12 April 2017):
 - Live virus vaccines were prohibited within 4 weeks prior to enrollment, during therapy, or for 6 weeks post-treatment.
- Amendment 4 (Version 3.0, 01 October 2017):
 - Inclusion criterion was modified to require subjects with FL or SLL to be relapsed or refractory after ≥ 2 prior lines of therapy, and all subjects must have received an anti-CD20 monoclonal antibody and an alkylating agent.
 - Inclusion criterion was modified to require creatinine clearance ≥ 30 mL/min for subjects with FL, SLL, or MZL and ≥ 40 mL/min for subjects with DLBCL.
 - Exclusion criterion was modified to allow use of concomitant medications known to cause QT prolongation or torsades de pointes with caution and at the Investigator's discretion.
 - The FL/SLL cohort was modified to include a Stage 1 to evaluate single agent umbralisib in up to 150 subjects prior to proceeding to Stage 2, which randomized subjects to either umbralisib alone or in combination with ublituximab.
 - More specific instructions were given around dose modifications in the event of diarrhea and/or colitis.
 - Futility stopping rules were added for the MZL cohort and the FL/SLL cohort based on Simon's 2-stage design.
- Amendment 5 (Version 4.0, 15 February 2018):
 - Mention of copanlisib was added as an excluded prior therapy.
- Amendment 6 (Version 5.0, 20 August 2018)
 - The primary objectives of the study were revised to reflect ORR as the primary endpoint for all cohorts.
 - The key secondary objectives of CR rate for subjects with FL or SLL and PFS for subjects with DLBCL were revised to be secondary objectives.

- Inclusion criterion was amended to require subjects with FL, SLL, or MZL to have documented evidence for requiring treatment.
 - Statistical assumptions for the MZL, FL/SLL, and DLBCL cohorts were revised in accordance with recent SAPs.
- Amendment 7 (Version 5.1, 20 September 2018)
 - Updated to include cytomegalovirus surveillance for all subjects
 - Revised to allow dose delays of any study medication for durations longer than 28 days to recover from toxicity
 - Updated to provide clarification on the liver toxicity dose modification guidelines

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant's Position:

This study was conducted according to the standards of Good Clinical Practice outlined in the ICH E6 Tripartite Guideline and Code of Federal Regulations Title 21 Part 312, applicable government regulations, institutional research policies and procedures, and any other local applicable regulatory requirement(s). Written informed consent was obtained from each subject prior to performing any study assessments.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Financial Disclosure

The Applicant's Position:

Details of financial disclosure are presented in Section 19.2.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Patient Disposition

The Applicant's Position:

In Study UTX-TGR-205, a total of 131 subjects with FL received at least 1 dose of umbralisib, of which 117 subjects were included in the ITT Population.

In the ITT Population of 117 subjects with FL, umbralisib was discontinued in 86 subjects (73.5%) with FL (Table 15). The most common reason for treatment discontinuation was PD (49.6%). AEs contributed to discontinuation in 14 subjects (12.0%) with FL.

Table 15: Summary of Disposition – End of Treatment and Reason of Discontinuation - Study UTX-TGR-205 (ITT Population)

	FL (N=117) n (%)
Discontinued	86 (73.5)
Reason for treatment discontinuation	
Progressive disease	58 (49.6)
Adverse event	14 (12.0)

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	FL (N=117) n (%)
Investigator decision	7 (6.0)
Withdrawal of consent	2 (1.7)
Other ^a	2 (1.7)
Lack of efficacy	1 (0.9)
Non-compliance with study	1 (0.9)
Completion of protocol-specified regimen	1 (0.9)

Source: CSR Study UTX-TGR-205, Table 14.1.2.1

Abbreviations: CSR, clinical study report; FL, follicular lymphoma; ITT, intent-to-treat.

^a Other: Subjects refused drug/further treatment.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Protocol Violations/Deviations

The Applicant's Position:

Major protocol deviations were reported in 28/131 FL subjects (21.4%). The most frequently reported deviations were those related to laboratory assessments (17/131 FL subjects [13.0%]).

The FDA's Assessment:

The FDA agrees with the Applicant's position. The protocol deviations related to laboratory assessments were primarily due to virology studies not being performed per protocol. Following review, the missed laboratory assessments were not likely to substantially impact the safety evaluation in regard to treatment-emergent laboratory abnormalities.

Table of Demographic Characteristics

Data:

A summary of the demographic and baseline characteristics for the ITT Population is shown in Table 16.

Table 16: Summary of Demographics and Baseline Characteristics - Study UTX-TGR-205 (ITT Population)

Parameter	FL (N=117)
Age (years)	
Mean (SD)	65 (10.9)
Median (minimum, maximum)	65 (29, 87)
Age categories, n (%)	
<65 years	56 (47.9)
≥65 years	61 (52.1)
Sex, n (%)	
Male	72 (61.5)
Female	45 (38.5)
Race, n (%)	
White	94 (80.3)
Non-White	23 (19.8)
Region, n (%)	
US	73 (62.4)
Non-US	44 (37.7)
Weight (kg)	
Mean (SD)	85.4 (21.40)
Median (minimum, maximum)	82.0 (49.6, 158.1)
ECOG performance status, n (%)	
0	65 (55.6)
1	48 (41.0)
2	4 (3.4)
FL grade at Screening, n (%)	
Grade 1	30 (25.6)
Grade 2	53 (45.3)
Grade 3a	32 (27.4)
Stage of disease at Screening, n (%)	

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Parameter	FL (N=117)
I	14 (12.0)
II	17 (14.5)
III	36 (30.8)
IV	49 (41.9)
Unknown	1 (0.9)
Prior systemic therapy	
Median (minimum, maximum)	3.0 (1, 10)
1	16 (13.7)
2	33 (28.2)
3	25 (21.4)
>3	43 (36.8)
Anti-CD20 therapies, n (%)	117 (100.0)
Anti-CD20 monotherapy only	0
Anti-CD20 based chemoimmunotherapy	117 (100.0)
Lenalidomide (mono or combo)	18 (15.4)
Lenalidomide and anti-CD20 antibody	14 (12.0)
Lenalidomide and rituximab	12 (10.3)
BTK inhibitor	10 (8.5)
Alkylating agent	117 (100.0)

Source: CSR Study UTX-TGR-205, Table 14.1.3.1, Table 14.1.4.1, Table 14.1.6.4, and Table 14.1.6.7

Abbreviations: BTK, Bruton's tyrosine kinase; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group;

FL, follicular lymphoma; ITT, intent-to-treat; MZL, marginal zone lymphoma; SD, standard deviation; US, United States.

The Applicant's Position:

For the 117 FL subjects in the ITT Population, the mean age was 65 years (range: 29 to 87 years); 61.5% of subjects were males, 80.3% of subjects were White, and 62.4% of subjects were enrolled at US sites (Table 16). The ECOG performance status was 0 or 1 for 96.6% of the subjects.

The FDA's Assessment:

The FDA agrees with the Applicant's position and have provided additional comments.

The incidence of FL is similar based on sex, although there was an under-representation of female patients in this trial. For racial and ethnic distribution, there were 6 patients

(5%) who identified as Hispanic and the racial representation was: 94 (80%) White, 2 (2%) Asian, 5 (4%) Black, 1 (1%) American Indian or Alaska Native, 1 (1%) Native Hawaiian or other Pacific Islander and race was missing for 12 (10%) patients.

Patients were enrolled in seven countries besides the United States, 3 (3%) Australia, 7 (6%) Great Britain, 2 (2%) Israel, 11 (9%) Italy, 1 (1%) South Korea, 18 (15%) Poland and 2 (2%) in Slovakia.]

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The Applicant's Position:

For the 117 FL subjects in the ITT Population, 30 subjects (25.6%) were Grade 1, 53 subjects (45.3%) were Grade 2, and 32 subjects (27.4%) were Grade 3a (Table 16). Most of the subjects were Stage III (30.8% of subjects) or Stage IV (41.9% of subjects). Fourteen subjects (12.0%) previously received lenalidomide and anti-CD20 antibody, of whom 12 subjects (10.3%) received lenalidomide in combination with rituximab (R²).

The FDA's Assessment:

The FDA agrees with the Applicant's position. In the ITT Population of 117 subjects with FL, 36% of the patients had disease refractory to last therapy and 31.6% had disease refractory to rituximab. More than half of the patients (57.3%) had received median of 3 or more prior lines of systemic therapies.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance

One subject with FL was discontinued due to non-compliance with study.

Concomitant Medications

All 131 subjects with FL received at least 1 concomitant medication. Concomitant medications were categorized according to their potential for inhibition/induction of P450 isozymes and inhibition of transporters. In the category of P450 inhibition, the most frequently used drugs (at least 10% of subjects overall) were acyclovir (73.3% of subjects), allopurinol (32.8% of subjects), and omeprazole (16.8% of subjects), all of which are classified as weak inhibitors based on FDA guidance (FDA: Drug development and drug interactions). Overall, P450 inducers were used infrequently ($\leq 1.1\%$). The most frequently used clinical OATP1B1/OATP1B3 inhibitor was clarithromycin (2.3% of subjects), which is also an inhibitor of P-gp. Other frequently used clinical P-gp inhibitors included carvedilol (4.6%).

Rescue Medication Use

Not applicable.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

The Applicant's Position:

In Study UTX-TGR-205, umbralisib 800 mg QD was administered to patients with FL who had relapsed or were refractory following at least 2 prior treatments. Subjects must have received an anti-CD20 monoclonal antibody and an alkylating agent. Efficacy results for subjects with FL in the ITT population (N=117) are summarized in Table 17.

Table 17: Summary of Overall Response for Subjects With FL - Study UTX-TGR-205 (ITT Population)

Parameter		IRC Assessment ^a FL (N=117)	Investigator Assessment FL (N=117)
ORR (CR+PR)	n (%)	50 (42.7)	47 (40.2)
	95% CI	33.6, 52.2	31.2, 49.6
CR	n (%)	4 (3.4)	5 (4.3)
	95% CI	0.9, 8.5	1.4, 9.7
PR	n (%)	46 (39.3)	42 (35.9)
	95% CI	30.4, 48.8	27.2, 45.3
DCR (CR+PR+stable disease)	n (%)	93 (79.5)	93 (79.5)
	95% CI	71.0, 86.4	71.0, 86.4
Stable disease	n (%)	43 (36.8)	46 (39.3)
	95% CI	28.0, 46.2	30.4, 48.8
Progressive disease	n (%)	22 (18.8)	22 (18.8)
	95% CI	12.2, 27.1	12.2, 27.1
Not evaluable	n (%)	2 (1.7)	2 (1.7)
	95% CI	0.2, 6.0	0.2, 6.0

Source: CSR UTX-TGR-205, Table 14.2.5.1

Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; DCR, disease control rate;

DOR, duration of response; FL, follicular lymphoma; IRC, Independent Review Committee; ITT, intent-to-treat; MZL, marginal zone lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; TTR, time to response.

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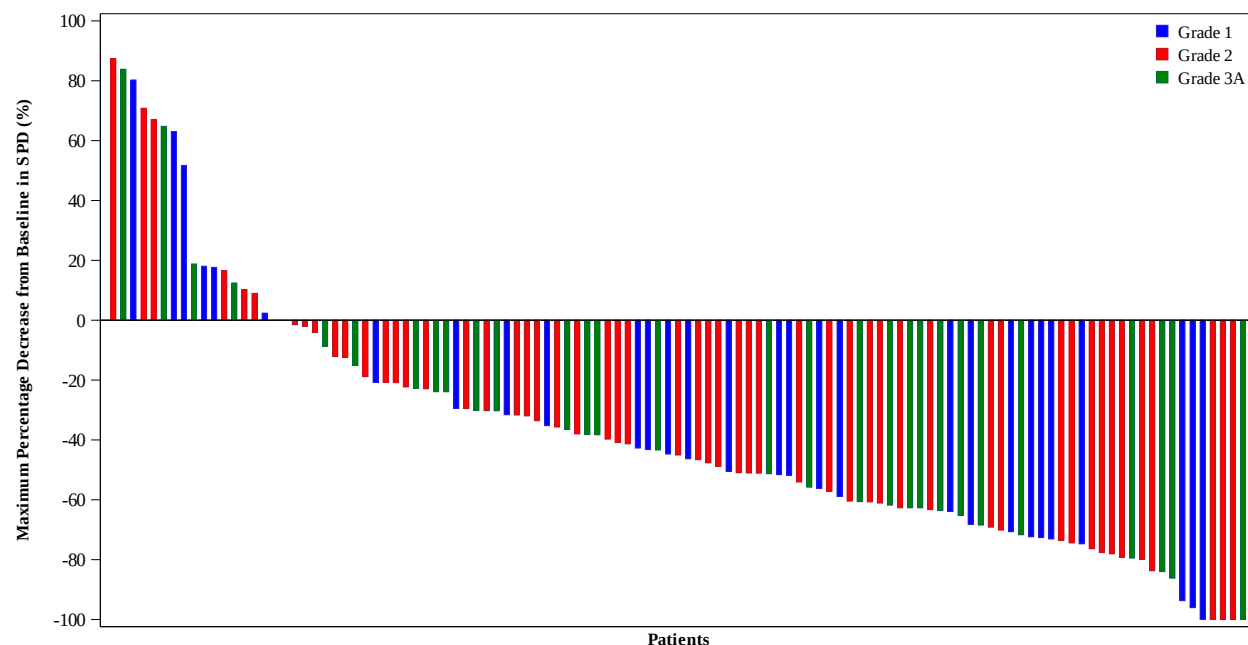
Note: For overall response, the 95% CI was exact using the Clopper-Pearson method based on the binomial distribution. For duration of response and time to response, 95% CIs were estimated using Kaplan-Meier method.

^a Denotes censored observation.

^b Based on Kaplan-Meier estimation.

The maximum percentage decrease in SPD by IRC assessment is presented in Figure 2. The majority of subjects showed a benefit with 95/111 (86%) of subjects with some reduction in tumor burden from baseline.

Figure 2: Waterfall Plot of Maximum Percentage Decrease in SPD for Subjects With FL by IRC Assessment - Study UTX-TGR-205 (ITT Population)



Source: CSR UTX-TGR-205, Figure 14.2.5.4

Abbreviations: CSR, clinical study report; FL, follicular lymphoma; IRC, Independent Review Committee; ITT, intent-to-treat; SPD, sum of the products of longest diameters.

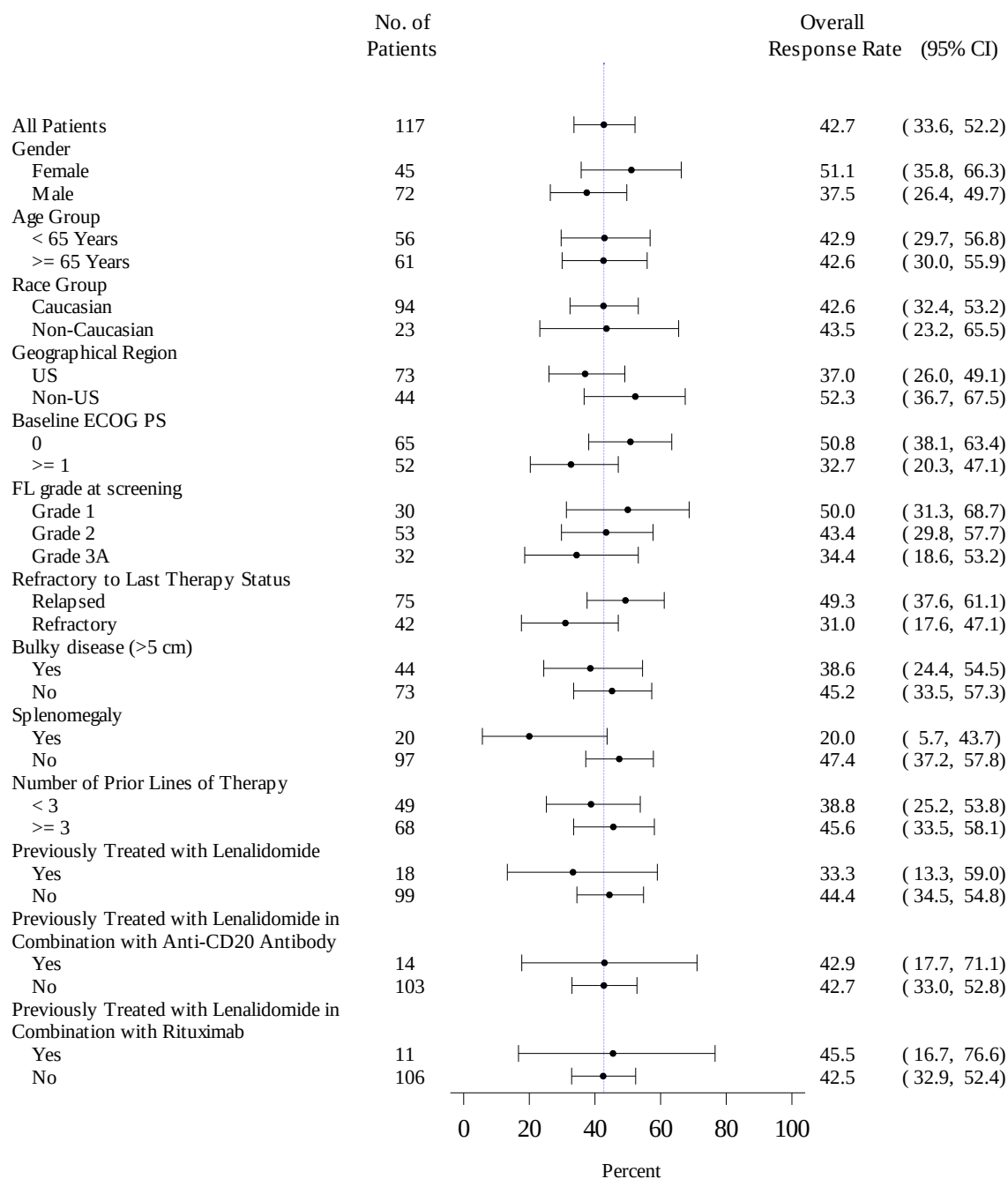
The median follow-up time on study to data cutoff was 20.1 months (range: 13.5 to 29.6 months), and the median TTR was 4.4 months (range: 2.2 to 15.5 months). Based on IRC assessment, the median PFS was 10.6 months (range: 0.0 to 25.4 months).

For the PP Population, the ORR was 43.4%, with CR in 3.5% of subjects and PR in 39.8% of subjects based on IRC assessment and 40.7%, with CR in 4.4% of subjects and PR in 36.3% of subjects based on Investigator assessment.

Subgroup Analyses

Subgroup analyses of ORR based on IRC assessments for the ITT Population are presented in Figure 3. With respect to FL grade at Screening, the ORR was highest in subjects with Grade 1 FL (50.0%), followed by Grade 2 FL (43.4%) and Grade 3A FL (34.4%). The ORR for subjects with <3 prior lines of therapy was 38.8% compared to 45.6% for subjects with ≥3 prior lines. Among the 18 subjects previously treated with a lenalidomide-containing regimen, a 33.3% ORR was observed compared to 44.4% for subjects without prior lenalidomide therapy. Among 14 subjects with prior R² treatment, the ORR was 42.9% compared to 42.7% among those without prior R² treatment.

Figure 3: Forest Plot of ORR for Subjects With FL Based on IRC Assessment - Study UTX-TGR-205 (ITT Population)



Source: CSR UTX-TGR-205, Figure 14.2.5.1

Abbreviations: CI, confidence interval; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; IRC, Independent Review Committee; ITT, intent-to treat; ORR, overall response rate; PS, performance status; US, United States.

The FDA's Assessment:

The FDA agrees with Applicant's presentation of ORR results and the subgroup analyses results. Some of the subgroups had insufficient number of patients needed to draw meaningful conclusions, e.g., the previously treated with lenalidomide categories have insufficient number of patients in the "Yes" subgroups to draw reasonable conclusions. In addition, these analyses are exploratory with no multiplicity adjustment and no pre-specified hypotheses. The outlier subgroups with wide confidence intervals can be attributed to the small number of patients and responders in that subgroup.

The ORR results by ethnicity are as follows:

There were 2 responders out of 6 Hispanic or Latino patients, 42 responders out of 100 non-Hispanic or Latino patients and 6 responders in the 11 patients who had not reported or had missing ethnicity .

For race, some of the subgroups had insufficient numbers, limiting the conclusions in this study to a broad patient population.

Based on the efficacy update provided on 9/11/2020 using the data cutoff of 15 July 2020, the ORR changed from 42.7 % (95% CI: 33.6, 52.2) to 45.3% (95% CI: 36.1, 54.8) with an addition of two patients with CR and one patient with PR.

Data Quality and Integrity

The Applicant's Position:

No data integrity concerns were reported following completion of site inspections.

The FDA's Assessment:

No issues were identified with the data quality from the pivotal study which would affect the efficacy results. The submitted datasets are generally consistent, and variables are clearly labeled and/or explained.

Efficacy Results – Secondary and other relevant endpoints

The Applicant's Position:

Duration of Response

The median DOR for subjects with FL was 11.1 months (95% CI: 8.3, 16.4) based on IRC assessment and 15.7 months (95% CI: 7.6, 18.5) based on Investigator assessment (Table 18). Based on IRC assessment, the DOR rates at 6 and 12 months were 74.4% and 49.2%, respectively.

Table 18: Summary of DOR for Subjects With FL - Study UTX-TGR-205 (ITT Population – Responders Only)

Subgroup	IRC Assessment FL (N=50)	Investigator Assessment FL (N=47)
Number of events, n (%)		
PD	21 (42.0)	17 (36.2)
Death (without PD)	2 (4.0)	2 (4.3)
Number of censored, n (%)	27 (54.0)	28 (59.6)
DOR (months)		
Median (95% CI) ^a	11.1 (8.3, 16.4)	15.7 (7.6, 18.5)
Minimum, maximum	0.03 ⁺ , 20.9 ⁺	0.03 ⁺ , 22.7 ⁺
DOR rate (%)		
At 3 months (95% CI) ^a	89.3 (76.1, 95.4)	88.1 (73.7, 94.9)
At 6 months (95% CI) ^a	74.4 (58.4, 85.0)	73.2 (56.8, 84.2)
At 12 months (95% CI) ^a	49.2 (30.8, 65.3)	61.9 (43.2, 76.0)

Source: CSR UTX-TGR-205, Table 14.2.6.1

Abbreviations: CI, confidence interval; DOR, duration of response; FL, follicular lymphoma; IRC, Independent Review Committee; ITT, intent to treat; PD, progressive disease.

⁺ Denotes censored observation.

^a Based on Kaplan-Meier estimation.

Progression-free Survival

Based on IRC assessment, the median PFS was 10.6 months (range: 0.0+ to 25.4+ months). The PFS rates were 45.9% at 12 months and 11.7% at 24 months (Table 19). Based on Investigator assessment, the median PFS was 11.1 months (range: 0.0+ to 25.4+ months), and the PFS rates were 49.0% at 12 months and 12.5% at 24 months.

Table 19: Summary of PFS for Subjects With FL - Study UTX-TGR-205 (ITT Population)

	IRC Assessment FL (N=117)	Investigator Assessment FL (N=117)
Number of events, n (%)		
PD	68 (58.1)	66 (56.4)
Death (without PD)	3 (2.6)	3 (2.6)
Number of censored, n (%)		
No baseline disease assessments	0	0

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	IRC Assessment FL (N=117)	Investigator Assessment FL (N=117)
No post-baseline disease assessments and no death	1 (0.9)	1 (0.9)
No PD and no death	43 (36.8)	45 (38.5)
Lost to follow-up without PD	0	0
Death or PD after ≥2 missed assessments	0	0
Withdrawal without further disease assessments	2 (1.7)	2 (1.7)
Use of new anticancer therapy	0	0
PFS (months)		
Median (95% CI)	10.6 (7.4, 13.7)	11.1 (7.3, 14.8)
Minimum, maximum	0.0 ⁺ , 25.4 ⁺	0.0 ⁺ , 25.4 ⁺
PFS rate, % (95% CI)^a		
6 months	69.1 (59.7, 76.7)	70.0 (60.6, 77.5)
12 months	45.9 (35.8, 55.4)	49.0 (38.8, 58.3)
18 months	31.0 (20.8, 41.8)	34.7 (24.2, 45.4)
24 months	11.7 (3.0, 26.9)	12.5 (3.3, 28.1)

Source: CSR Study UTX-TGR-205, Table 14.2.8.1

Abbreviations: CSR, clinical study report; CI, confidence interval; FL, follicular lymphoma; IRC, Independent Review Committee; ITT, intent-to-treat; PD, progressive disease; PFS, progression-free survival.

Note: Median PFS with 95% CIs and PFS rates were estimated using Kaplan-Meier method. The 95% CIs of PFS rates were estimated using a normal approximation.

⁺ Denotes censored observation.

^a Based on Kaplan-Meier estimation.

The FDA's Assessment:

The FDA agrees with the estimates provided for the duration of response.

Based on the efficacy update provided on 9/11/2020 using the data cutoff of 15 July 2020, the ORR changed from 42.7 % (95% CI: 33.6, 52.2) to 45.3% (95% CI: 36.1, 54.8) with the addition of two patients with CR and one patient with PR. The point estimates of the IRC assessed median duration of response remained the same at 11.1 (95%CI: 8.3, 15.6) months (the confidence interval changed).

As discussed in Section 8.1.1 under study endpoint, time-to event endpoints in single-arm studies have limited interpretability. Therefore, the PFS results are considered descriptive and exploratory.

Dose/Dose Response

The Applicant's Position:

PPK and E-R relationship after umbralisib administration was performed using data from Studies TGR-1202-101 and UTX-TGR-205. The exposure-efficacy analyses included 79 subjects with FL. The pooled PPK/E-R analyses robustly evaluated biologically inter-dependent endpoints of efficacy and safety. Overall, the dose response results demonstrate an acceptable balance between benefits and risk at the recommended dose of umbralisib 800 mg and justify the use of this dose regimen in subjects with FL.

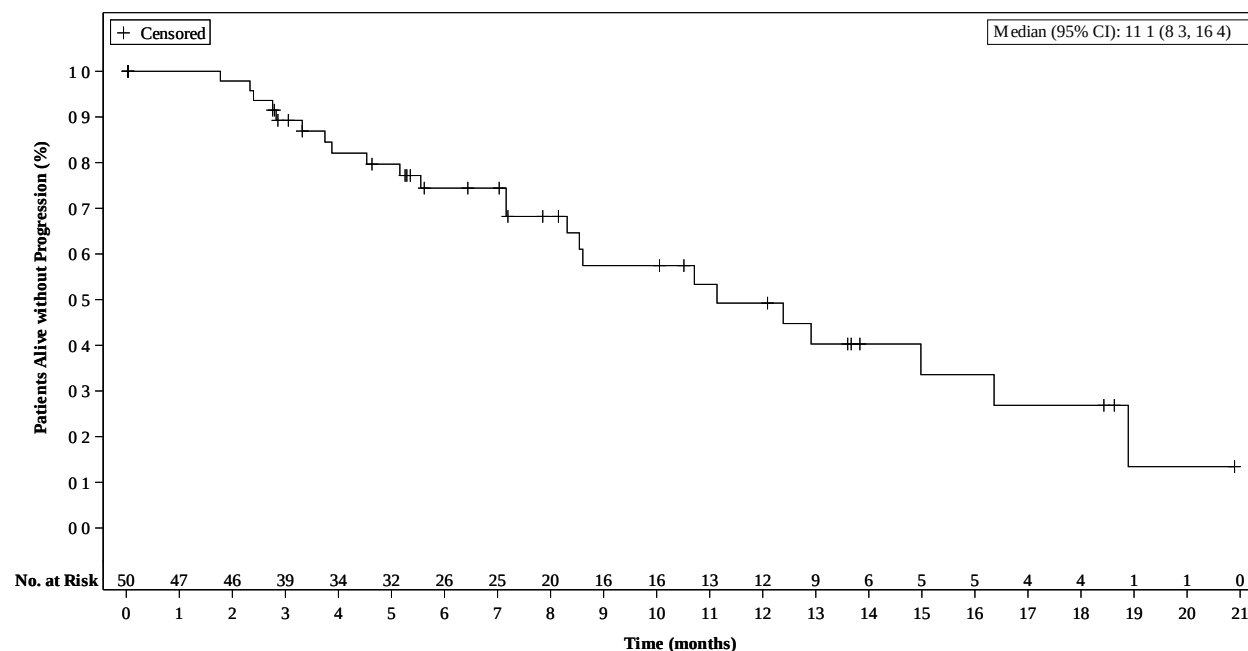
The FDA's Assessment:

The FDA agrees with the Applicant's position.

Durability of Response

In the pivotal study (Study UTX-TGR-205), 35 of the 117 subjects with FL were exposed to umbralisib for at least 12 months. No separate analyses were carried out on these subsets of subjects. Kaplan-Meier plots of DOR and PFS rates are used to provide estimated DOR and survival with continued umbralisib treatment. For subjects with FL, the DOR rate at 12 months was 49.2% (Figure 4).

Figure 4: Kaplan-Meier Plot of DOR for Subjects With FL Based on IRC Assessment (ITT Population) – Responders Only

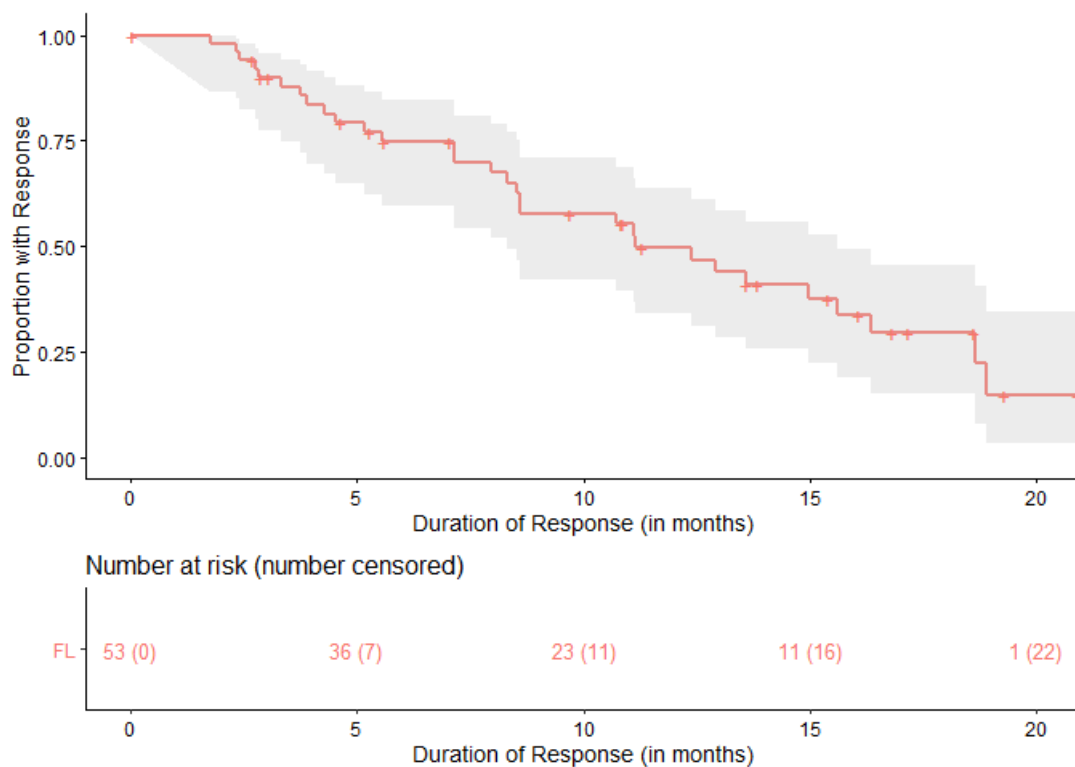


Source: CSR Study UTX-TGR-205, Figure 14.2.6.1

Abbreviations: CI, confidence interval; DOR, duration of response; FL, follicular lymphoma; IRC, Independent Review Committee; ITT, intent to treat.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment of the duration of response (DoR). The Kaplan Meier curve for the updated DoR based on the 9/11/2020 submission is provided in the figure below with the 95% CI bands. As mentioned previously, the point estimates of the median DoR remain unchanged[median 11.1 (95%CI: 8.3, 15.6) months].



Source: adtte.xpt, reviewer generated

8.1.3. Supportive Study for Efficacy - Study TGR-1202-101

The Applicant's Position:

Study TGR-1202-101 is a completed, Phase I, first-in-human, open-label study of umbralisib, administered as a single agent to subjects with relapsed or refractory hematologic malignancies. The study included eligible subjects aged 18 years or older with histologically confirmed Hodgkin lymphoma, B-cell NHL, peripheral T cell lymphoma, CLL, SLL, MZL, or other B-cell lymphoproliferative disorders whose disease had relapsed after, or was refractory to, at least 1 previous treatment regimen.

This study consisted of a dose-escalation phase and a dose-expansion phase. The dose-escalation phase used a traditional 3+3 design to determine the maximum tolerated dose (MTD). Subjects were to receive umbralisib daily in the absence of disease progression, unacceptable toxicity, or withdrawal from treatment. In the initial dose-escalation phase, subjects received (b) (4) umbralisib under a fasted condition starting at 50 mg orally QD with increasing doses for each subsequent cohort until the MTD was identified. For the majority of the study, subjects received (b) (4) umbralisib, which was subsequently used in Study UTX-TGR-205. Each treatment cycle was 4 weeks (28 days), with the first efficacy evaluation at 8 weeks (± 7 days) and at 8-

week intervals thereafter. After Cycle 12, restaging was performed every 6 months at the discretion of the treating physician on a subject-by-subject basis secondary to the clinical presentation of the subject. Disease assessments were conducted by treating investigators. Subjects with PD or unacceptable toxicity were discontinued, and subjects achieving stable disease or better were allowed to continue daily treatment with umbralisib. Subjects on umbralisib who received benefit at the conclusion of this study were eligible to enroll in an open-label extension study, Study UTX TGR-501, to continue to receive single agent umbralisib.

The primary objective of this study was to evaluate safety and MTD of umbralisib in subjects with hematologic malignancies and to evaluate the PK effects of umbralisib. The secondary objectives of the study included evaluation of ORR and DOR in subjects with hematologic malignancies treated with umbralisib.

Efficacy analyses were based on the ITT and modified intent-to-treat (mITT) Populations. The ITT Population included all subjects who received at least 1 dose of umbralisib and who had a baseline assessment and at least 1 post-baseline efficacy assessment. The mITT Population included all subjects in the ITT Population treated with ≥ 800 mg dose of the (b) (4) DP of umbralisib or any dose of the (b) (4) DP of umbralisib.

Of the 90 subjects enrolled in this study, 19 subjects had FL. Treatment was discontinued for all subjects, and the most common reason for discontinuation was disease progression (12 subjects [63.2%]). The median age was 65.0 years (range: 43 to 76 years). The mean duration of exposure to umbralisib was 14.1 months (range: 0.1 to 55.4 months). Six of the 19 subjects were exposed for ≥ 12 months.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.1.4. Efficacy Results - Study TGR-1202-101

The Applicant's Position:

Results from the Phase I dose expansion phase of Study TGR-1202-101 provide additional support for efficacy of umbralisib in subjects with FL. However, because of the small number of subjects in this study and the differences in response evaluation and dosing of umbralisib, direct comparison with the FL cohort in Study UTX-TGR-205 is not feasible. Of the 19 FL subjects enrolled in this study, the ORR was 47.1% based on the ITT Population and 57.1% based on the mITT Population. The CR rates were 5.9% based on the ITT Population and 7.1% for the mITT Population. The DCR was 82.4% based on the ITT Population and 92.9% based on the mITT Population. The median DOR was 16.3 months for both ITT Population and mITT Population.

The FDA's Assessment:

The FDA's assessment of efficacy was based primarily on Study UTX-TGR-205. The efficacy data from Study UTX-TGR-101 is descriptive and considered supportive.

8.1.5. Integrated Review of Effectiveness

The FDA's Assessment:

Not applicable, the primary efficacy data for umbralisib is from Study UTX-TGR-205 as reviewed in the above sections.

8.1.6. Assessment of Efficacy Across Trials

The Applicant's Position:

Study UTX-TGR-205 was the pivotal study. Data from this study provide primary support for efficacy of umbralisib in subjects with FL. Data from the other study (Study TGR-1202-101) that included subjects with FL provide additional support for efficacy of umbralisib in subjects with FL. However, because of the small number of subjects in this study and the differences in response evaluation and dosing of umbralisib, direct comparison with the FL cohort in Study UTX-TGR-205 is not feasible, and efficacy results are instead presented side-by-side in Table 20. DOR and TTR were not calculated for TGR-1202-101 because of the limited number of subjects.

Table 20: Efficacy Results (Response Rate) - Subjects With FL

Endpoint	Statistic	UTX-TGR-205 (N=117)	TGR-1202-101 (N=14) ^a
ORR (CR+PR)	n (%)	50 (42.7)	8 (57.1)
	95% CI	33.6, 52.2	28.9, 82.3
CR	n (%)	4 (3.4)	1 (7.1)
	95% CI	0.9, 8.5	0.2, 33.9
DCR (ORR+stable disease)	n (%)	93 (79.5)	13 (92.9)
	95% CI	71.0, 86.4	66.1, 99.8

Source: CSR Study UTX-TGR-205, Table 14.2.5.1, Table 14.2.6.1, and Table 14.2.7.1; CSR Study TGR-1202-101, Table 14.2.1.1, Table 14.2.2.1, and Table 14.2.2.2

Abbreviations: CI, confidence interval; CR, complete response; CSR, clinical study report; DCR, disease control rate; FL, follicular lymphoma; ITT, intent-to-treat; mITT, modified intent-to-treat; ORR, overall response rate; PR, partial response.

Note: Responses in Study UTX-TGR-205 were assessed by independent central review, while Study TGR-1202-101 was by investigator assessment. The efficacy analyses were carried out using the ITT population in Study UTX-TGR-205 and the mITT population in Study TGR-1202-101. The mITT population for Study TGR-1202-101 was used because it required ≥800-mg dose of (b) (4) umbralisib or any dose of (b) (4) umbralisib.

^a Based on mITT Population.

The FDA's Assessment:

The FDA's assessment of efficacy was based on Study UTX-TGR-205.

8.1.7. Integrated Assessment of Effectiveness

The Applicant's Position:

The primary study to characterize the efficacy of umbralisib in FL is Study UTX-TGR-205. One additional study, Study TGR-1202-101, also included 19 subjects with FL.

A comparison of the efficacy results across studies was not conducted due to the limited number of subjects with FL enrolled outside of the pivotal study UTX-TGR-205 as well as the differences in response evaluation and dosing of umbralisib. Given the minimal number of additional subjects with FL in Study TGR-1202-101, interpretation of these results will be limited and will not meaningfully contribute to the description of efficacy.

Unlike Study UTX-TGR-205, Study TGR-1202-101 did not require FL subjects to have at least 2 prior therapies including an anti-CD20 monoclonal antibody and an alkylating agent.

The FDA's Assessment:

The FDA agrees with the Applicant's assessment that the data from the two trials cannot be pooled together due to the differences in the inclusion/exclusion criteria of the two trials. The evaluation of efficacy is based on the data from UTX-TGR-205.

The efficacy of umbralisib in patients with FL is based on a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, single-arm, multi-cohort trial which included 131 patients with relapsed or refractory FL following at least two prior systemic therapies, including an anti-CD20 monoclonal antibody and an alkylating agent. The trial excluded patients with Grade 3b FL, large cell transformation, prior allogeneic transplant, history of CNS lymphoma, and prior exposure to a PI3K inhibitor. Patients received umbralisib 800 mg orally once daily until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) assessed by an independent review committee (IRC) based on modified 2007 International Working Group criteria. Secondary endpoints included duration of response and progression-free survival.

For efficacy, the Applicant provided data for 117 patients with FL. The median age was 65 years (range: 29 to 87 years), 38% were female, 80% were White, 4% were Black, 73% had Stage III-IV disease, 38% had bulky disease and 97% had a baseline ECOG performance status of 0 to 1. The median number of prior systemic therapies was 3 (range 1 to 10) and 57% of the patients had received three or more regimens with 36% refractory to their last therapy. One-hundred percent had received prior anti-CD20 therapy and 12% had received lenalidomide and anti-CD20 therapy. The median follow-up time was 20.1 months (range: 13.5 to 29.6 months). The overall response rate (ORR) per IRC was 42.7% (95% CI: 33.6, 52.2), with 3.4% achieving a complete response. The median duration of response was 11.1 months, 95% CI (8.3, 16.4).

Based on the characteristics of the FL patient population enrolled in UTX-TGR-205, specifically the median of 3 prior lines of therapy, the data support the determination that umbralisib has clinically meaningful activity in patients with relapsed or refractory FL who have received at least three prior lines of systemic therapy.

8.2. Review of Safety

The Applicant's Position:

Safety data for subjects exposed to single agent umbralisib from the pivotal Study UTX-TGR-205 as of the cutoff date of 01 September 2019 were integrated with data from 4 other studies (Studies TGR-1202-101, TGR-1202-202, UTX-TGR-103, and UTX-TGR-501) to form an integrated database (IDB), which included a total of 371 subjects (82 subjects with MZL, 147 subjects with FL, and 142 subjects with other hematologic malignancies) hereafter referred to as the Umbralisib Safety Population.

Safety data from Study TGR-1202-102, a completed Phase I study in 32 subjects with

solid tumor cancers, and safety data from 6 clinical pharmacology studies in healthy subjects (Studies TGR 1202-PK101, TGR 1202-PK102, TGR-1202-901, TGR-1202-902, TGR-1202-904, and TGR-1202-908) were not integrated with the other studies.

Data from these studies allow for an informed assessment of the safety profile of umbralisib 800 mg QD and an evaluation of the overall benefit-risk in subjects with FL. This safety population is also considered appropriate for the detection and characterization of common AEs and to provide guidance on toxicity management.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.1. Safety Review Approach

The Applicant's Position:

The Umbralisib Safety Population included all subjects who received at least 1 dose of single agent umbralisib at doses ≥ 800 mg and was used for all analyses for single agent umbralisib. Pooled safety analyses included TEAEs, laboratory assessments, vital signs, and subgroup analyses (gender [male, female], age group [<65 years, ≥ 65 years], race [Caucasian, non-Caucasian], geographic region [US, non-US], prior lines of therapy [<2 , ≥ 2], prior lenalidomide therapy [yes, no], previous treatment with lenalidomide in combination with an anti-CD20 therapy [yes, no], eGFR at baseline [mildly decreased, moderately decreased, severely decreased renal function, or end stage renal disease], and hepatic impairment [mild, moderate, severe]). In addition, physical examinations and ECGs were not pooled and were examined by study.

The FDA's Assessment:

The FDA agrees with the Applicant's position. The FDA reviewed data from the pivotal trial as well as the Safety Pool population (N = 371) and the 120-day Safety update, extending data collection to January 2020.

Safety endpoints listed below were used to evaluate the safety and tolerability of single agent umbralisib in this population of patients with FL and patients with hematologic malignancies:

- Incidence and severity of all Treatment-emergent adverse events (TEAE)
- Grade 3-5 TEAEs
- Serious adverse events
- TEAEs leading to treatment modifications
- Adverse events of Special Interest
- Clinical laboratory test abnormalities
- Prior therapies

The frequency of TEAEs was tabulated by the Medical Dictionary for Regulatory Activities (MedDRA) Version 22.1. The NCI CTCAE version 4.03 was used to grade and summarize adverse events.

To inform the safety review, FDA used grouped preferred terms for more sensitive and informative safety analyses. The FDA preferred terms are listed in Section **Error! Reference source not found.** APPEARS THIS WAY ON ORIGINAL

8.2.2. Review of the Safety Database

Overall Exposure

The Applicant's Position:

Overall, 371 subjects received at least 1 dose of umbralisib, 82 subjects with MZL, 147 subjects with FL, 74 subjects with DLBCL/MCL, 43 subjects with CLL/SLL, and 25 subjects with other tumor types (Table 21). The median duration of exposure to umbralisib was 5.91 months (range: 0.1 to 75.1 months). A total of 92 subjects (24.8%) were exposed to umbralisib for 12 to <24 months, and 15 subjects (4.0%) were exposed for ≥24 months.

Table 21: Summary of Umbralisib Administration and Extent of Exposure (Umbralisib Safety Population)

Extent of Exposure	UTX-TGR-205	Pooled	
	FL (N=131)	FL (N=147)	Total (N=371)
Duration (months)			
Mean (SD)	8.70 (5.82)	9.80 (9.77)	9.06 (9.66)
Median	7.33	7.33	5.91
Minimum, maximum	1.0, 22.5	0.1, 75.1	0.1, 75.1
Duration, n (%)			
<3 months	26 (19.8)	30 (20.4)	111 (29.9)
3 to <6 months	30 (22.9)	32 (21.8)	76 (20.5)
6 to <12 months	40 (30.5)	44 (29.9)	77 (20.8)
12 to <18 months	22 (16.8)	23 (15.6)	56 (15.1)
18 to <24 months	13 (9.9)	13 (8.8)	36 (9.7)
≥24 months	0	5 (3.4)	15 (4.0)

Source: Table 2.7.4.1.2.1

Abbreviations: FL, follicular lymphoma; SD, standard deviation.

Note: Duration of exposure (months)=(date of last dose - date of first dose + 1)/30.4375.

Dose Modifications

Overall in the Umbralisib Safety Population (N=371), 57.4% of subjects had at least 1 dose adjustment (46.4% of subjects due to AEs). Umbralisib dose was reduced in 16.7% of subjects (13.2% of subjects due to AEs), umbralisib dosing was interrupted in 52.6% of subjects (43.7% of subjects due to AEs), and umbralisib was withdrawn in 21.8% of subjects (14.8% of subjects due to AEs).

The FDA's Assessment:

The FDA agrees with the Applicant's description of exposure. A median exposure of 7.3 months in patients with FL and approximately 6 months in patients with hematologic malignancies provides sufficient data to support the evaluation of safety. However, there is a paucity of data to evaluate long-term toxicity.

For the dose modifications, the following table below depicts umbralisib treatment modifications due to treatment-emergent adverse events per FDA review.

Table 22: Umbralisib Treatment Modifications Due to Adverse Events - FDA Review

Treatment Modifications due to Adverse Events	UTX-TGR-205	Safety Pool (N = 371) n (%)
	FL (N = 131) n (%)	
Any dose adjustment	66 (50.4)	213 (57.4)
Any TEAE leading to discontinuation	16 (12.2)	57 (15.4)
Any TEAE leading to dose interruption	59 (45)	168 (45.3)
Any TEAE leading to dose reduction	15 (11.4)	39 (10.5)
Abbreviations: FL, Follicular lymphoma; TEAE, Treatment-emergent adverse event Source: FDA review of ADSL (Subject-level Analysis) Dataset and ADAE (Adverse Events Analysis) Dataset		

Relevant characteristics of the safety population:

The Applicant's Position:

The Umbralisib Safety Population included subjects with MZL, FL, and other hematologic

malignancies from 5 studies. Overall, the median age was 67 years (range: 22 to 95 years); 56.3% of subjects were male, 82.7% of subjects were White, and 72.8% of subjects were enrolled in the US. The ECOG performance status was 0 or 1 for most of the subjects (96.0%).

For subjects with FL, the median age was 65 years (range: 29 to 87 years); 61.9% of subjects were male, 81.6% of subjects were White, and 66.0% of subjects were enrolled in the US.

Overall, the median number of prior systemic therapy was 2 (range: 1 to 14); 76.5% of subjects had ≥ 2 prior lines of therapy, and 49.1% of subjects had ≥ 3 prior lines of therapy. For subjects with FL, the median number of prior systemic therapy was 3 (range: 1 to 10); 85.7% of subjects had ≥ 2 prior lines of therapy, and 57.8% of subjects had ≥ 3 prior lines of therapy.

Overall, 11.9% of subjects had prior lenalidomide therapy, and 7.8% of subjects had prior lenalidomide plus anti-CD20 therapy.

Median time since the most recent progression was 2.1 months (range: 0.3 to 447.4 months); 55.8% of subjects relapsed from prior treatment (progression of disease occurring greater than 6 months after last treatment), and 39.1% of subjects were refractory to prior treatment (progression during or within 6 months of completing prior therapy).

Overall, at Baseline, the percentage of subjects with mild, moderate, and severe renal impairment were 53.6%, 26.1%, and 0.5% of subjects, respectively. No subjects had severe hepatic impairment, 14.8% of subjects had mild hepatic impairment, and 0.5% of subjects had moderate hepatic impairment.

The FDA's Assessment:

Per FDA review, in 131 subjects with FL, the median age was 65 years (range: 29 to 87 years); 60.3% of subjects were male, 80.9% of subjects were White, 3.8% were Black and 2.3% were Asian. Sixty six percent of subjects were enrolled in the US. The ECOG performance status was 0 or 1 for most of the subjects (96.9%).

Overall, the median number of prior systemic therapies was 3 (range: 1 to 10); 86.3% of subjects had ≥ 2 prior lines of therapy, and 57.3% of subjects had ≥ 3 prior lines of therapy. Overall, 15.3% of subjects had prior lenalidomide therapy, and 12.2% of subjects had prior lenalidomide plus anti-CD20 therapy. Among these patients, 35.9% had disease refractory to the last line of systemic therapy and 31.2% had disease refractory to rituximab. The table below provide a summary of the demographics and disease characteristics per FDA review.

Table 23: Summary of Demographics and Disease Characteristics - Safety Population

Parameter	UTX-TGR-205	Safety Pool (N = 371)
	FL (N=131) n (%)	n (%)
Age		
Median (range)	65 (29-87)	67 (22, 95)
≥ 65 years	66 (50.4)	209 (56.3)
Gender male	79 (60.3)	209 (56.3)
Race		
White	106 (80.9)	307 (82.7)
Black	5 (3.8)	22 (5.9)
Asian	3 (2.3)	7 (1.8)
Other	17 (13)	35 (9.6)
Ethnicity		
Not Hispanic/Latino	113 (86.3)	321 (86.5)
Hispanic/Latino	6 (4.6)	17 (4.6)
EGOG PS		
0	71 (54.2)	177 (47.7)
1	56 (42.7)	179 (48.2)
2	4 (3.1)	15 (4.0)
Country		
US	81 (61.8)	270 (72.8)
Disease stage at screening		
I	14 (10.7)	22 (5.9)
II	18 (13.7)	30 (8.1)
III	43 (32.8)	80 (21.6)
IV	55 (42.0)	145 (39.1)
Prior rituximab refractory status	41 (31.3)	79 (21.3)
Immediate prior treatment status		
Relapsed/Refractory	84 (64.1)/47 (35.9)	207 (55.8)/145 (39.1)
Prior lines systemic therapies		
Median (range)	3 (1-10)	2 (1, 14)

1	18 (13.7)	87 (23.5)
2	38 (29)	102 (27.4)
3	28 (21.4)	69 (18.5)
>3	47 (35.9)	113 (30.4)
Anti-CD20	131 (100)	359 (96.7)
Anti-CD20 monotherapy	3 (2.3)	26 (7)
Anti-CD20 based chemoimmunotherapy	128 (97.7)	325 (87.6)
Lenalidomide therapy (mono/combo)	20 (15.3)	44 (11.9)
Lenalidomide and Anti-CD20 therapy	16 (12.2)	29 (7.8)
BTKi therapy	11 (8.4)	54 (14.5)
Source: FDA review of ADSL (Subject-level Analysis) Dataset and ADAE (Adverse Events Analysis) Dataset		

Adequacy of the safety database:

The Applicant's Position:

The evaluation of safety is based on data for subjects exposed to single agent umbralisib from the pivotal Study UTX-TGR-205 as of the cutoff date of 01 September 2019 and from 4 other studies (Studies TGR-1202-101, TGR-1202-202, UTX-TGR-103, and UTX-TGR-501). Further details are provided in Section 8.2. This population allows for an informed assessment of the safety profile of umbralisib and a judgment of the overall benefit-risk in subjects with FL.

The FDA's Assessment:

The safety database was acceptable for review. The initial submission did not include toxicity grades in the laboratory (ADLB) dataset. An information request was sent to the Applicant to enable a lab-shift analysis by the reviewers.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's Position:

No meaningful concerns are anticipated in the quality and integrity of the submitted datasets and individual case narratives; these were sufficiently complete to allow for a thorough review of safety. Furthermore, no data integrity concerns were reported following completion of site inspections; data in the CRFs and adverse event databases were consistent.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Categorization of Adverse Event

The Applicant's Position:

Each AE term was mapped to a SOC and PT using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. The AE severity was graded using Common Terminology Criteria for Adverse Event (CTCAE) version 4.03.

A TEAE was defined as an AE that first occurred or worsened in intensity from the first dose of study drug through 30 days after the last dose of study drug. The AEs that started before the first dose of study drug but considered related to study drug by the Investigator were assumed worsened in intensity during treatment and therefore were reported as TEAEs. The analysis of AEs included subjects with any TEAE, serious TEAE, CTCAE Grade ≥ 3 TEAE, TEAEs that led to death, TEAEs that led to discontinuation of study drug, TEAEs that led to dose reduction or interruption of study drug, AESIs, and drug-related AESIs. In addition, the number and percentage of subjects with TEAEs, serious TEAEs, TEAEs leading to discontinuation of study drug, TEAEs leading to dose reduction, TEAEs leading to dose interruption, and TEAEs leading to death were summarized by period of exposure to umbralisib (<3 months, 3 to <6 months, 6 to <12 months, 1 to <2 years, and ≥ 2 years).

Adverse events of special interest (AESIs) were predefined in the integrated SAP; the criteria used to define AESIs were drug causality assessment, serious adverse event (SAE) rate, severity grade, frequency of TEAEs, class effect, discontinuation rate, and clinical context. All AESIs had SAEs (at least possibly related) plus one or more of the other criteria. Standardized MedDRA Queries relevant to the AESI list were used to select any additional PTs associated with AESI.

The Umbralisib Safety Population (N=371) supported predominantly by the pivotal UTX-TGR-205 study, provide the primary source for adverse drug reaction (ADR) determination. Safety data were reviewed systematically for TEAEs irrespective of Investigator's causality assessment, which includes serious TEAEs, TEAEs leading to dose modification, and AESIs. This was accompanied by individual case reviews of selected events. New or worsening laboratory parameters were also analyzed.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Routine Clinical Tests

The Applicant's Position:

Laboratory assessments were pooled for the Umbralisib Safety Population and included changes from baseline, laboratory abnormalities based on CTCAE grade, shifts from baseline to post-baseline worst value based on CTCAE grade for hematology and serum chemistry (including liver function tests) parameters measured in the clinical trials.

The clinical monitoring of subject safety was considered adequate for the expected toxicities associated with umbralisib. Subjects were questioned about AEs at each clinic visit. In addition, AEs could also be detected when reported by the subjects during or between visits or through physical examination, laboratory test results, or other assessments. Further to the standard safety evaluations outlined above, AE categories expected to be associated with umbralisib were also analyzed.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.4. Safety Results

Deaths

The Applicant's Position:

Overall, 4 deaths due to AEs (pleural effusion, septic shock, myocardial infarction, and pneumonia legionella) were reported, and all 4 subjects died within 30 days of last dose of umbralisib (Table 24). The events of pleural effusion, septic shock, myocardial infarction were considered not related to umbralisib; pneumonia legionella was considered unlikely related to umbralisib.

Other deaths include death due to PD in 22 subjects (5.9%) and death due to "other/unknown/missing" after 30 days of last dose of umbralisib in 3 subjects (0.8%) due to heart failure, myelodysplasia, respiratory failure.

Table 24: Summary of Deaths (Umbralisib Safety Population)

Primary Cause of Death	UTX-TGR-205	Pooled	
	FL (N=131) n (%)	FL (N=147) n (%)	Total (N=371) n (%)
All deaths	6 (4.6)	6 (4.1)	29 (7.8)
Progressive disease	4 (3.1)	4 (2.7)	22 (5.9)
Adverse event	0	0	4 (1.1)
Other/unknown/missing	2 (1.5)	2 (1.4)	3 (0.8)
Death within 30 days of last dose of umbralisib	1 (0.8)	1 (0.7)	11 (3.0)
Progressive disease	1 (0.8)	1 (0.7)	7 (1.9)
Adverse event	0	0	4 (1.1)

Source: Table 2.7.4.2.3.1

Abbreviations: FL, follicular lymphoma.

Note: No deaths were reported in subjects in the “Other” cohort.

The FDA’s Assessment:

Overall, 7 deaths occurred in the patients with FL (N=131) and none were due to adverse events. Among these deaths, 3 were due to progressive disease. One death occurred within 30 days of last dose of umbralisib and was due to progressive disease.

Four patients died due to other reasons:

- 1- A 72 year old male with relapsed/refractory FL developed MDS and died 4 months after discontinuing umbralisib.
- 2- A 73 year old man with relapsed/refractory FL died due to unknown paraneoplastic disease 3 months after stopping umbralisib.
- 3- An 83 year old man with relapsed/refractory FL died due to respiratory failure 10 months after umbralisib was discontinued.
- 4- A 73 year old female with relapsed/refractory FL which was later transformed to diffuse large B-cell lymphoma and was started on multi-agent systemic chemotherapy died due to unknown cause 4 months after discontinuing umbralisib.

Table 25: Summary of Deaths in Safety Population - FDA Review

Primary Cause of Death	UTX-TGR-205	Safety Pool	
	FL (N=131) n (%)	FL (N=147) n (%)	Total (N=371) n (%)
All deaths	7 (5.3)	6 (4.1)	29 (7.8)
Progressive disease	3 (2.3)	4 (2.7)	22 (5.9)
Adverse event	0	0	4 (1.1)
Other/unknown/missing	4 (3)	2 (1.4)	3 (0.8)
Death within 30 days of last dose of umbralisib	1 (0.8)	1 (0.7)	11 (3.0)
Progressive disease	1 (0.8)	1 (0.7)	7 (1.9)
Adverse event	0	0	4 (1.1)
Source: FDA review of ADSL and ADAE datasets			

Serious Adverse Events

The Applicant's Position:

Overall, serious TEAEs were reported in 95 subjects (25.6%), including 34 subjects (23.1%) with FL (Table 26). The most frequently reported serious TEAEs (at least 2% of total pooled subjects) were pneumonia (3.0% of subjects) and diarrhea (2.4% of subjects). Serious TEAEs reported in at least 2 subjects with FL were urinary tract infection (4 subjects), pneumonia (3 subjects), diarrhea (3 subjects), sepsis (2 subjects), syncope (2 subjects), and acute kidney injury (2 subjects).

Table 26: Summary of Serious TEAEs (at Least 1% Total by PT) by SOC and PT (Umbralisib Safety Population)

System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	FL (N=131) n (%)	FL (N=147) n (%)	Total (N=371) n (%)
Any serious TEAE	29 (22.1)	34 (23.1)	95 (25.6)
Infections and infestations			
Pneumonia	1 (0.8)	3 (2.0)	11 (3.0)
Sepsis	2 (1.5)	2 (1.4)	5 (1.3)
Urinary tract infection	3 (2.3)	4 (2.7)	4 (1.1)
Gastrointestinal disorders			
Diarrhea	3 (2.3)	3 (2.0)	9 (2.4)
Colitis	0	0	4 (1.1)
Respiratory, thoracic, and mediastinal disorders			
Pleural effusion	0	0	4 (1.1)
Metabolism and nutrition disorders			
Dehydration	1 (0.8)	1 (0.7)	4 (1.1)
Hypercalcemia	0	0	4 (1.1)
Pyrexia	1 (0.8)	1 (0.7)	4 (1.1)
Renal and urinary disorders			
Acute kidney injury	2 (1.5)	2 (1.4)	4 (1.1)

Source: Table 2.7.4.2.4.1.1

Abbreviations: FL, follicular lymphoma; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

Serious TEAEs related to umbralisib were reported in 44 subjects (11.9%) overall, including 12 subjects (8.2%) with FL. The most frequently reported serious TEAEs related to umbralisib (at least 1% of total pooled subjects) were pneumonia (1.9% of subjects), diarrhea (1.9% of subjects), and sepsis (1.1% of subjects). Diarrhea (2 subjects) was the only serious TEAE related to umbralisib reported in more than 1 subject with FL.

Grade ≥ 3 serious TEAEs were reported in 82 subjects (22.1%) overall, including 29 subjects (19.7%) with FL. Of these, 41 subjects (11.1%) had Grade ≥ 3 serious TEAEs related to umbralisib, including 12 subjects (8.2%) with FL.

The FDA's Assessment:

In general, the FDA agrees with the Applicant's description of all-cause serious TEAEs in 371 patients with hematologic malignancies. Overall, serious TEAEs were reported in 98 subjects (26.4%). For additional information, SAEs are shown in the table below using grouped preferred terms (Section 19.5), which allows for increased sensitivity and informative analyses. There was a higher incidence of any grade SAEs in the safety pool compared to the FL cohort (26.4% versus 22.1%) with diarrhea/colitis more pronounced. In patients with FL, the most common SAEs were diarrhea/colitis (2.3%), urinary tract infection (2.3%), and sepsis (1.5%).

Table 27: Summary of Serious Adverse Events - FDA Review

Serious Adverse Events	UTX-TGR-205 FL (N=131) n (%)		Safety Pool (N= 371) n (%)	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Any SAE	29 (22.1)	25 (19.1)	98 (26.4)	84 (22.6)
Diarrhea/colitis	3 (2.3)	2 (1.5)	12 (3.2)	9 (2.4)
Urinary tract infection	3 (2.3)	2 (1.5)	4 (1.1)	2 (0.5)
Sepsis	2 (1.5)	2 (1.5)	7 (1.8)	7 (1.8)
Pneumonia	1 (0.8)	1 (0.8)	14 (3.7)	12 (3.2)
Febrile neutropenia	1 (0.8)	1 (0.8)	4 (1.1)	4 (1.1)
Pyrexia	1 (0.8)	0	4 (1.1)	0
Pneumonitis	0	0	2 (0.5)	2 (0.5)
Lower respiratory tract infection	0	0	3 (0.8)	2 (0.5)
Hepatitis	0	0	1 (0.3)	1 (0.3)
Rash	0	0	2 (0.5)	2 (0.5)
Source: FDA review of ADAE dataset				

Dropouts and/or Discontinuations Due to Adverse Effects

The Applicant's Position:

Overall, TEAEs led to discontinuation of umbralisib in 57 subjects (15.4%), including 18 subjects (12.2%) with FL (Table 28). The most frequently reported TEAEs leading to discontinuation of umbralisib (at least 2% of total pooled subjects) were diarrhea (3.8% of subjects), ALT increased (2.7% of subjects), and AST increased (2.7% of subjects).

TEAEs leading to discontinuation of umbralisib considered related to umbralisib were reported in 46 subjects (12.4%) overall, including 16 subjects (10.9%) with FL. The most frequently reported TEAEs leading to discontinuation of umbralisib considered related to umbralisib (at least 2% of total pooled subjects) were diarrhea (3.5% of subjects), ALT increased (2.7% of subjects), and AST increased (2.7% of subjects).

Table 28: Summary of TEAEs Leading to Discontinuation of Umbralisib (at Least 1% Total by PT) by SOC and PT (Umbralisib Safety Population)

System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	FL (N=131) n (%)	FL (N=147) n (%)	Total (N=371) n (%)
Any TEAE leading to discontinuation	16 (12.2)	18 (12.2)	57 (15.4)
Gastrointestinal disorders			
Diarrhea	8 (6.1)	9 (6.1)	14 (3.8)
Colitis	0	0	4 (1.1)
Investigations			
Alanine aminotransferase increased	4 (3.1)	4 (2.7)	10 (2.7)
Aspartate aminotransferase increased	4 (3.1)	4 (2.7)	10 (2.7)
General disorders and administration site conditions			
Fatigue	1 (0.8)	1 (0.7)	4 (1.1)
Blood and lymphatic system disorders			
Neutropenia	1 (0.8)	1 (0.7)	4 (1.1)

Source: Table 2.7.4.2.4.2.1

Abbreviations: FL, follicular lymphoma; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.
Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

The FDA's Assessment:

The following table presents the FDA's analysis of the drug discontinuation data, including the specific AEs responsible for treatment discontinuation.

Table 29: Treatment Discontinuation Due to Adverse Events - FDA Review

Outcome/event	UTX-TGR-205	Safety pool (N=371) n (%)
	FL (N=131) n (%)	
Any TEAE leading to discontinuation	16 (12.2)	57 (15.4)
Transaminase elevation	9 (6.8)	12 (3.2)
Diarrhea/colitis	8 (6.1)	18 (4.8)
Neutropenia	1 (0.8)	4 (1.1)
Thrombocytopenia	1 (0.8)	0
Fatigue	1 (0.8)	4 (1.1)
Source: FDA review of ADAE dataset		

Dose Interruption/Reduction Due to Adverse Effects

The Applicant's Position:

Overall, TEAEs leading to umbralisib dose reduction were reported in 39 subjects (10.5%), including 18 subjects (12.2%) with FL (Table 30). The most frequently reported TEAEs leading to umbralisib dose reduction (at least 1% of total pooled subjects) were diarrhea (2.2% of subjects), nausea (1.6% of subjects), neutropenia (1.6% of subjects), ALT increased (1.1% of subjects), and fatigue (1.1% of subjects).

TEAEs leading to umbralisib dose reduction related to umbralisib were reported in 34 subjects (9.2%) overall, including 16 subjects (10.9%) with FL. The most frequently reported TEAEs leading to umbralisib dose reduction related to umbralisib (at least 1% of total pooled subjects) were diarrhea (2.2% of subjects), nausea (1.6% of subjects), neutropenia (1.6% of subjects), and fatigue (1.1% of subjects).

Table 30: Summary of TEAEs Leading to Umbralisib Dose Reduction (at Least 1% Total by PT) by SOC and PT (Umbralisib Safety Population)

System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	FL (N=131) n (%)	FL (N=147) n (%)	Total (N=371) n (%)
Any TEAE leading to dose reduction of umbralisib	15 (11.5)	18 (12.2)	39 (10.5)
Gastrointestinal disorders			
Diarrhea	5 (3.8)	6 (4.1)	8 (2.2)

Nausea	3 (2.3)	3 (2.0)	6 (1.6)
Blood and lymphatic system disorders			
Neutropenia	2 (1.5)	2 (1.4)	6 (1.6)
Investigations			
Alanine aminotransferase increased	0	1 (0.7)	4 (1.1)
General disorders and administration site conditions			
Fatigue	0	2 (1.4)	4 (1.1)

Source: Table 2.7.4.2.4.3.1

Abbreviations: FL, follicular lymphoma PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

Overall, TEAEs leading to umbralisib dose interruption were reported in 168 subjects (45.3%), including 67 subjects (45.6%) with FL. The most frequently reported TEAEs leading to umbralisib dose interruption (at least 2% of total pooled subjects) were diarrhea (11.9% of subjects), vomiting (4.9% of subjects), neutropenia (4.9% of subjects), ALT increased (4.6% of subjects), AST increased (4.3% of subjects), nausea (3.8% of subjects), pneumonia (2.7% of subjects), upper respiratory tract infection (2.2% of subjects), and pyrexia (2.2% of subjects).

TEAEs leading to umbralisib dose interruption related to umbralisib were reported in 131 subjects (35.3%) overall, including 52 subjects (35.4%) with FL. The most frequently reported TEAEs leading to umbralisib dose interruption related to umbralisib (at least 1% of total pooled subjects) were diarrhea (10.8% of subjects), neutropenia (4.9% of subjects), ALT increased (4.3% of subjects), AST increased (4.0% of subjects), vomiting (4.0% of subjects), nausea (3.2% of subjects), pneumonia (1.3% of subjects), thrombocytopenia (1.3% of subjects), fatigue (1.1% of subjects), and decreased appetite (1.1% of subjects).

The FDA's Assessment:

Overall, all-cause TEAEs leading to umbralisib dose reduction in the safety pool were reported in 39 subjects (10.5%). The most common reasons were diarrhea/colitis (2.2%), nausea (1.6%), and neutropenia (1.6%). Adverse events leading to umbralisib dose interruption in the safety pool were reported in 162 subjects (43.6%), most often due to diarrhea/colitis (12.3%), vomiting (4.9%), neutropenia (4.9%) and transaminase elevation (4.6%).

In patients with FL, all-cause TEAEs leading to umbralisib dose reduction were reported in 15 subjects (11.5%). The most common reasons were diarrhea/colitis (4.5%), nausea (2.3%), headache (1.5%), neutropenia (1.5%) and rash (1.5%). Adverse events leading to umbralisib dose interruption in this group were reported in 59 subjects (45%) overall, which were mostly diarrhea/colitis (16.7%), upper respiratory tract infection (6.1%), vomiting (5.3%) and transaminase elevation (5.3%).

The table below demonstrates the most common TEAEs leading to umbralisib dose reduction

and interruption using grouped preferred terms (Section 19.5), which allows for increased sensitivity and informative analyses.

Table 31: Adverse Events Leading to Dose Reduction and Interruption - FDA Review

Outcome/event	UTX-TGR-205	Safety pool (N=371) n (%)
	FL (N=131) n (%)	
Any TEAE leading to dose reduction	15 (11.5)	39 (10.5)
Diarrhea/colitis	6 (4.5)	8 (2.2)
Nausea	3 (2.3)	6 (1.6)
Headache	2 (1.5)	0
Neutropenia	2 (1.5)	6 (1.6)
Rash	2 (1.5)	0
Any TEAE leading to dose interruption	59 (45)	162 (43.6)
Diarrhea/colitis	22 (16.7)	46 (12.3)
URI	8 (6.1)	10 (2.7)
Vomiting	7 (5.3)	18 (4.9)
Transaminase elevation	7 (5.3)	17 (4.6)
Neutropenia	5 (3.8)	18 (4.9)
Musculoskeletal pain	4 (3)	6 (1.6)
Abdominal pain	3 (2.3)	7 (1.9)
Fatigue	3 (2.3)	8 (2.2)
Nausea	3 (2.3)	10 (2.7)
Pneumonia	2 (1.5)	10 (2.7)
Rash	2 (1.5)	6 (1.6)
Sepsis	2 (1.5)	7 (1.9)
Source: FDA review of ADAE dataset		

Significant Adverse Events

The Applicant's Position:

The significant AEs reported are described in other sections of this document.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Treatment Emergent Adverse Events and Adverse Reactions

The Applicant's Position:

Most Frequent TEAEs

Overall, the most common TEAEs (at least 20% of total pooled subjects) were diarrhea (52.3% of subjects), nausea (41.5% of subjects), fatigue (31.8% of subjects), and vomiting (23.2% of subjects) (Table 32). For subjects with FL, the most common TEAEs were diarrhea (56.5% of subjects), nausea (42.2% of subjects), fatigue (32.0% of subjects), and vomiting (23.8% of subjects).

Table 32: Summary of Common TEAEs (at Least 10% Total by PT) by SOC and PT (Umbralisib Safety Population)

System Organ Class/ Preferred Term	UTX-TGR-205	Pooled	
	FL (N=131) n (%)	FL (N=147) n (%)	Total (N=371) n (%)
Any TEAE	128 (97.7)	144 (98.0)	366 (98.7)
Gastrointestinal disorders			
Diarrhea	75 (57.3)	83 (56.5)	194 (52.3)
Nausea	51 (38.9)	62 (42.2)	154 (41.5)
Vomiting	29 (22.1)	35 (23.8)	86 (23.2)
Constipation	10 (7.6)	14 (9.5)	39 (10.5)
Abdominal pain	14 (10.7)	16 (10.9)	38 (10.2)
General disorders and administration site conditions			
Fatigue	39 (29.8)	47 (32.0)	118 (31.8)
Pyrexia	13 (9.9)	14 (9.5)	47 (12.7)
Edema peripheral	12 (9.2)	14 (9.5)	39 (10.5)
Nervous system disorders			
Dizziness	22 (16.8)	27 (18.4)	65 (17.5)
Headache	16 (12.2)	21 (14.3)	60 (16.2)
Infections and infestations			
Upper respiratory tract infection	17 (13.0)	21 (14.3)	46 (12.4)
Metabolism and nutrition disorders			
Decreased appetite	21 (16.0)	25 (17.0)	65 (17.5)

Hypokalemia	14 (10.7)	18 (12.2)	39 (10.5)
Cough	22 (16.8)	25 (17.0)	72 (19.4)
Investigations			
Alanine aminotransferase increased	21 (16.0)	23 (15.6)	56 (15.1)
Aspartate aminotransferase increased	16 (12.2)	18 (12.2)	55 (14.8)
Blood creatinine increased	17 (13.0)	17 (11.6)	39 (10.5)
Blood and lymphatic system disorders			
Neutropenia	17 (13.0)	19 (12.9)	53 (14.3)
Anemia	11 (8.4)	13 (8.8)	41 (11.1)
Psychiatric disorders			
Insomnia	18 (13.7)	21 (14.3)	47 (12.7)

Source: Table 2.7.4.2.1.2

Abbreviations: FL, follicular lymphoma; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event.

Note: TEAE sorting is done by decreasing frequency of SOC and PT based on the total column.

TEAEs of at Least Grade 3

Overall, 189 subjects (50.9%) had Grade ≥ 3 TEAEs. Of these, 124 subjects (33.4%) had Grade ≥ 3 TEAEs related to umbralisib. The most frequently reported Grade ≥ 3 TEAEs (at least 5% of total pooled subjects) were neutropenia (11.3% of subjects), diarrhea (7.3% of subjects), ALT increased (5.7% of subjects), and AST increased (5.7% of subjects). The most frequently reported Grade ≥ 3 TEAEs related to umbralisib (at least 5% of total pooled subjects) were neutropenia (8.9% of subjects), diarrhea (6.7% of subjects), ALT increased (5.4% of subjects), and AST increased (5.4% of subjects).

Adverse Drug Reactions

The Umbralisib Safety Population, supported predominantly by the pivotal Study UTX-TGR-205, provide the primary source for ADR determination. Safety data were reviewed systematically for TEAEs irrespective of Investigator's causality assessment, which includes serious TEAEs, TEAEs leading to dose modification, and AESIs, observed in the Umbralisib Safety Population. This was accompanied by individual case reviews of selected events. New or worsening laboratory parameters were also analyzed. Each TEAE and laboratory parameter evaluated for ADR determination were assessed against pre-specified criteria as follows: frequency, severity, and seriousness; clinical experience to date with umbralisib; observed dose-response relationship; association with mechanism of action of umbralisib as an inhibitor of PI3K δ and CK1 ϵ ; consistency with non-clinical findings with umbralisib; underlying malignancy, comorbidities, or concurrent illness; and/or clinically meaningful shift for laboratory parameter. Common adverse reactions reported in $\geq 10\%$ of subjects with MZL, FL, and other hematologic

malignancies treated with umbralisib are summarized in (Table 33). ADRs of any grade were reported in 351 subjects (94.6%), and ADRs of Grade 3 and Grade 4 were reported in 135 subjects (36.4%) and 31 subjects (8.4%), respectively. The most frequently reported ADRs of any grade ($\geq 20\%$) were diarrhea (52.3%), nausea (41.5%), fatigue (38.8%), musculoskeletal pain (28.6%), and vomiting (23.2%); none of these were of Grade 4.

Table 33: Adverse Reactions Reported in at Least 10% of Subjects With MZL, FL, and Other Hematologic Malignancies (Umbralisib Safety Population)

System Organ Class Preferred Term or Groups	Umbralisib (N=371)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Any adverse drug reaction	351 (94.6)	135 (36.4)	31 (8.4)
Blood and lymphatic system disorders			
Anemia ^a	42 (11.3)	18 (4.9)	2 (0.5)
Neutropenia (including febrile neutropenia) ^b	53 (14.3)	34 (9.2)	18 (4.9)
Gastrointestinal disorders			
Abdominal pain ^c	66 (17.8)	7 (1.9)	0
Constipation	39 (10.5)	1 (0.3)	0
Diarrhea	194 (52.3)	27 (7.3)	0
Nausea	154 (41.5)	4 (1.1)	0
Vomiting	86 (23.2)	1 (0.3)	0
General disorders and administration site conditions			
Fatigue ^d	144 (38.8)	15 (4.0)	0
Peripheral edema ^e	50 (13.5)	2 (0.5)	0
Pyrexia	47 (12.7)	0	0
Hepatobiliary disorders			
Transaminase elevation ^f	63 (17.0)	24 (6.5)	4 (1.1)
Infections and infestations			
Upper respiratory tract infection ^g	49 (13.2)	0	0
Investigations			
Blood creatinine increased	39 (10.5)	1 (0.3)	0
Metabolism and nutrition disorders			
Decreased appetite	65 (17.5)	5 (1.3)	0

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System Organ Class Preferred Term or Groups	Umbralisib (N=371)		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hypokalemia	39 (10.5)	9 (2.4)	1 (0.3)
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain ^h	106 (28.6)	7 (1.9)	0
Psychiatric disorders			
Insomnia	47 (12.7)	1 (0.3)	0
Respiratory, thoracic, and mediastinal disorders			
Dyspnea ⁱ	37 (10.0)	6 (1.6)	0
Skin and subcutaneous tissue disorders			
Rash ^j	52 (14.0)	8 (2.2)	0

Source: Table 2.7.4.6.1

Abbreviations: FL, follicular lymphoma; MZL, marginal zone lymphoma.

Note: Summary based on treatment-emergent adverse event with the worst grade. Any grade = Grades 1 to 4 or missing.

Grouped term for reactions with multiple preferred terms:

^a Anemia Anemia and hemoglobin decreased

^b Neutropenia and febrile neutropenia

^c Abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and abdominal tenderness

^d Fatigue and asthenia

^e Edema peripheral and peripheral swelling

^f Alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, and hepatic enzyme increased

^g Upper respiratory tract infection and viral upper respiratory tract infection

^h Musculoskeletal pain, back pain, myalgia, pain in extremity, musculoskeletal discomfort, musculoskeletal chest pain, neck pain, groin pain, spinal pain, bone pain, non-cardiac chest pain, pain in jaw, and limb discomfort

ⁱ Dyspnea Dyspnea and dyspnea exertional

^j Rash, rash maculopapular, rash pruritic, rash erythematous, and rash macula

The FDA's Assessment:

Based on the use of grouped preferred terms (Section 19.5), the table below provides a summary of the most common adverse events.

Overall, in the safety pool, the most common TEAEs (at least 10% of total pooled subjects) were diarrhea/colitis (52.3%), nausea (41.5%), fatigue (39.4%), musculoskeletal pain (28.3%) and vomiting (23.2%). For patients with FL, the most common TEAEs were diarrhea/colitis (58%), nausea (38.9%), fatigue (38.1%), and vomiting (22.1%).

The incidence of Grade ≥ 3 adverse events was 51.2% and 46.6% in the safety pool and patients with FL, respectively. The most common Grade ≥ 3 adverse events in the safety pool and in patients with FL were neutropenia (11.3%, 9.2%), diarrhea/colitis (8.4%, 9.2%) and increased

transaminases (6.5%, 5.3%), respectively.

Table 34: Summary of Common (≥10%) Treatment Emergent Adverse Events - FDA Review

Preferred Term	UTX-TGR-205		Safety pool (N=371)	
	FL (N=131) n (%)		n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any TEAE	128 (97.7)	61 (46.6)	366 (98.7)	190 (51.2)
Diarrhea/colitis	76 (58)	12 (9.2)	194 (52.3)	31 (8.4)
Musculoskeletal pain	34 (25.9)	0	104 (28.3)	9 (2.4)
Nausea	51 (38.9)	2 (1.5)	154 (41.5)	4 (1)
Transaminase increased	21 (16)	7 (5.3)	64 (17.2)	24 (6.5)
Rash	19 (14.5)	3 (2.3)	70 (18.9)	10 (3)
Edema	15 (11.4)	1 (0.8)	58 (15.6)	5 (1.3)
Headache	16 (12.2)	1 (0.8)	61 (16.4)	5 (1.3)
Decreased appetite	21 (16.0)	3 (2.3)	65 (18)	5 (1.3)
Cough	25 (19)	0	85 (23)	0
Vomiting	29 (22.1)	1 (0.8)	87 (23.2)	1 (1)
Upper respiratory tract infection	29 (22.1)	2 (1.5)	57 (16.4)	0
Abdominal pain	27 (20.6)	5 (3.8)	68 (18.3)	7 (2)
Neutropenia	17 (13)	12 (9.2)	53 (14.2)	42 (11.3)
Dizziness	23 (17.5)	0	68 (18.3)	0
Insomnia	18 (13.7)	1 (0.8)	48 (13)	1 (1)
Renal insufficiency	22 (16.8)	2 (1.5)	40 (10.8)	1 (1)
Hyperuricemia	3 (2.3)	0	14 (3.8)	4 (1.1)
Dyspnea	9 (6.8)	0	39 (10.5)	6 (2)
Pyrexia	13 (9.9)	0	47 (12.7)	4 (1.1)
Urinary tract infection	13 (9.9)	2 (1.5)	29 (7.8)	7 (2)
Taste disorder	10 (7.6)	0	40 (10.8)	0

Preferred Term	UTX-TGR-205		Safety pool (N=371) n (%)	
	FL (N=131) n (%)			
Fatigue	50 (38.1)	4 (3)	146(39.4)	15 (4)
Hypokalemia	15 (11.4)	3 (2.3)	39 (10.5)	10 (3)
Abbreviations: FL, Follicular lymphoma; PT, preferred term; TEAE, treatment-emergent adverse event. Source: FDA review of the ADAE dataset				

Laboratory Findings

The Applicant's Position:

Hematological and chemistry parameters were reviewed as CTCAE version 4.03-derived new or worsening abnormalities from baseline. The frequency cut-off for inclusion in the laboratory abnormality ADR table was based on frequency and severity. Based on the observed data with umbralisib, the cutoff was determined to be $\geq 20\%$ any grade plus $\geq 5\%$ Grade ≥ 3 new or worsening laboratory abnormality, and these data are provided in Table 35.

Table 35: Treatment-emergent Laboratory Abnormalities With Umbralisib (at Least 20% of Subjects and at Least 5% of Subjects With Grade ≥ 3) (Umbralisib Safety Population)

Laboratory Parameter	Number of Evaluable Subjects	Umbralisib (N=371)		
		Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematology				
Leukocytes decreased	369	143 (38.8)	19 (5.1)	7 (1.9)
Neutrophils decreased	368	135 (36.7)	33 (9.0)	30 (8.2)
Hemoglobin decreased	369	112 (30.4)	20 (5.4)	0
Lymphocytes decreased	369	89 (24.1)	37 (10.0)	16 (4.3)
Chemistry				
Aspartate aminotransferase increased	369	111 (30.1)	22 (6.0)	0
Alanine aminotransferase increased	369	107 (29.0)	21 (5.7)	4 (1.1)

Source: Table 2.7.4.6.3.1

The FDA's Assessment:

In the FL cohort, the most common grade 3-4 lab shift abnormalities were neutropenia (14%), ALT increase (6%) and AST increase (6%). No patient developed grade 3-4 increase in creatinine

despite a large number of patients with any grade increase in creatinine. A similar trend was seen in the safety pool.

Table 36: Treatment Emergent Laboratory Abnormalities - FDA Laboratory Shift Analysis

Laboratory Parameter	UTX-TGR-205		Safety pool (N=371) %	
	FL (N=131) %			
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Hematologic				
Neutropenia	32%	14%	36%	17%
Thrombocytopenia	24%	3%	25%	5%
Anemia	28%	2%	30%	5%
Chemistry				
Creatinine increase	75%	0	77%	0
ALT increase	27%	6%	29%	7%
AST increase	27%	6%	30%	6%
ALT, alanine aminotransferase; AST, aspartate aminotransferase Source: FDA review of ADLB (laboratory) dataset				

Vital Signs

The Applicant's Position:

Vital sign results were not pooled due to the heterogeneity of assessment schedule across studies. In general, the changes from baseline were not clinically meaningful. Of the TEAEs associated with vital signs, the most frequently reported in the Umbralisib Safety Population were pyrexia (12.7%), hypertension (7.0%), and weight decreased (7.0%).

The FDA's Assessment:

The FDA agrees with the Applicant's position

Electrocardiograms (ECGs)

The Applicant's Position:

ECG data were summarized by study for Study TGR-1202-101 and Study TGR-1202-102. No pooled analyses based on IDB were performed due to limited data and heterogeneity of assessment schedules across studies. Of the TEAEs associated with ECG parameters, the most frequently (at least 1% total) reported in the Umbralisib Safety Population were atrial fibrillation (1.3%) and sinus tachycardia (1.1%). No TEAEs of supraventricular tachycardia or ventricular extrasystoles were reported.

The FDA's Assessment:

The FDA agrees with the Applicant's position

QT

The Applicant's Position:

A concentration-QTc analysis based on data from the 32 subjects of Cohort S (umbralisib monotherapy) in Study TGR-1202-102 was conducted to characterize the relationship of the change from baseline QTc interval with umbralisib plasma concentration. The concentration QTc analysis did not reveal a significant relationship or risk of ≥ 20 ms corrected QT interval by Fredericia (QTcF) prolongation at the time points evaluated. The predicted Δ QTcF was higher at the 4-hour post dose time point than for other time points, reaching 3.6 ms with a 90% CI upper bound of 10.2 ms.

The FDA's Assessment:

The FDA disagrees with the Applicant's position that there is no risk of QTc prolongation with umbralisib. The Applicant's exposure-corrected QT interval (QTc) analyses were conducted using steady state exposure ($C_{\max,ss}$) data in Study TGR-1202-102. The geometric mean $C_{\max}$ on Cycle 2 Day 1 was 4012 ng/mL (n=20), which was lower than the therapeutic exposure (7266 ng/mL) obtained from PPK analysis. The 1200 mg QD dose group in Study TGR-1202-102 did not provide higher exposure (4172 ng/mL) as compared to the 800 mg QD dose group. Thus, the Applicant's QT assessment was not adequate to extrapolate the risk of QTc prolongation to the higher exposure range. The FDA agrees that there were no large mean increases (i.e., 20 msec) with umbralisib treatment.

Immunogenicity

The Applicant's Position:

There are no immunogenicity data about umbralisib in this application.

The FDA's Assessment:

The FDA agrees with the Applicant's position

8.2.5. Analysis of Submission-Specific Safety Issues

Overall, TEAEs of special interest were reported in 288 subjects (77.6%), including 123 subjects (83.7%) with FL (Table 37).

Table 37: Summary of TEAEs of Special Interest (at Least 5% Total by PT) by Category and PT (Umbralisib Safety Population)

AE Special Interest/ Preferred Term	UTX-TGR-205	Pooled	
	FL (N=131) n (%)	FL (N=147) n (%)	Total (N=371) n (%)
At least 1 TEAE of special interest	110 (84.0)	123 (83.7)	288 (77.6)
Diarrhea			
Diarrhea	75 (57.3)	83 (56.5)	194 (52.3)
Hepatic dysfunction			
Alanine aminotransferase increased	21 (16.0)	23 (15.6)	56 (15.1)
Aspartate aminotransferase increased	16 (12.2)	18 (12.2)	55 (14.8)
Neutropenia			
Neutropenia	17 (13.0)	19 (12.9)	53 (14.3)
Rash			
Rash	8 (6.1)	11 (7.5)	31 (8.4)
Anemia			
Anemia	11 (8.4)	13 (8.8)	41 (11.1)
Thrombocytopenia			
Thrombocytopenia	12 (9.2)	12 (8.2)	34 (9.2)
Pneumonia			
Pneumonia	5 (3.8)	10 (6.8)	22 (5.9)

Source: Table 2.7.4.2.4.6.1

Abbreviations: AE, adverse event; FL, follicular lymphoma; PT, preferred term; TEAE, treatment-emergent adverse event.

Note: AE sorting is done by decreasing frequency of system organ class and AE of special interest based on the total column.

8.2.5.1 Diarrhea

The Applicant's Position:

Overall in the Umbralisib Safety Population, the most frequently reported TEAE of special interest was diarrhea (194 subjects [52.3%]), including 83 subjects (56.5%) with FL (Table 37). A total of 27 subjects (7.3%) had Grade ≥ 3 diarrhea, including 13 subjects (8.8%) with FL. A total of 165 subjects (44.5%) had a TEAE of diarrhea that was considered related to umbralisib, including 73 subjects (49.7%) with FL. Of these, 25 subjects (6.7%) reported Grade ≥ 3 diarrhea related to umbralisib, including 12 subjects (8.2%) with FL. There were no Grade 4 TEAEs of diarrhea.

8.2.5.2 Hepatic Dysfunction

The Applicant's Position:

Overall in the Umbralisib Safety Population, ALT increased was reported by a total of 56 subjects (15.1%), including 23 subjects (15.6%) with FL (Table 37). A total of 21 subjects (5.7%) had Grade ≥ 3 ALT increased, including 8 subjects (5.4%) with FL. A total of 45 subjects (12.1%) had a TEAE of ALT increased that was considered related to umbralisib, including 17 subjects (11.6%) with FL. Of these, 20 subjects (5.4%) reported Grade ≥ 3 ALT increased related to umbralisib, including 8 subjects (5.4%) with FL. Grade 4 TEAEs of ALT increased were reported by a total of 4 subjects (1.1%), including 2 subjects (1.4%) with FL.

Overall in the Umbralisib Safety Population, AST increased was reported by a total of 55 subjects (14.8%), including 18 subjects (12.2%) with FL (Table 37). A total of 21 subjects (5.7%) had Grade ≥ 3 AST increased, including 9 subjects (6.1%) with FL. A total of 45 subjects (12.1%) had a TEAE of AST increased that was considered related to umbralisib, including 16 subjects (10.9%) with FL. Of these, 20 subjects (5.4%) reported Grade ≥ 3 AST increased related to umbralisib, including 9 subjects (6.1%) with FL. There were no Grade 4 TEAEs of AST increased.

8.2.5.3 Neutropenia

The Applicant's Position:

Overall in the Umbralisib Safety Population, neutropenia was reported by a total of 53 subjects (14.3%), including 19 subjects (12.9%) with FL (Table 37). A total of 42 subjects (11.3%) had Grade ≥ 3 neutropenia, including 14 subjects (9.5%) with FL. A total of 42 subjects (11.3%) had a TEAE of neutropenia that was considered related to umbralisib, including 18 subjects (12.2%) with FL. Of these, 33 subjects (8.9%) reported Grade ≥ 3 neutropenia related to umbralisib, including 13 subjects (8.8%) with FL. Grade 4 TEAEs of neutropenia were reported by a total of 18 subjects (4.9%), including 8 subjects (5.4%) with FL.

8.2.5.4 Rash

The Applicant's Position:

Overall in the Umbralisib Safety Population, rash was reported by a total of 31 subjects (8.4%), including 11 subjects (7.5%) with FL (Table 37). A total of 2 subjects (0.5%) had Grade ≥ 3 rash, including 1 subjects (0.7%) with FL. There were no Grade 4 TEAEs of rash. There were no TEAEs of rash that were considered related to umbralisib.

8.2.5.5 Anemia

The Applicant's Position:

Overall in the Umbralisib Safety Population, anemia was reported by a total of 41 subjects (11.1%), including 13 subjects (8.8%) with FL (Table 37). A total of 18 subjects (4.9%) had Grade ≥ 3 anemia, including 4 subjects (2.7%) with FL. A total of 22 subjects (5.9%) had a TEAE of anemia that was considered related to umbralisib, including 6 subjects (4.1%) with FL. Of these,

none of the Grade ≥ 3 TEAEs of anemia were considered related to umbralisib. Grade 4 TEAEs of anemia were reported by a total of 2 subjects (0.5%); there were no subjects with FL who reported a Grade 4 TEAE of anemia.

8.2.5.6 Thrombocytopenia

The Applicant's Position:

Overall in the Umbralisib Safety Population, thrombocytopenia was reported by a total of 34 subjects (9.2%), including 12 subjects (8.2%) with FL (Table 37). A total of 11 subjects (3.0%) had Grade ≥ 3 thrombocytopenia, including 3 subjects (2.0%) with FL. A total of 22 subjects (5.9%) had a TEAE of thrombocytopenia that was considered related to umbralisib, including 7 subjects (4.8%) with FL. Of these, none of the Grade ≥ 3 TEAEs of thrombocytopenia were considered related to umbralisib. Grade 4 TEAEs of thrombocytopenia were reported by a total of 8 subjects (2.2%), including 1 subject (0.7%) with FL.

8.2.5.7 Pneumonia

The Applicant's Position:

Overall in the Umbralisib Safety Population, pneumonia was reported by a total of 22 subjects (5.9%), including 10 subjects (6.8%) with FL (Table 37). A total of 11 subjects (3.0%) had Grade ≥ 3 pneumonia, including 3 subjects (2.0%) with FL. Overall, there was 1 Grade 4 TEAE of pneumonia reported by 1 subject (0.3%); there were no subjects with FL who reported a Grade 4 TEAE of pneumonia. There were no TEAEs of pneumonia that were considered related to umbralisib.

The FDA's Assessment:

The information below summarizes the FDA review of adverse events of special interest with umbralisib and includes diarrhea/colitis, hepatotoxicity, rash, neutropenia, anemia, thrombocytopenia, pneumonia, infection, and pneumonitis.

Table 38: Summary of Adverse Events of Special Interest - FDA Review

AE Special Interest/ Preferred Term	UTX-TGR-205		Safety Pool	
	FL (N=131) n (%)		Total (N=371) n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
At least 1 TEAE of special interest	110 (84)	38 (29)	288 (77.6)	166 (44.8)
Diarrhea/colitis	76 (58)	12 (9.2)	194 (52.3)	27 (7.3)
Hepatic dysfunction	25 (19)	10 (7.6)	70 (18.9)	25 (6.7)
Neutropenia	18 (13.7)	13 (9.9)	53 (14.3)	52 (14.1)
Rash	15 (10.6)	3 (2.3)	70 (18.9)	10 (2.6)
Anemia	12 (9.1)	4 (3.1)	42 (11.3)	20 (5.4)
Thrombocytopenia	12 (9.1)	3 (2.3)	35 (9.4)	11 (3)
Pneumonia	9 (6.8)	1 (0.8)	24 (6.5)	13 (3.5)
Sepsis	2 (1.5)	2 (1.5)	8 (2.2)	8 (2.2)
Pneumonitis	0	0	4 (1.1)	2 (0.5)
Source: FDA review of ADAE dataset				

Table 39: Incidence of Adverse Events of Special Interest by Prior Lines of Therapy - FDA Review

Adverse events of special interest	Safety pool N=371				Risk Difference
	# prior therapies				
	≤2 N=189		≥3 N=182		
	n	%	n	%	
Diarrhea/colitis					
All-grade events	106	56%	88	48%	8
Grade ≥3	23	12%	7	4%	8

Adverse events of special interest	Safety pool N=371				Risk Difference
	# prior therapies				
	≤2 N=189		≥3 N=182		
	n	%	n	%	
Hepatotoxicity All-grade events* Grade ≥3*	65 17	34% 9%	49 8	27% 4%	7 5
Pneumonitis All-grade events Grade ≥3	4 2	2% 1%	0 0	0 0	2 1
Rash All-grade events Grade ≥3	44 8	23% 4%	21 2	12% 1%	11 3
Infection All-grade events Grade ≥3	85 17	45% 9%	75 20	41% 11%	4 -2
*Based on laboratory data Source: FDA review of ADAE and ADLB datasets					

Adverse Events of Special Interest

The FDA's incidence of AESIs, differed in some instances due to grouping of preferred terms, consistent throughout this review. In the following section, the FDA considerations are provided for each AESI. Any grade AESIs occurred in 110 patients (84%) with FL in the UTX-TGR-205 FL cohort (N = 131).

Diarrhea/colitis

Diarrhea or colitis is an important identified risk for patients who receive treatment with umbralisib. The Applicant identified events of diarrhea or colitis based on selected MedDRA preferred terms for diarrhea or colitis. Because the clinical presentation of diarrhea or colitis overlaps, FDA used a grouped MedDRA PT (Appendix 19.4) to evaluate the incidence and pattern of umbralisib-associated diarrhea or colitis.

Diarrhea/colitis was the most common toxicity reported in the safety pool (52.3%), as well as the FL population in UTX-TGR-205 (58%). Grade 3 diarrhea/colitis occurred in 7.3% and 9.2% of patients in the safety pool and FL cohort, respectively.

Based on the 371 patients in the safety pool, diarrhea or colitis led to dose interruption in 12.3%, dose reduction in 2.2%, and treatment discontinuation in 4.8% of patients. It is one of the most common reasons for treatment modification. For all grade diarrhea or colitis, the median time to onset was 1 month, with 75% occurring within 2.8 months. For patients with grade ≥ 3 diarrhea or colitis, the median time to onset was 4.5 months, with 75% occurring within 8 months.

Based on the data, there is no established standard of treatment for umbralisib-associated diarrhea or colitis. Labeling will include a Warning and Precaution for diarrhea or colitis and dose modifications to ensure safe use of the drug. Patients should be aware that umbralisib should be discontinued in the event of severe diarrhea or colitis.

Hepatotoxicity

Based on lab-shift analyses in the safety pool population (N = 371), any grade transaminase elevation occurred in 29% (ALT) and 30% (AST) of the population, and grade 3-4 toxicities were 7% and 6%, respectively. These incidences were lower in the UTX-TGR-205 FL population in which 27% of patients experienced any grade ALT/AST elevation with 6% reaching severity of grade 3-4. In the safety pool, the median onset of grade 3-4 hepatotoxicity was 2 months, with 75% occurring by 3 months. Transaminase elevation led to umbralisib dose interruption in 4.6%, dose reduction in 1.1%, and treatment discontinuation in 3.2%. The Applicant reported no cases of liver failure in patients with hematologic malignancies. The study did not enroll patients with moderate or severe hepatic dysfunction.

Given the concerns for hepatotoxicity with umbralisib, labeling will include hepatotoxicity as a Warning and Precaution to ensure safe use of umbralisib. The pattern of umbralisib-associated hepatotoxicity, specific monitoring procedures, and dose modifications will need to be included in labeling to inform healthcare providers and patients.

Rash

In the safety pool, one patient developed a fatal case of Grade 3 exfoliative dermatitis. The event of exfoliative dermatitis led to bacteremia and sepsis and multi-organ failure. In the FL cohort of study UTX-TGR-205, 14% of the patients developed all grade rash. The incidence in the safety pool of any grade rash was 18.9%, with 3% experiencing Grade 3 rash events. Rash lead to umbralisib dose interruption in 1.6% of the patients.

In addition, severe cutaneous reactions, including SJS, TEN, and DRESS, are a known class effect with PI3K inhibitors. Based on a fatal case of exfoliative dermatitis with umbralisib, the incidence of cutaneous reactions, and the known class effect, a Warning and Precaution for severe cutaneous reactions should be included in labeling.

Neutropenia

Based on lab-shift analyses in the safety pool population, any grade neutropenia occurred in 36% of the population, and grade 3-4 neutropenia of 17%. In patients with FL, any grade neutropenia was 32%, with 14% being Grade 3-4.

For the 371 patients in the safety pool, the median time to onset of grade 3-4 neutropenia was 2 months, with 75% occurring by 3.7 months. Neutropenia led to umbralisib dose interruption in 5%, reduction in 2%, and discontinuation in 1%.

Given the concerns for Grade 3-4 neutropenia coupled with the potential risk for infection with umbralisib, labeling will include neutropenia as a Warning and Precaution to ensure safe use of umbralisib. The pattern of umbralisib-associated neutropenia, monitoring procedures, and dose modifications will need to be included in labeling to inform healthcare providers and patients.

Anemia

Based on lab-shift analysis data in the safety pool population, any grade anemia occurred in 30% of the population and grade 3-4 anemia in 5%. In patients with FL, any grade anemia was 28%, with 2% being Grade 3-4.

Thrombocytopenia

Based on lab-shift analysis data in the safety pool population, any grade thrombocytopenia occurred in 25% of the population and grade 3-4 thrombocytopenia in 5%. In patients with FL, any grade thrombocytopenia was 24%, with 3% being Grade 3-4. In patients that developed thrombocytopenia, there was no association with clinically significant bleeding event.

Pneumonia

Overall in the umbralisib safety population, pneumonia was reported 6.5% of the patients, including 3.5% with Grade ≥ 3 pneumonia. In the FL cohort of study UTX-TGR-205, 6.8% and 0.8% of the patients had any grade and Grade ≥ 3 pneumonia, respectively. Incidence of SAE in the safety population and FL cohort were 0.8% and 3.7%, respectively.

Infection

Though not included as an AESI, infection is a significant issue with umbralisib use. In the safety pool of 371 patients, there were 160 patients (43%) with the reported event of infection, with 37 (20%) of grade 3-4 severity. There were two deaths attributable to infection. These included pneumonia legionella and sepsis. Sepsis occurred in eight patients (2%) and led to two deaths.

Given the concerns for the risk of infection and the incidence of Grade 3-4 neutropenia, labeling will include infection as a Warning and Precaution to ensure safe use of umbralisib.

Pneumonitis

In the Safety Population, pneumonitis was reported in 1% of patients, with <1% being Grade 3.

Pneumonitis was reported as a SAE and led to treatment discontinuation in 2 patients (<1%) each, respectively.

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

The Applicant's Position:

Not applicable.

The FDA's Assessment:

There were no clinical outcome or patient-reported outcome data submitted with this application.

8.2.7. Safety Analyses by Demographic Subgroups

The Applicant's Position:

Subgroup analyses were conducted to identify potential safety issues restricted to particular subpopulations; no clinically meaningful differences were observed as compared to the overall Umbralisib Safety Population.

Sex

Overall, diarrhea, nausea, and vomiting were reported more frequently in female subjects than male subjects. Neutropenia was reported with a similar incidence between male and female subjects overall but more frequently in male than female subjects with FL. The observed differences by gender were not considered clinically meaningful.

Age

Overall, Grade ≥ 3 TEAEs, serious TEAEs, and TEAEs leading to discontinuation of umbralisib were reported more frequently in subjects in the age group ≥ 65 years than subjects < 65 years (54.5% versus 46.3%, 31.6% versus 17.9%, and 18.2% versus 11.7%, respectively). Nausea was reported more frequently in subjects in the age group ≥ 65 years than subjects < 65 years (44.0% versus 38.3%) overall and in subjects with MZL (41.2% versus 22.6%). Neutropenia and anemia were reported more frequently in subjects in the age group ≥ 65 years than subjects < 65 years (17.2% versus 11.7% and 15.3% versus 6.2%, respectively) overall and in subjects with FL (18.9% versus 8.2% and 14.9% versus 4.1%, respectively). The observed differences by age were not considered clinically meaningful.

Race

The incidences of TEAEs, serious TEAEs, and TEAEs leading to discontinuation of umbralisib were similar between White and subjects of other races. Vomiting was reported more

frequently in Non-White than White subjects (28.1% versus 22.1%) overall and in subjects with MZL (26.7% versus 17.9%). The incidence of hepatic dysfunction and rash were also higher in Non-White than White subjects (23.4% versus 17.9% and 18.8% versus 13.0%, respectively). The observed differences by race were not considered clinically meaningful.

The FDA's Assessment:

There was limited representation of racial or ethnic minorities in the FL cohort of study UTX-TGR-205 with few African American (3.8%) or Asian (2.3%) patients to allow broad generalization of these results. In addition, only 4.6% were of Hispanic/Latino ethnicity. This reflects an overall limitation in the data as it applies to the US population and a postmarketing commitment was issued to address this concern (Section 13).

8.2.8. Specific Safety Studies/Clinical Trials

The Applicant's Position:

There were no special safety studies or clinical trials in this application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

The Applicant's Position:

There were no analyses for second primary malignancies in the application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Human Reproduction and Pregnancy

The Applicant's Position:

Umbralisib has not been studied in pregnant or lactating women. Based on findings in animals and its mechanism of action, umbralisib can cause fetal harm when administered to a pregnant woman. The presence of umbralisib in human milk and its effects on the breastfed child or on milk production have not been investigated.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Pediatrics and Assessment of Effects on Growth

The Applicant's Position:

There were no children enrolled in any of the studies submitted with this application. The safety of copanlisib in pediatric patients has not been established.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant's Position:

Two subjects reported an accidental overdose as a TEAE with one subject taking 1600 mg and the other subject taking 1200 mg instead of 800 mg. For both subjects no action was taken.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable. Umbralisib is not currently registered or approved in the US or in any other country.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

Expectations on Safety in the Postmarket Setting

The Applicant's Position:

Safety in the postmarket setting is expected to be similar to that observed on the clinical trials reviewed in this application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

8.2.11. Integrated Assessment of Safety

The Applicant's Position:

The safety of single agent umbralisib was evaluated in 371 subjects, including 147 subjects with FL. Key safety findings were as follows:

- Death due to TEAEs were reported in 4 subjects (1.1%), and none were in subjects with FL.
- The common TEAEs of diarrhea, nausea, fatigue, and vomiting were reported at similar rates across duration of exposure groupings suggesting that these TEAEs occurred at generally the same rate regardless of the duration of exposure to umbralisib.

- Common ADRs of any grade ($\geq 10\%$) were reported in 94.6% of subjects, and ADRs of Grade 3 and Grade 4 were reported in 36.4% and 8.4% of subjects, respectively. The most frequently reported adverse reactions of any grade ($\geq 20\%$) were diarrhea (52.3%), nausea (41.5%), fatigue (38.8%), musculoskeletal pain (28.6%), and vomiting (23.2%); none of these were of Grade 4.
- Overall, TEAEs of special interest were reported in 77.6% of subjects. The most frequently reported TEAEs of special interest (at least 10% of total pooled subjects) were diarrhea (52.3% of subjects), ALT increased (15.1% of subjects), AST increased (14.8% of subjects), neutropenia (14.3% of subjects), and anemia (11.1% of subjects).
- The most frequently reported laboratory abnormalities with umbralisib treatment ($>30\%$ of subjects and at least 5% of subjects with Grade ≥ 3) were leukocytes decreased (38.8%, Grade 3: 5.1%), neutrophils decreased (36.7%, Grade 3: 9.0%), hemoglobin decreased (30.4%, Grade 3: 5.4%), and AST increased (30.1%, Grade 3: 6.0%).

In conclusion, single agent umbralisib was well tolerated and had a manageable safety profile in the overall and FL populations.

The FDA's Assessment:

The FDA agrees with the Applicant's position that the safety data demonstrates that umbralisib demonstrated a tolerable safety profile in patients with follicular lymphoma. Although, given the median exposure of 7 months in patients with FL and approximately 6 months in patients with hematologic malignancies, there is limited data to support longer-term safety.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

The FDA's Assessment:

There are no major statistical issues identified from this submission. The trials included in the review of this application were designed to be single arm open-label studies with different study objectives. No statistical inference on comparison was conducted. The primary efficacy endpoint was overall response rate (CR + PR). The single-arm aspect of the analyses limits the ability to perform any comparative evaluations.

There were insufficient number of patients in the race and ethnicity demographic subgroups to provide an assessment of efficacy in this patient subpopulation.

In the absence of a control arm, it was difficult to interpret the time-to-event endpoint of PFS in these trials. The results of the analysis were descriptive and considered exploratory.

8.4. Conclusions and Recommendations

The FDA's Assessment:

The benefit-risk assessment is favorable for umbralisib for the treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least three prior systemic therapies.

Efficacy:

Efficacy of umbralisib in patients with relapsed or refractory (R/R) follicular lymphoma (FL) is based on the results from a single-arm cohort of Study UTX-TGR-205, an open-label, multi-center, single-arm, multi-cohort trial which included 131 patients. Patients received umbralisib 800 mg twice daily continuously until disease progression or unacceptable toxicity. The primary endpoint was overall response rate (ORR) per independent review committee (IRC) based on modified International Working Group Revised Response Criteria for Malignant Lymphoma (Cheson et al. 2007). Among the 117 patients with FL evaluable for efficacy, the median follow-up time was 20.1 months (range: 13.5 to 29.6 months). The ORR per IRC was 42.7% (95% CI 33.6, 52.2), with 3.4% achieving a complete response. The median duration of response (DOR) was 11.1 months, 95% CI (8.3, 16.4).

Safety:

The safety profile was supported by analysis of the 131 patients with follicular lymphoma from the study UTX-TGR-205 and a combined safety database of 371 patients with hematologic malignancies [marginal zone lymphoma (22%), follicular lymphoma (40%), diffuse large B-cell lymphoma or mantle cell lymphoma (20%), and other hematologic malignancies (18%)] who received umbralisib doses $\geq$ 800 mg daily.

In 131 patients with relapsed or refractory FL, the median duration of treatment was 7.3 months (range 1 day to 22.5 months) and the most common adverse events ($\geq$ 20% of patients) were diarrhea-colitis, nausea, fatigue, musculoskeletal pain, vomiting, upper respiratory tract infection and abdominal pain. Treatment-emergent laboratory abnormalities of any grade occurring in $\geq$ 20% of patients were increase in creatinine (75%), neutropenia (32%), anemia (28%), increase in ALT/AST (27%) and thrombocytopenia (24%). Serious adverse events occurred in 22% of patients and no fatal adverse events occurred. Dose discontinuations due to any adverse events were reported in 12% of patients, most often due to diarrhea-colitis.

The primary safety issues identified with umbralisib include serious, including fatal, infections and cutaneous reactions, and serious diarrhea or colitis, hepatotoxicity, and neutropenia. In the 371 patients with hematologic malignancies, 51% of patients experienced a grade 3 or 4 toxicity, the most common including neutropenia (17%), diarrhea-colitis (8%), and increased AST/ALT (6%). Fifteen percent of patients discontinued umbralisib due to an adverse event, most often due to diarrhea-colitis and increased AST/ALT.

Benefit-Risk:

Umbralisib has an overall favorable benefit-risk in patients with relapsed or refractory follicular lymphoma; however, the benefit-risk determination was considered in the context of available therapy to support an accelerated approval.

The eligibility criteria for study UTX-TGR-205 required patients with relapsed or refractory FL to have received at least two prior systemic therapies. The patients with FL enrolled had a median number of 3 prior therapies, 36% were refractory to their last therapy and 31% were refractory to rituximab. The ORR of 42.7% (95% CI: 33.6%, 52.2%) warrants additional consideration in the context of available therapy in the 3rd line setting and beyond. Available therapy includes anti-CD20 therapy (i.e., rituximab and obinutuzumab) as a single agent and in combination, bendamustine monotherapy and in combination, and immunotherapy combinations such as rituximab plus lenalidomide. In the 3rd line setting and beyond, the ORRs for these therapies, including single-agent and combinations, ranges from 57% to 80% with associated durability. Taking into consideration the ORR of 42.7% with a lower bound of the confidence interval of 33.6%, and available therapies in a comparable treatment setting, the review team determined that the residual uncertainty regarding the benefit of umbralisib in these patients warrants restriction of the indication to patients with relapsed or refractory FL who have received 3 prior systemic therapies.

Therefore, the benefit-risk of umbralisib is deemed favorable to support accelerated approval under 21 CFR 314.510 Subpart H for the following indication:

- Treatment of adult patients with relapsed or refractory follicular lymphoma who have received at least three prior lines of systemic therapy.

X

X

Laura Fernandes, PhD
Primary Statistical Reviewer

Yu-Te Wu, PhD
Statistical Team Leader

X

X

Maryam Sarraf Yazdy, MD
Primary Clinical Reviewer

Nicholas Richardson, DO, MPH
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

This application was not presented to the Oncologic Drugs Advisory Committee or other external consultants because umbralisib is not first-in-class, and the application did not raise new efficacy or safety issues for the recommended indications.

10 Pediatrics

The Applicant's Position:

The efficacy and safety of umbralisib in pediatric patients have not been studied. Umbralisib has an orphan drug designation for treatment of FL based on Request # 2019-7268 and granted on 04 March 2020. Due to the orphan drug designation of umbralisib for this indication, it is exempt from Pediatric Research Equity Act requirements. This information was submitted in Section 1.9.1 of the NDA Application.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

11 Labeling Recommendations

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

Data:

Summary of Significant Labeling Changes		
Section	Applicant's Proposed Labeling	FDA's proposed Labeling
Highlights of Prescribing Information		FDA revised Highlights to align with Format and Content with Selected Requirements of Prescribing Information (SRPI) as per regulations (21 CFR 201.56 and 201.57) and FDA Guidances.
1. Indications and Usage	UKONIQ is indicated for the treatment of adult patients with follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.	Indication for follicular lymphoma revised based on the trial population enrolled correlating with the data supporting a favorable benefit-risk profile and the comparative efficacy evaluation in the context of available therapy. Accelerated approval language modified per recommendations found in the Labeling for Human Prescription Drug and Biological Products Approved Under the Accelerated Approval Regulatory Pathway Guidance for Industry.
2. Dosage and Administration		
2.1 Recommended	The recommended dose of UKONIQ is	FDA generally agreed with

Dosage	800 mg taken orally (b) (4) (b) (4) once daily (b) (4) (b) (4) with food. Tablets should be swallowed whole. Do not chew the tablets. (b) (4)	proposal but made changes to align with current labeling practices. FDA added dosage instructions for patients who vomit because vomiting occurred in >15% of patients.
2.2 (b) (4)	(b) (4)	Deleted this section (b) (4)
2.3 Dosage Modifications for Adverse Reactions	(b) (4)	Revised tables to add cross-references to related information in sections 5 and 6 and removed (b) (4) (b) (4) Added dosage modifications for infections, diarrhea, thrombocytopenia, and severe cutaneous reactions to support new W&P and ARs.
3. Dosage Forms and Strengths	(b) (4) green, film-coated, oval-shaped, 200-mg tablet (b) (4) with "L474" on one side and plain on the other.	Edited to align with recommendations in draft Guidance for Industry: Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for

		Human Prescription Drug and Biological Products – Content and Format
4. Contraindications	None	FDA agreed.
5. Warnings and Precautions		
5.1 Infections	Serious, including fatal (b) (4), infections occurred in (b) (4) patients treated with UKONIQ (b) (4) (b) (4) (b) (4) For Grade 3 or (b) (4) infection, withhold UKONIQ until infection has resolved. Resume UKONIQ at the same or a reduced dose. (b) (4) (b) (4) monitor (b) (4) for CMV infection (b) (4) UKONIQ in patients with a history of CMV infection.	Revised to describe infections in a pooled safety population of 335 adults with hematological malignancies as described in Section 6 Adverse Reactions; this pooled safety approach applies to all adverse reactions described in Section 5 Warnings and Precautions. Added risk mitigation strategies where appropriate per 21 CFR 201.57 (c)(6)(i). Added recommendations for prophylaxis and dosage modifications for <i>Pneumocystis jirovecii</i> (PJP). Added recommendations for monitoring, prophylaxis, and dosage modifications for cytomegalovirus (CMV).
5.2 Neutropenia	Serious (b) (4) neutropenia occurred in (b) (4) patients treated with UKONIQ (b) (4) (b) (4) The median time to onset for neutropenia (b) (4) (b) (4) Withhold, reduce dose, or discontinue UKONIQ depending on the severity and	Revised to describe neutropenia in the pooled safety population and to include recommendations for monitoring.

	persistence of neutropenia	
5.3 Non-Infectious Colitis	Serious non-infectious colitis occurred in (b) (4) patients treated with UKONIQ (b) (4). The median time to onset for any grade (b) (4) (b) (4) (b) (4) Upon resolution (b) (4) resume UKONIQ at a reduced dose. Discontinue UKONIQ for life-threatening colitis.	Added diarrhea to this Warning and Precaution subsection such that it reads: Diarrhea or Colitis. Revised to describe colitis in pooled safety population. Added median time to onset. Modified risk mitigation strategies to include withholding until resolved, providing supportive care, resuming at a reduced dose, and discontinuing for recurrent Grade 3 diarrhea or recurrent colitis of any grade.
5.4 Hepatotoxicity	Grade 3 and 4 transaminase elevations (ALT and/or AST) occurred in (b) (4) (b) (4) (b) (4) The median time to onset (b) (4) Monitor hepatic function during treatment with UKONIQ. (b) (4) (b) (4)	Revised to describe hepatotoxicity using the pooled safety population based on the lab dataset, (b) (4)
5.5 Severe Cutaneous		Added a Warning & Precaution subsection for

Reactions		Severe Cutaneous Reactions because there were cases of grade 3 cutaneous reactions, including a fatal case of exfoliative dermatitis. Described these adverse reactions in the pooled safety population and included appropriate risk mitigation strategies.
5.6 Allergic Reactions Due to Inactive Ingredient FD&C Yellow No. 5		Added a Warning and Precaution subsection based on regulation (21 CFR 201.20(b)).
5.7 Embryo-Fetal Toxicity	Based on findings in animals and its mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of umbralisib to pregnant mice during the period of organogenesis (b) (4) (b) (4) (b) (4) (b) (4). Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least (b) (4) after the last dose.	FDA generally agreed but changed the duration of contraception to one month based on information on non-genotoxic drugs in the Guidance to Industry – Oncology Pharmaceuticals: Reproductive Toxicity Testing and Labeling Recommendations . Additional edits made to align with current OOD labeling practices.
6. Adverse Reactions		
6.1 Clinical Trials	(b) (4)	Modified this subsection to

Experience	(b) (4)	align with current OOD labeling practices. Described the pooled safety population of 335 adult patients used to inform the Warnings and Precautions section and based the remaining discussion of safety on the 221 patients with FL and MZ who received the recommended dosage. Added descriptions of serious adverse reactions, fatal adverse reactions, and dosage modifications. Revised laboratory table to populate from the laboratory dataset, (b) (4) Reordered terms in tables to be listed in descending order per 21 CFR 201.57(c)(7)(ii).
(b) (4)		
8. Use in Specific Populations		

8.1 Pregnancy	<u>Risk Summary:</u> Based on findings from animal studies and the mechanism of action, UKONIQ can cause fetal harm when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. <u>Data:</u> Animal Data	Revised risk summary and data based on review of nonclinical data and for consistency with current labeling practices.
8.2 Lactation	<u>Risk Summary:</u> There are no data on the presence of umbralisib in human milk, the effects on the breastfed child, or (b) (4) milk production. Because of the potential for serious adverse reactions from umbralisib in a breastfed child, advise lactating women not to breastfeed while taking UKONIQ and for (b) (4) after the last dose.	Shortened the duration not to breastfeed based on elimination half-life.
8.3 Females and Males of Reproductive Potential	(b) (4)	Revised duration of contraception based on guidance as described in Warnings and Precaution subsection 5.7.
8.4 Pediatric Use	Safety and effectiveness of UKONIQ have not been established in pediatric patients.	FDA agreed.
8.5 Geriatric Use	(b) (4)	Modified this section to align with 21 CFR 201.57(c)(9)(v) and draft Geriatric Information in Human Prescription Drug and Biological Product Labeling Guidance for Industry .

		Revised the percentage of 65 years and older and added 75 years and older for the pooled safety population of 221 patients with MZL or FL who received the recommended dosage.
8.6 Renal Impairment		Added this section to inform healthcare providers (HCP) that no dosage adjustments are recommended in patients with mild or moderate renal impairment and that Ukoniq has not been studied in patients with severe renal impairment based on 21 CFR 201.57(c)(9)(vi).
8.7 Hepatic Impairment		Added this subsection to inform HCP that the recommended dosage has not been established in patients with mild hepatic impairment and that Ukoniq has not been studied in patients with moderate or severe hepatic impairment based on 21 CFR 201.57(c)(9)(vi).
11. Description	(b) (4)	Revised to add pharmacologic or therapeutic class as required by 21 CFR 201.57(c)(12)(i). Used established pharmacologic class (EPC) for consistency with Highlights. Added pKa or pH value for the drug substance based on 21 CFR

		201.57(c)(12)(ii).
12. Clinical Pharmacology		
12.1 Mechanism of Action	(b) (4)	Revised to include inhibition of the ABL1 mutant and deleted (b) (4) (b) (4)
12.2 Pharmacodynamics		Added <u>Exposure- Response Relationships</u> heading to describe exposure-response relationship between umbralisib and overall response rate and safety and the time course of pharmacodynamic response based on 21 CFR 201.57 (c)(13)(i)(B). Modified the <u>Cardiac Electrophysiology</u> section to read: “The effect of UKONIQ on QT interval has not been fully characterized.” because the QTc assessment was inadequate to characterize the effects of umbralisib on the QT interval.
12.3 Pharmacokinetics		Revised description of the pharmacokinetics of umbralisib in patients with

	(b) (4)	cancer based on FDA review of the results of the various clinical pharmacology studies. Omitted (b) (4) Added description of meal as recommended in the Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format Guidance for Industry.
13. Nonclinical Toxicology		
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Carcinogenicity studies have not been conducted with umbralisib. (b) (4)	Edited the fertility information to reflect the study design and findings.
14. Clinical Studies	(b) (4)	Revised description of the study and population to align with current labeling. Deleted (b) (4) (b) (4) Removed (b) (4) (b) (4)

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		(b) (4)
16. How Supplied/Storage and Handling	(b) (4)	Removed (b) (4) (b) (4)
17. Patient Counseling Information		Edited to align with the remaining sections of labeling, including adding diarrhea, cutaneous reactions, thrombocytopenia, infertility, Yellow no 5, vomited doses, and modifying advice for contraception.

The Applicant's Position:

The final USPI for UKONIQ reflects several changes from the version originally submitted by the Applicant.

The FDA's Assessment:

The FDA made changes to several sections of the USPI as described above. Additionally, the Applicant proposed Patient Labeling; FDA determined that a Medication Guide would be required in place of the proposed Patient Labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

The FDA's Assessment:

The clinical review team and Division of Risk Management (DRISK) agree that a REMS is not necessary for the safe use of umbralisib. There are no additional risk management strategies needed beyond recommended labeling and an associated Medication Guide.

13 Postmarketing Requirements and Commitment

The FDA's Assessment:

The review team recommends five postmarketing requirements (PMR) and two postmarketing commitments (PMC). The goal of the postmarketing requirements are to confirm clinical benefit in patients with FL and MZL, determine a safe and appropriate dose in patients with moderate to severe hepatic impairment, characterize QTc prolongation risk with umbralisib, and evaluate drug-drug interactions. The postmarketing commitments are to provide information on racial and ethnic minorities consistent with the U.S. FL and MZL population and evaluate the PK of umbralisib with a strong CYP3A inducer.

Postmarketing Requirements

1. Conduct a randomized, Phase 3 clinical trial that verifies and describes the clinical benefit of umbralisib in patients with relapsed or refractory follicular lymphoma and marginal zone lymphoma. The trial should include sufficient numbers of racial and ethnic minority patients to better reflect the U.S. patient population and allow for interpretation of the results in these patient populations. Patients should be randomized to receive immunotherapy with or without umbralisib. The primary endpoint should be progression-free survival, with secondary endpoints that include overall survival and objective response rate

Final Protocol Submission:	06/2021
Trial Completion:	12/2026
Final Report Submission:	06/2027

2. Conduct a clinical pharmacokinetic study to determine a safe and appropriate dose of umbralisib in patients with moderate to severe hepatic impairment. Design and conduct the study in accordance with the FDA Guidance for Industry titled [Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	09/2021
Trial Completion:	03/2024
Final Report Submission:	09/2024

3. Conduct a clinical study to characterize QTc prolongation risk with umbralisib at steady-state maximal concentrations. The QT study can be conducted as a dedicated study or as a sub-study of ongoing trials. Design and conduct the QT study in accordance with

the ICH E14 Guidances for industry titled [E14 Clinical Evaluation of QT/QTc](#) and [E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs Questions and Answers \(R3\) Guidance for Industry](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	06/2021
Study Completion:	12/2026
Final Report Submission:	06/2027

4. Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of umbralisib on the single dose pharmacokinetics of a sensitive CYP2C8, CYP2C9, CYP2C19, and CYP3A and P-gp substrate to address the potential for excessive drug toxicity. Design and conduct the study in accordance with the FDA Guidance for Industry entitled [Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	09/2021
Study Completion:	10/2024
Final Report Submission:	04/2025

5. Conduct a clinical pharmacokinetic study to evaluate the effect of repeat doses of a strong CYP3A and a moderate CYP2C9 inhibitor on the single dose pharmacokinetics of umbralisib to address the potential for excessive drug toxicity. Design and conduct the study in accordance with the FDA Guidance for Industry entitled [Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry](#).

Draft Protocol Submission:	06/2021
Final Protocol Submission:	09/2021
Study Completion:	12/2024
Final Report Submission:	06/2025

Postmarketing Commitment

6. Submit a final report containing data from clinical trials, post-marketing reports, compassionate use/expanded access program, real-world evidence, and other sources to further characterize the safety and efficacy of umbralisib monotherapy and in

combination with immunotherapy among U.S. racial and ethnic minority patients with follicular lymphoma or marginal zone lymphoma.

Final Report Submission: 06/2028

7. Conduct a clinical pharmacokinetic study with repeat doses of a strong CYP3A inducer on the single dose pharmacokinetics of umbralisib to assess the magnitude of decreased drug exposure and to determine appropriate dosing recommendations. Design and conduct the study in accordance with the FDA Guidance for Industry entitled [Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry.](#)

Draft Protocol Submission: 06/2021

Final Protocol Submission: 09/2021

Study Completion: 12/2023

Final Report Submission: 06/2024

14 Division Director (DHOT) (NME ONLY)

X

Haleh Saber, PhD, MS

15 Division Director (OCP)

X

Brian Booth, PhD

16 Division Director (DBIX)

X

Thomas Gwise, PhD

17 Division Director (Clinical)

X

Nicole Gormley, MD

18 Office Director (or designated signatory authority)

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

19 Appendices

19.1. References

- Brice P, Bastion Y, Lepage E, et al. Comparison in low-tumor-burden follicular lymphomas between an initial no-treatment policy, prednimustine, or interferon alfa: a randomized study from the Groupe d'Etude des Lymphomes Folliculaires. Groupe d'Etude des Lymphomes de l'Adulte. *Journal of Clinical Oncology*. 1997;15(3):1110-1117.
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- Maurer MJ, Bachy E, Ghesquieres H, et al. Early event status informs subsequent outcome in newly diagnosed follicular lymphoma. *American Journal of Hematology*. 2016;91(11):1096-1101.
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Rivas-Delgado A, Magnano L, Moreno-Velazquez M, et al. Response duration and survival shorten after each relapse in patients with follicular lymphoma treated in the rituximab era. Br J Haematol. 2019;184(5):753-759.

19.2. Financial Disclosure

The Applicant's Position:

Covered Clinical Study (Name and/or Number):* UTX-TGR-205

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>1592</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
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: <u>0</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in study: <u>1</u> Sponsor of covered study: <u>0</u>		
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) <u>0</u>		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

The FDA's Assessment:

The FDA agrees with the Applicant's position.

19.3. **Nonclinical Pharmacology/Toxicology**

The Applicant's Position:

No additional nonclinical data reviewed.

The FDA's Assessment:

Not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

The FDA's Assessment:

19.4.1. Summary of Bioanalytical Method Validation and Performance

Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Plasma, feces and urine concentrations or amount of umbralisib were measured in clinical pharmacology trials (TGR-1202-902, TGR-1202-PK101, TGR-1202-PK102, TGR-1202-908, TGR-1202-901, TGR-1202-904) and clinical trials (TGR-1202-101, UTX-TGR-205, TGR-1202-102). Based on results of human mass-balance Study TGR-1202-902, umbralisib is the predominant circulating moiety (79%) in plasma.

For all moieties measured, is free, bound, or total measured?

The total plasma or serum concentrations of umbralisib were measured in the clinical trials. The average binding of umbralisib is about 99.7-99.8%.

Bioanalytical methods

The bioanalytical method validations and performance for measurements of umbralisib concentrations in all clinical trials are summarized in Table 40 and Table 41 (plasma method MET126) and in Table 42 (serum method MET193v1). The plasma method was modified to provide an alternative assay range, i.e., from 1.00 – 2000 ng/mL to 10.0 – 10000 ng/mL. This change was partially validated and is summarized in Table 43.

Table 40: Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126)

Bioanalytical method validation report name, amendments, and hyperlinks	Analytical method and validation report for the determination of TGR-1202 (base) in human plasma by LC/MS/MS. Method report MET126 and Addendum 3 .		
Method description	The method used an analog internal standard, RP-5182. An aliquot of each plasma sample (100 µL) was added to internal standard solution in methanol (750 µL), mixed, and centrifuged. Supernatant was analyzed by LC-MS/MS. Analyte separation was performed with a Synergi Polar RP column with a mobile phase of 25:75 0.1% formic acid in water and acetonitrile run isocratically at a flow rate of 0.4 mL/min. Analytes were detected using an Applied Biosystems Sciex API-3000 triple quadrupole mass spectrometer using turbo ion spray in positive ionization mode.		
Materials used for standard calibration curve and concentration	Umbralisib tosylate, lot number: RP-5307/F/1905/45/PTSA. Stock solution: 1.0 mg/mL in methanol.		
Validated assay range	1.08 to 2029.85 ng/mL (and 10.00 to 10060.27 ng/mL [NEBA/STY202]; see Error! Reference source not found.). APPEARS THIS WAY ON ORIGINAL		
Material used for QCs & concentration	Umbralisib tosylate, lot number: RP-5307/F/1905/45/PTSA. Stock solution: 1.0 mg/mL in methanol.		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	Acetonitrile, HPLC grade (J.T.Baker, cat # 9012-03) Water, HPLC grade (Milli-Q® purified water prepared in-house) Formic Acid (Fisher, cat # A118p-500) Human Plasma, lot BRH647681, 682, & 683 (Bio-Reclamation, NY, cat# HMPLLIHP), anti-coagulant Li-heparin		
Regression model & weighting	Linear, weighted 1/x ²		
Validation parameters	Method validation summary		Source Location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	9	MET126, Table 3 , Table 4 , and Table 5
	Cumulative accuracy (%bias) from LLOQ to ULOQ umbralisib	NR (within run bias was -6.8% to 4.7%)	MET126, Table 3 , Table 4 , and Table 5

	Cumulative precision (%CV) from LLOQ to ULOQ umbralisib	NR	NA

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 4 QCs QCs umbralisib	-2.1% to 1.6%	MET126, Table 9
	Inter-batch %CV QCs umbralisib	≤4.7%	MET126, Table 9
	Total error (TE) QCs umbralisib	NR	NA
Selectivity & matrix effect	No interference (bias=2.7%) was observed at the retention time of umbralisib from 6 lots of blank matrix.		MET126, Table 15
Interference & specificity	NR		NA
Hemolysis effect	NR		NA
Lipemic effect	NR		NA
Dilution linearity & hook effect	4-fold dilution of 6238.53 ng/mL QC (bias=7.2%, CV=0.3%), Hook effect not applicable		MET126, Table 10
Bench-top/process stability	4 hours at room temperature umbralisib		MET126, Table 13
Freeze-thaw stability	3 cycles umbralisib		MET126, Table 12
Long-term storage	1145 days at -70°C and 33 days at -20°C umbralisib		MET126 Addendum 3, Table 2 and Table 3
Parallelism	NA umbralisib		NA
Carry over	Sample to sample carryover was evaluated by running a blank or wash after the highest standard and assessing the relative peak area of this blank versus the signal at LLOQ. Carryover was not observed at the retention time of umbralisib. umbralisib		MET126, Section 5.2

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-101 Bioanalytical report: TGR-1202-101 NEBA/STY202		
Assay passing rate	100%	STY202, Table 3
Standard curve performance	Cumulative bias range (calibrator set 1): -5.7% to 2.0% Cumulative bias range (calibrator set 2): -2.4% to 1.8% Cumulative bias range (calibrator set 3): -4.1% to 1.8% Cumulative bias range (calibrator set 4): -2.2% to 1.6% Cumulative precision (calibrator set 1): $\leq 4.6\%$ CV Cumulative precision (calibrator set 2): $\leq 7.0\%$ CV Cumulative precision (calibrator set 3): $\leq 7.7\%$ CV Cumulative precision (calibrator set 4): $\leq 6.1\%$ CV	STY202, Table 5
QC performance	Cumulative bias range (QC set 1): -7.6% to 2.4% Cumulative bias range (QC set 2): -2.0% to 1.6% Cumulative bias range (QC set 3): -2.1% to 2.4% Cumulative bias range (QC set 4): -1.8% to 6.9% Cumulative precision (QC set 1): $\leq 5.4\%$ CV Cumulative precision (QC set 2): $\leq 6.3\%$ CV Cumulative precision (QC set 3): $\leq 8.1\%$ CV Cumulative precision (QC set 4): $\leq 5.4\%$ CV TE: NA (LBA only)	STY202, Table 6
Method reproducibility	Incurring sample reanalysis was performed in approximately 11% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY202, Section 2.3 and Table 8
Study sample analysis/stability	All samples were analyzed within 216 days after collection (within established stability of 1145 days).	STY202, Section 4

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-102 Bioanalytical report: TGR-1202-102 NEBA/STY272, Amendment 1 and Amendment 2		
Assay passing rate	100%	STY272, Table 1
Standard curve performance	Cumulative bias range (calibrator set 1): -1.3% to 1.0% Cumulative bias range (calibrator set 2): -6.0% to 2.6% Cumulative bias range (calibrator set 3): -2.8% to 2.1% Cumulative bias range (calibrator set 4): -8.8% to 11.8% Cumulative bias range (calibrator set 5): -9.0% to 9.9% Cumulative precision (calibrator set 1): ≤11.9% CV Cumulative precision (calibrator set 2): ≤6.9% CV Cumulative precision (calibrator set 3): ≤5.9% CV Cumulative precision (calibrator set 4): ≤11.6% CV Cumulative precision (calibrator set 5): ≤4.0% CV	STY272, Table 12 , Table 13 , Table 14 , Table 15 , and Table 16 , and Amendment 2, Table 1
QC performance	Cumulative bias range (QC set 1): -4.4% to -0.5% Cumulative bias range (QC set 2): -9.5% to 4.1% Cumulative bias range (QC set 3): -1.8% to 6.3% Cumulative bias range (QC set 4): -1.2% to 2.6% Cumulative bias range (QC set 5): 1.9% to 9.8% Cumulative precision (QC set 1): ≤10.7% CV Cumulative precision (QC set 2): ≤5.8% CV Cumulative precision (QC set 3): ≤7.2% CV Cumulative precision (QC set 4): ≤7.0% CV Cumulative precision (QC set 5): ≤9.5% CV TE: NA (LBA only)	STY272, Table 18 , Table 19 , Table 20 , Table 21 , and Table 22 , and Amendment 1, Table 1
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of non-zero study samples and 92% were within ±20% of the original result.	STY272, Table 25
Study sample analysis/stability	All samples were analyzed within 440 days after collection (within established stability of 1145 days).	STY272, Section 4

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-PK101 Bioanalytical report: TGR-1202-PK101 NEBA/STY219		
Assay passing rate	100%	STY219, Table 3
Standard curve performance	Cumulative bias range: -4.6% to 2.5% Cumulative precision: $\leq 7.2\%$ CV	STY219, Table 5
QC performance	Cumulative bias range: -4.1% to 0.3% Cumulative precision: $\leq 3.6\%$ CV TE: NA (LBA only)	STY219, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 11% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY219, Table 8
Study sample analysis/stability	All samples were analyzed within 37 days after collection (within established stability of 1145 days).	STY219, Section 4
Method performance in Study TGR-1202-PK102 Bioanalytical report: TGR-1202-PK102 NEBA/STY221		
Assay passing rate	100%	STY221, Table 3
Standard curve performance	Cumulative bias range: -5.4% to 2.5% Cumulative precision: $\leq 6.6\%$ CV	STY221, Table 5
QC performance	Cumulative bias range: -3.6% to 2.1% Cumulative precision: $\leq 4.3\%$ CV TE: NA (LBA only)	STY221, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 11% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY221, Table 8
Study sample analysis/stability	All samples were analyzed within 29 days after collection (within established stability of 1145 days).	STY221, Section 4
Method performance in Study TGR-1202-901 Bioanalytical report: TGR-1202-901 NEBA/STY341		
Assay passing rate	100%	STY341, Table 3
Standard curve performance	Cumulative bias range: -4.2% to 3.7% Cumulative precision: $\leq 5.4\%$ CV	STY341, Table 5
QC performance	Cumulative bias range: -0.4% to 2.7% Cumulative precision: $\leq 3.0\%$ CV TE: NA (LBA only)	STY341, Table 6

Method reproducibility	Not required	NA
Study sample analysis/stability	All samples were analyzed within 14 days after collection (within established stability of 1145 days).	STY341, Section 4

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study TGR-1202-904 Bioanalytical report: TGR-1202-904 NEBA/STY367		
Assay passing rate	100%	STY367, Table 3
Standard curve performance	Cumulative bias range: -10.5% to 5.4% Cumulative precision: $\leq 4.9\%$ CV	STY367, Table 5
QC performance	Cumulative bias range: -1.2% to 8.4% Cumulative precision: $\leq 8.0\%$ CV TE: NA (LBA only)	STY367, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY367, Table 8
Study sample analysis/stability	All samples were analyzed within 67 days after collection (within established stability of 1145 days).	STY367, Section 4
Method performance in Study TGR-1202-908 Bioanalytical report: TGR-1202-908 NEBA/STY371		
Assay passing rate	100%	STY371, Table 3
Standard curve performance	Cumulative bias range: -8.7% to 4.0% Cumulative precision: $\leq 7.8\%$ CV	STY371, Table 5
QC performance	Cumulative bias range: 1.1% to 5.5% Cumulative precision: $\leq 7.0\%$ CV TE: NA (LBA only)	STY371, Table 6
Method reproducibility	Incurred sample reanalysis was performed in 10.1% of non-zero study samples and 97% were within $\pm 20\%$ of the original result.	STY371, Table 8
Study sample analysis/stability	All samples were analyzed within 41 days after collection (within established stability of 1145 days).	STY371, Section 4
Method performance in Study UTX-TGR-205 Bioanalytical report: UTX-TGR-205 NEBA/STY360		
Assay passing rate	100%	STY360, Table 1
Standard curve performance	Cumulative bias range: -7.3% to 4.0% Cumulative precision: $\leq 10.6\%$ CV	STY360, Table 7

QC performance	Cumulative bias range: 8.4% to 11.8% Cumulative precision: $\leq 7.0\%$ CV TE: NA (LBA only)	STY360, Table 9
Method reproducibility	Incurred sample reanalysis was performed in 10.7% of non-zero study samples and 100% were within $\pm 20\%$ of the original result.	STY360, Table 13
Study sample analysis/stability	All samples were analyzed within 827 days after collection (within established stability of 1145 days).	STY360, Section 3

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Plasma (Method MET126) - Continued

Method performance in Study UTX-TGR-205 (extra samples) Bioanalytical report: UTX-TGR-205 NEBA/STY360 ADD-1		
Assay passing rate	67%	STY360 ADD-1, Table 1
Standard curve performance	Cumulative bias range: -6.8% to 5.8% Cumulative precision: $\leq 9.5\%$ CV	STY360 ADD-1, Table 3
QC performance	Cumulative bias range: 3.5% to 12.9% Cumulative precision: $\leq 9.1\%$ CV TE: NA (LBA only)	STY360 ADD-1, Table 6
Method reproducibility	Not performed.	NA
Study sample analysis/stability	All samples were analyzed within 1140 days after collection (within established stability of 1145 days).	STY360 ADD-1, Section 3

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; HPLC=high performance liquid chromatography; LBA=ligand binding assay; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LLOQ=lower limit of quantification; MRD=minimum required dilution; NA=not applicable; NR=not reported; QC=quality control; TE=total error; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

Table 41: Summary of Method Modification and Partial Validation Results (Method MET126, Reported in TGR-1201-101 NEBA/STY202)

Bioanalytical method validation report name and hyperlinks	The partial validation of the determination of umbralisib in human plasma is reported in the bioanalytical report for Study TGR-1202-101 (NEBA/STY202): Bioanalytical report for the analysis of TGR-1202 in human plasma (protocol HEMREF31/TGR-1202-101) Report: NEBA/STY202, Section 6.1.3		
Changes in method	The existing validated method (MET126 [Error! Not a valid result for table.]) had a range of approximately 1.00 to 2000 ng/mL. A new range of approximately 10.0 to 10000 ng/mL was implemented for the analysis of clinical samples with high concentrations of umbralisib.		
New validated assay range if any	10.00 to 10060.27 ng/mL		
Validation parameters	Partial validation performance		Source location
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	NR	NA
	Cumulative precision (%CV) from LLOQ to ULOQ	NR	NA
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 4 QCs</u>	-5.6% to 8.9%	STY202, Section 6.1.3
	<u>Inter-batch %CV</u>	≤11.6%	STY202, Section 6.1.3
	<u>Percent total error (TE)</u>	NR	NA
Cross-validation	NA		NA
List other parameters	NA		NA

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; LLOQ=lower limit of quantification; NA=not applicable; NR=not reported;
QC=quality control; TE=total error; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

Table 42: Summary Method Performance for the Determination of Umbralisib Concentrations in Human Serum (Method MET193)

Bioanalytical method validation report name, amendments, and hyperlinks	Analytical method and validation report for determination of TGR-1202 in human serum by LC/MS/MS. Method report MET193 and Addendum 1 .		
Method description	The method used an analogue internal standard, RP-5182. An aliquot of each serum sample (100 µL) was added to internal standard solution in methanol (750 µL), mixed, and centrifuged. Supernatant was analyzed by LC-MS/MS. Analyte separation was performed with a Phenomenex Synergi Polar RP column with a mobile phase of 25:75 0.1% formic acid in water and acetonitrile run isocratically at a flow rate of 0.4 mL/min. Analytes were detected using an Applied Biosystems Sciex API-3000 triple quadrupole mass spectrometer using turbo ion spray in positive ionization mode.		
Materials used for standard calibration curve & concentration	Umbralisib, lot number: TGR-21506. Stock solution: 1.0 mg/mL in methanol.		
Validated assay range	10.69 to 10175.95 ng/mL		
Material used for QCs & concentration	Umbralisib, lot number: TGR-21506. Stock solution: 1.0 mg/mL in methanol.		
Minimum required dilutions (MRDs)	NA		
Source & lot of reagents (LBA)	Acetonitrile HPLC Grade Methanol HPLC Grade HPLC grade Water Formic acid, 88% Human Serum, Source: Bioreclamation Inc.		
Regression model & weighting	Linear, weighted 1/x ²		
Validation parameters	Method validation summary		Source Location
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	9	MET193, Table 3 , Table 4 , and Table 5
	Cumulative accuracy (%bias) from LLOQ to ULOQ umbralisib	NR (within run bias was -12.9% to 10.6%)	MET193, Table 3 , Table 4 , and Table 5

	Cumulative precision (%CV) from LLOQ to ULOQ umbralisib	NR	NA

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Serum (Method MET193) - Continued

QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 4 QCs</u> QCs umbralisib	-10.6% to 2.0%	MET193, Table 9
	<u>Inter-batch %CV</u> QCs umbralisib	≤7.1%	MET193, Table 9
	<u>Total error</u> QCs umbralisib	NR	NA
Selectivity & matrix effect	No interference (bias=12.6%) was observed at the retention time of umbralisib from 6 lots of blank matrix.		MET193, Table 15
Interference & specificity	NR		NA
Hemolysis effect	NR		NA
Lipemic effect	NR		NA
Dilution linearity & hook effect	4-fold dilution of 33822.58 ng/mL QC (Bias=-10.4%, CV=2.2%), Hook effect not applicable		MET193, Table 11
Bench-top/process stability	6 hours at room temperature umbralisib		MET193, Table 16
Freeze-thaw stability	3 cycles umbralisib		MET193, Table 15
Long-term storage	301 days at -70°C and 27 days at -20°C (Further long-term stability testing is ongoing) umbralisib		MET193 Addendum 1, Table 1 and Table 2
Parallelism	NA umbralisib		NA
Carry over	Sample to sample carryover was evaluated by running a blank or rinse after the highest standard of each analyte and assessing the relative peak height of this blank versus the signal at LLOQ. In the six instances from 3 batches the carryover was less than 15% of the LLOQ. umbralisib		MET193, Section 5.4.3

Summary Method Performance for the Determination of Umbralisib Concentrations in Human Serum (Method MET193) - Continued

Method performance in Study UTX-TGR-205 Bioanalytical report: UTX-TGR-205 NEBA/STY360		
Assay passing rate	100%	STY360, Table 1
Standard curve performance	Cumulative bias range: -2.7% to 1.7% Cumulative precision: $\leq 5.5\%$ CV	STY360, Table 8
QC performance	Cumulative bias range: -8.4% to 0.1% Cumulative precision: $\leq 7.6\%$ CV TE: NA (LBA only)	STY360, Table 10
Method reproducibility	Incurred sample reanalysis was performed in 10.2% of non-zero study samples and 95% were within $\pm 20\%$ of the original result.	STY360, Table 14
Study sample analysis/stability	All samples were analyzed within 808 days after collection (further long-term stability testing is ongoing [currently established for 301 days]).	STY360, Section 3
Method performance in Study UTX-TGR-205 (extra samples) Bioanalytical report: UTX-TGR-205 NEBA/STY360 ADD-1		
Assay passing rate	75%	STY360 ADD-1, Table 1
Standard curve performance	Cumulative bias range: -4.1% to 4.6% Cumulative precision: $\leq 9.5\%$ CV	STY360 ADD-1, Table 4
QC performance	Cumulative bias range: -12.3% to -4.2% Cumulative precision: $\leq 17.0\%$ CV TE: NA (LBA only)	STY360 ADD-1, Table 6
Method reproducibility	Not performed.	NA
Study sample analysis/stability	All samples were analyzed within 1142 days after collection (further long-term stability testing is ongoing [currently established for 301 days]).	STY360 ADD-1, Section 3

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; HPLC=high performance liquid chromatography; LBA=ligand binding assay; LC-MS/MS=liquid chromatography with tandem mass spectrometry; LLOQ=lower limit of quantification; MRD=minimum required dilution; NA=not applicable; NR=not reported; QC=quality control; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

Table 43: Summary of Method Modification and Cross-validation Results (Method MET126 Addendum 1)

Bioanalytical method validation report name and hyperlinks	Cross validation of TGR-1202 in human plasma and human serum. Method report MET126 Addendum 1 .		
Changes in method	Methods for the determination of umbralisib in human plasma (MET126) and for the determination of umbralisib in human serum (MET193) were fully validated. This cross validation was to demonstrate the equivalency of the 2 methods when human serum QC samples were quantified using a human plasma calibration curve.		
New validated assay range if any	9.72 to 10024.78 ng/mL (no change)		
Validation parameters	Cross-validation performance		Source Location
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	NR (within run bias was -10.2% to 12.5%)	MET126 Addendum 1, Table 1
	Cumulative precision (%CV) from LLOQ to ULOQ	NR	NA
QCs performance during accuracy & precision	<u>Cumulative accuracy (%bias) in 3 QCs</u>	-3.7% to 1.8%	MET126 Addendum 1, Table 2
	<u>Inter-batch %CV</u>	≤11.3%	MET126 Addendum 1, Table 2
	<u>Percent total error (TE)</u>	NR	NA
Cross-validation	Acceptable results obtained from serum QCs analyzed using a plasma calibration curve.		NA
List other parameters	NA		NA

Source: As detailed in the source location column in the table.

Abbreviations: CV=coefficient of variation; LLOQ=lower limit of quantification; NA=not applicable; NR=not reported; QC=quality control; TGR-1202=umbralisib; ULOQ=upper limit of quantification.

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There were 6 PK samples that had concentration measurements for both plasma and serum matrices (**Error! Reference source not found.**). Using the standard acceptance criteria for incurred sample reproducibility (within $\pm 20\%$), 4 of the 6 samples met the acceptance criteria. The results suggest that there appears to be no difference in the concentrations determined in the two matrices although the sample size is small.

Table 44: Umbralisib Concentrations in Plasma and Serum at the Same Nominal Timepoint (Study UTX-TGR-205)

Subject	Nominal Timepoint	Concentration, ng/mL		Deviation, %
		Plasma	Serum	
(b) (6)	Cycle 2, predose	4470	3890	-14.9
	Cycle 3, predose	8790	7460	-17.8
	Cycle 6, predose	8240	8010	-2.9
	Cycle 1, predose	<LLOQ	<LLOQ	0
	Cycle 2, predose	4690	3710	-26.4
	Cycle 2, pre-dose	11200	<LLOQ	ND
Count				6
Failure count (>20% deviation)				2
Mean deviation, %				-15.5
Minimum, %				-26.4
Maximum, %				-2.9

Source: Addendum-1 to Study NEBA/STY360, [Table 7](#) and [Table 8](#).

Abbreviations: LLOQ=lower limit of quantification; ND = not determinable.

Of note: Except for Subject (b) (6), the average of the plasma and serum concentrations at the same timepoint was used in the PPK analysis.

19.4.2. Pharmacometrics Review

A population pharmacokinetics (PPK) model was developed by the Applicant to characterize the PK of umbralisib in patients with select hematologic malignancies, previously treated indolent NHL, MCL, or DLBCL and healthy subjects. Subjects intrinsic and extrinsic factors which influence the PK and PK variability of umbralisib were identified. Individual umbralisib exposure metrics were generated for subsequent exposure-response (E-R) analyses for efficacy and safety. In this review, the FDA Pharmacometrics Reviewer validated the Applicant's PPK model and E-R analyses for both efficacy and safety.

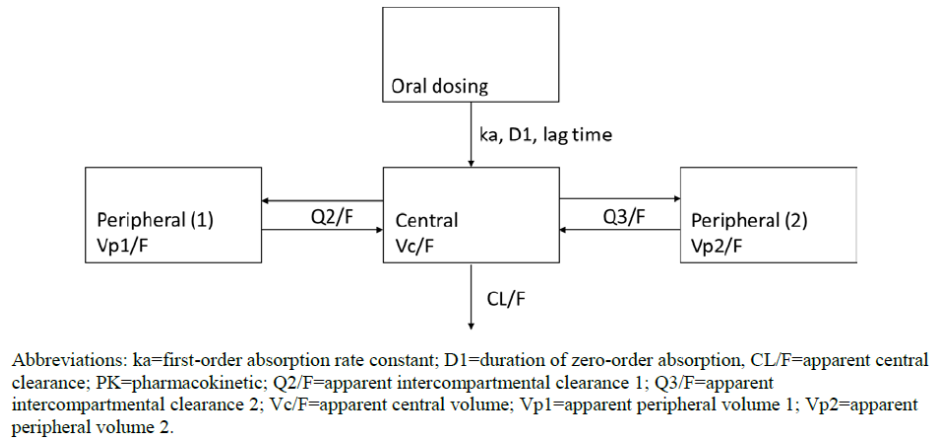
1. Population PK analyses

Three clinical trials were included in the PPK analyses: Study 101, 205 and 1102. Total of 2014 PK samples collected from 247 subjects across the three studies were included in the final population PK analysis. Concentration range for the analysis was from 1.08 to 16061.5 ng/mL. In Study 101, the subjects with select hematologic malignancies were administrated with (b) (4) umbralisib with the dose range of 50 to 1800 mg QD under fasted or fed condition. In Study 205, the subjects with previously treated indolent NHL, MCL or DLBCL were administrated with (b) (4) umbralisib at the dose level of 800 mg QD under fed condition. In Study 1102, the healthy subjects were administrated with (b) (4) umbralisib at the dose level of 200 mg QD under fasted condition.

The intrinsic and extrinsic factors of healthy subjects versus subjects with hematological malignancies, disease type (MZL vs FL vs others), age, baseline body weight (BW), sex race (White vs non-White), hepatic function, renal function, and coadministration of strong cytochrome P450 (CYP) 3A inhibitors, strong CYP3A inducers, or acid-reducing agents (ARAs) were evaluated.

The PK of umbralisib following oral administration was adequately described by a three-compartment disposition model with combined first- and zero-order absorption (**Figure 5**).

Figure 5: Structure of the PK Model for Umbralisib



Source: Applicant's population PK and E-R study report

The equations for the final model are presented as below:

$$CL/F \text{ (L/h)} = 15.5 \times e^{\eta_{CL}}$$

$$Vc/F \text{ (L)} = 312 \times e^{\eta_{Vc}} \times (0.205 \text{ if healthy subject})$$

$$F = 1 \times (0.702 \text{ if in Study 1102}) \times (1.41 \text{ if in Study 205}) \times (1.93 \text{ if DP containing (b) (4) DS}) \times (1.38 \text{ if fed condition with DP containing (b) (4) DS in Study 101})$$

The PK parameter estimates of the final model are presented in the table below.

Table 45: Parameters of the Final Umbralisib PPK Model

Parameter	Estimate	BSV ^a (CV%)	Shrinkage ^b (%)	Bootstrap (N=1000)		
				Median	2.5% CI	97.5% CI
Fixed effect						
Duration of zero-order absorption, D1 (h)	2.02	-	-	2.02	1.25	2.27
First-order absorption rate, ka (1/h)	0.404	-	-	0.409	0.325	0.473
Apparent clearance, CL/F (L/h)	15.5	51.9	8.78	15.4	13.5	17.6
Apparent central volume, Vc/F (L)	312	185	36.7	311	215	446
Apparent intercompartmental clearance 1, Q2/F (L/h)	151	-	-	150	125	184
Apparent peripheral volume 1, Vp1/F (L)	1990	-	-	1990	1630	2390
Apparent intercompartmental clearance 2, Q3/F (L/h)	9.88	-	-	9.93	6.24	15.1

Parameter	Estimate	BSV ^a (CV%)	Shrinkage ^b (%)	Bootstrap (N=1000)		
				Median	2.5% CI	97.5% CI
Apparent peripheral volume 2, Vp2/F (L)	2300	-	-	2390	1570	3704
Absorption lag time, Tlag ^c (h)	0.208	-	-	0.208	0.208	0.208
Covariate effect						
Study 1102 on residual error	0.763	-	-	0.753	0.645	0.864
Study 205 on residual error	0.497	-	-	0.492	0.389	0.606
Study 1102 on F	0.702	-	-	0.707	0.597	0.832
Study 205 on F	1.41	-	-	1.41	1.22	1.62
(b) (4) DS on F	1.93	-	-	1.94	1.80	2.09
Fed condition with (b) (4) DS in Study 101 on F	1.38	-	-	1.38	1.06	1.75
Reduction in Vc/F for healthy subjects	-0.795	-	-	-0.788	-0.873	-0.618
Residual error						
Proportional residual error (SD)	0.438	-	5.77	0.436	0.407	0.466
Others						
Covariance of CL/F and Vc/F ^d	0.006	-	-	0.003	-0.164	0.160
Half-life, t _{1/2} alpha (h)	1.10	-	-	-	-	-
Half-life, t _{1/2} beta (h)	59.5	-	-	-	-	-
Half-life, t _{1/2} gamma (h)	317	-	-	-	-	-

Abbreviations: BSV=between-subject variability; CI=confidence interval; CV%=percent coefficient of variation; DS=drug substance; F=relative oral bioavailability; (b) (4); SD=standard deviation; Tlag=absorption lag time; (b) (4) Vc/F=apparent central volume.

^a Estimates for random effects and BSV are presented in CV% and based on the estimated variances, calculated as $\sqrt{(\exp[\text{variance}^2] - 1) \times 100}$.

^b Shrinkage (%) is calculated as $100 \times (1 - \text{SD}[\text{ETA}]/\sqrt{[\text{variance}]})$.

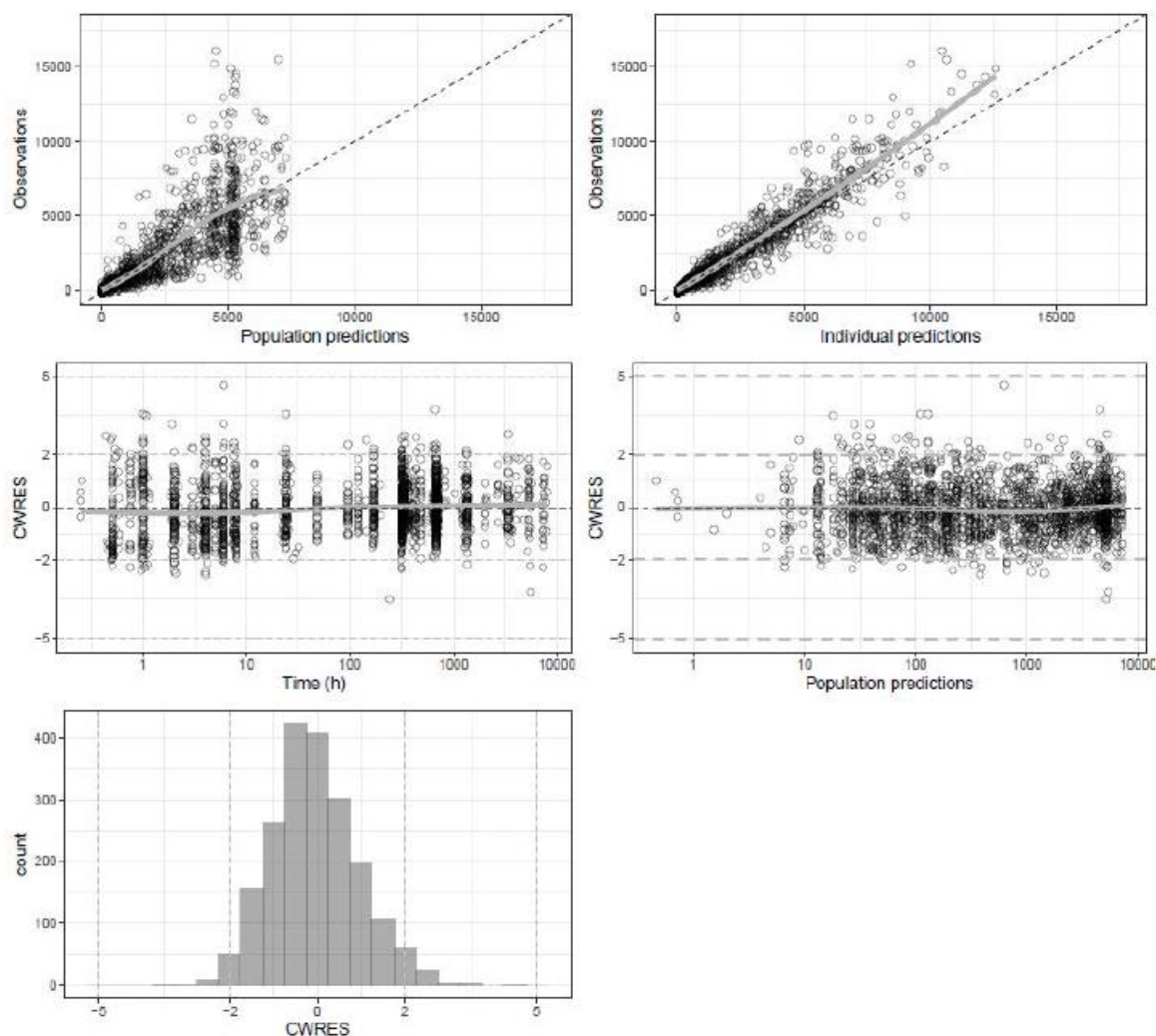
^c Tlag estimate was fixed during the final model development.

^d The correlation coefficient between CL/F and Vc/F was estimated as 0.968.

Source: Applicant's population PK and E-R study report

The goodness-of-fit (GOF) diagnostic plots and pcVPCs are shown in **Figure 6** and **Figure 7**.

Figure 6: GOF Diagnostics of the Umbralisib Final Model

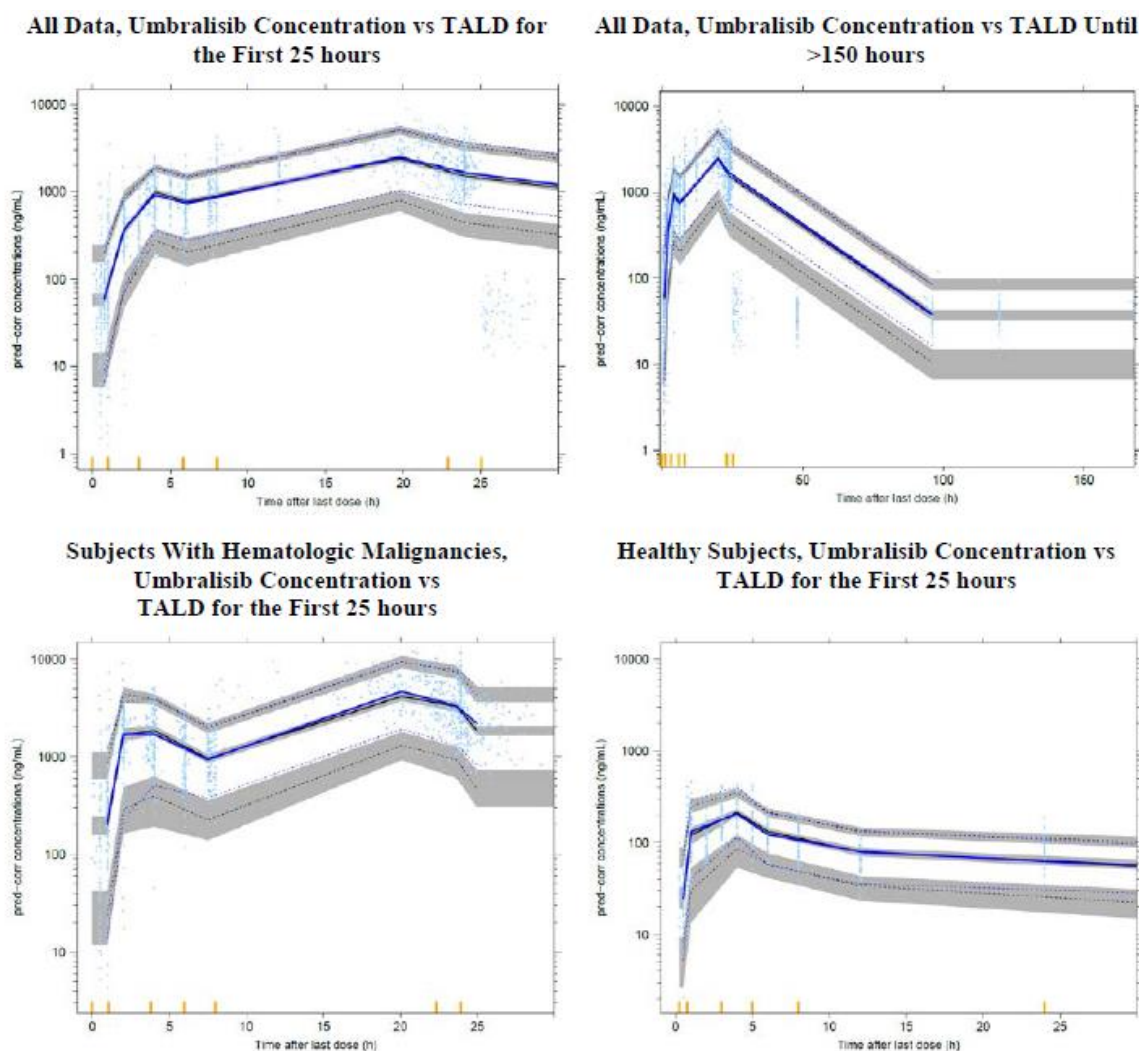


Abbreviations: CWRES=conditional weighted residuals; GOF=goodness-of-fit.

Note: Circles are individual data points, and solid gray lines are smoothed regression lines. In the CWRES versus time and population predictions, dashed black lines show the boundaries of the CWRES ± 2 and ± 5 intervals.

Source: Applicant's population PK and E-R study report

Figure 7: pcVPC for the Umbralisib Final Model



Abbreviations: pcVPC=prediction-corrected visual predictive check; PI=prediction interval; pred-con=prediction-corrected; TALD=time after last dose; vs=versus.

Note: Blue dots are prediction-corrected observed concentrations; blue lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of observed concentrations; and black lines are 50th (solid), 5th (dashed), and 95th (dashed) percentiles of simulations. Gray bands are 95% PI for corresponding black lines based on 500 simulations. Short yellow lines indicate bin intervals.

Source: Applicant's population PK and E-R study report

The Applicant evaluated the impact of concomitant acid reducing agents (ARAs) and strong CYP3A4 inhibitors using population PK analysis to support the labeling claim. For ARAs coadministration, the PPK analysis included 20 subjects who had quantifiable umbralisib concentrations during the period of co-administration of ARAs. Out of the 20 subjects, 6 subjects had intense PK and 14 subjects had sparse PK. For strong CYP3A4 inhibitors, 10 subjects were included in the PPK analysis. Out of the 10 subjects, 4 subjects had intense PK

and 6 subjects had sparse PK. As shown in **Table 46**, the change in objective function values (OFV) relative to the base model were all statistically non-significant ($p>0.01$). Thus, the Applicant determined that the use of concomitant strong CYP3A4 inhibitors and ARAs had no clinically meaningful impact on the PK of umbralisib.

Table 46: Results of Model Evaluation

Description	Run number	OFV	Δ OFV compared to run056
Base model	run056_6	23053.551	-
Including CYP3A4 effect on CL/F	run059_6	23053.347	-0.204
Including ARA effect on CL/F	run060_6	23053.491	-0.06
Including ARA effect on F*	run061_6	23047.497	-6.054
Including CYP3A4 effect on F*	run062_6	23053.504	-0.047

Abbreviations: ARA=acid-reducing agent; CL/F=apparent clearance; OFV=objective function value.

Source: Applicant's response to Clin Pharm IR

In addition, the Applicant assessed the impact of mild/moderate renal and mild hepatic impairment on the PK of umbralisib using the PPK analysis. As shown in **Table 47**, no statistically significant effects were detected for mild hepatic impairment (N=6), mild (N=121) and moderate (N=62) renal impairment on the PK of umbralisib.

Table 47: Model-predicted geometric mean (CV%) of umbralisib exposure metrics by subgroup following administration of 800 mg QD in MZL and FL populations

Parameters	Cmin C1 ng/mL GM (CV%)	Cminss ng/mL GM (CV%)	Cmax C1 ng/mL GM (CV%)	Cmaxss ng/mL GM (CV%)	AUC C1 ng·h/mL GM (CV%)	AUCss ng·h/mL GM (CV%)	Cavss ng/mL GM (CV%)
Hepatic function							
Normal (N=241)	443 (48.0)	3585 (73.3)	1417 (41.8)	5026 (56.3)	16181 (44.1)	97549 (67.3)	4065 (67.3)
Mild impairment (N=6)	499 (35.8)	4283 (84.3)	1441 (36.3)	5806 (62.1)	17440 (31.8)	115426 (75.9)	4809 (75.9)
Renal function							
Normal (N=64)	344 (57.6)	2631 (84.4)	1252 (46.9)	3946 (63.4)	13061 (51.9)	72665 (77.5)	3028 (77.5)
Mild impairment (N=121)	486 (41.0)	4114 (69.0)	1479 (40.5)	5593 (54.7)	17442 (38.8)	110990 (63.5)	4625 (63.5)
Moderate impairment (N=62)	486 (37.8)	3837 (56.1)	1482 (35.3)	5312 (42.1)	17560 (35.5)	104451 (50.9)	4352 (50.9)

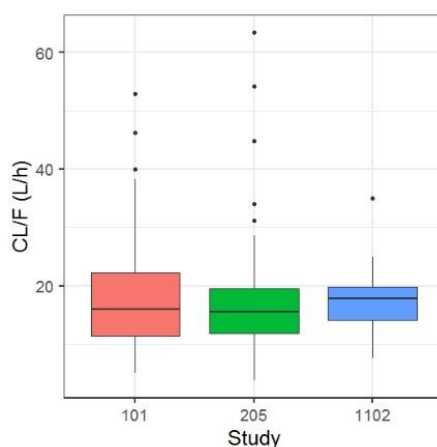
Source: adapted from Applicant's population PK report Table 4-14

The effects of severe renal impairment and moderate to severe hepatic impairment are not evaluated.

Reviewer's comment:

The Applicant's PPK analysis is acceptable for describing the PK of umbralisib in the healthy subjects and select hematologic malignancies patients. The CL of umbralisib estimated by the Applicant's PPK model across different studies are comparable (Figure 8).

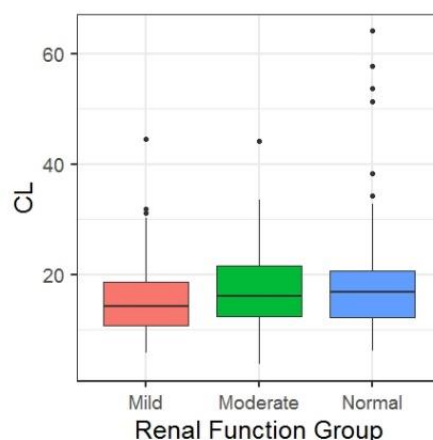
Figure 8: Clearance of umbralisib estimated by the final PPK model across different studies



Source: Reviewer's analysis

*The evaluations of the impact of mild/moderate renal impairment on the PK of umbralisib using PPK analysis appear to be reasonable. In the Applicant's PPK analysis for renal impairment, the renal function was categorized based on eGFR estimated by Modification of Diet in Renal Disease (MDRD). FDA Reviewer also evaluated the CL in different renal function groups categorized by creatinine clearance estimated by Cockcroft-Gault equation. As shown in **Figure 9**, the CL of umbralisib across different renal function groups based on creatinine clearance was comparable, further supporting (b) (4) that no dose adjustment would be needed for mild/moderate renal impairment subjects.*

Figure 9: Clearance of umbralisib across different renal function groups categorized by creatinine clearance estimated by Cockcroft-Gault equation



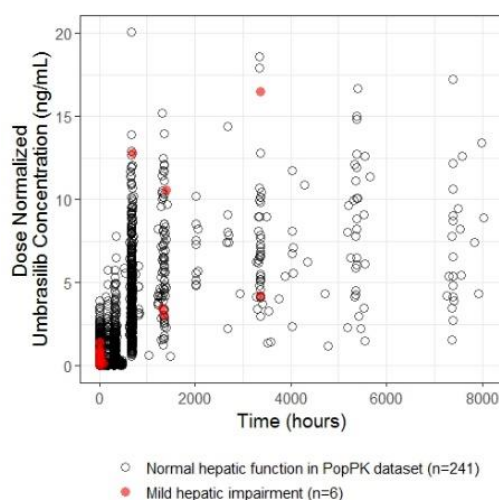
Note: normal renal function: ≥ 90 mL/min ($n=116$); mild renal impairment: 60 – 89 mL/min ($n=85$); moderate renal impairment: 30-59 mL/min ($n=46$).

Source: Reviewer's analysis

In the Applicant's evaluation of the impact of concomitant strong CYP3A4 inhibitors and acid reducing agents (ARAs), the frequency and dosing time of the co-administrated strong CYP3A4 inhibitors and ARAs were not clearly provided. In addition, out of the 10 subjects who were co-administrated with strong CYP3A4 inhibitors, only 4 of them had intense PK, while 6 subjects only had sparse PK of 1-3 PK samples; out of 20 subjects who were co-administrated with ARAs, only 5 of them had intense PK, while 14 subjects only had sparse PK of mostly 1-3 PK samples. Based on the limited PK data and information on the administration time of concomitant medications, the Applicant's proposal that no dose adjustment would be needed for concomitant administration of strong CYP3A4 inhibitors and ARAs based on PPK analysis is not acceptable. The Applicant conducted dedicated study (TGR-1202-904) to evaluate the effect of ARAs. The result from that study should be used as the primary evidence to make the conclusion for dose adjustment when ARAs are co-administrated.

*In the Applicant's evaluation of impact of mild hepatic impairment, only 6 patients with mild hepatic impairment were included. Out of the 6 patients, 4 of them had only 1 PK sample. Although the observed dose-normalized umbralisib concentrations from mild hepatic impairment patients were within the range of those from normal hepatic function patients (**Figure 10**), the available data were limited to conclude the effect of mild hepatic impairment on PK of umbralisib.*

Figure 10: Comparison of umbralisib observed concentrations between normal hepatic function and mild hepatic impairment patients



Source: Reviewer's analysis

2. Exposure-Efficacy Analyses in FL Population

The PPK and exposure-safety analyses were based on the pooled data from both MZL and FL populations. Thus, the review regarding PPK, exposure-safety analyses and integrated efficacy/safety analyses refers to the Appendix in the Assessment Aid for FL population. In the following pharmacometrics review, the Reviewer will discuss about the exposure-efficacy analyses for FL population.

Summary of the observed efficacy endpoints for the FL population in the E-R analyses for efficacy is shown in **Table 48**. Statistically significant relationships were observed for C_{minss} and ORR, TTR and best %CfB in target lesion dimensions. **Figure 11** shows the univariate E-R relationships for ORR and %CfB in target lesion dimensions in the FL population. From the multivariate exposure-efficacy analysis, at 800 mg QD, the model predicted ORR was 56.1% (90% CI: 46.2, 65.1) (**Table 49**), and the model predicted probability of best %CfB in target lesion dimensions was -47.3% (90% CI: -56.9, -38.4) (**Table 50**).

Table 48: Summary of observed endpoints in the exposure-efficacy dataset by dose group in FL population

Efficacy Endpoint	<800 mg QD	800 mg QD	>800 mg QD	Overall
ORR				
N	7	65	7	79
Count (%)	2 (28.6)	35 (53.8)	4 (57.1)	41 (51.9)
TTR (month)				
N	2	35	4	41
Median (90% CI)	27.8 (27.6, NE)	5.49 (4.40, 7.36)	3.80 (3.52, NE)	5.49 (4.40, 7.36)
DOR (month)				
N	2	35	4	41
Median (90% CI)	22.1 (NE, NE)	7.85 (5.62, 12.1)	NE (3.94, NE)	8.48 (7.03, 12.9)
PFS (month)				
N	7	65	7	79
Median (90% CI)	49.7 (26.4, NE)	15.5 (12.5, NE)	NE (7.73, NE)	15.5 (12.9, 16.4)
Best %CfB in target lesion dimensions				
N	7	65	7	79
Median (range [5th, 95th percentile])	-38.9 (-60.1, 91.9)	-56.2 (-100.0, 62.2)	-55.9 (-87.0, 18.6)	-55.8 (-100.0, 65.2)
Subjects with >50% decrease, count (%)	2 (28.6)	38 (58.5)	4 (57.1)	44 (55.7)

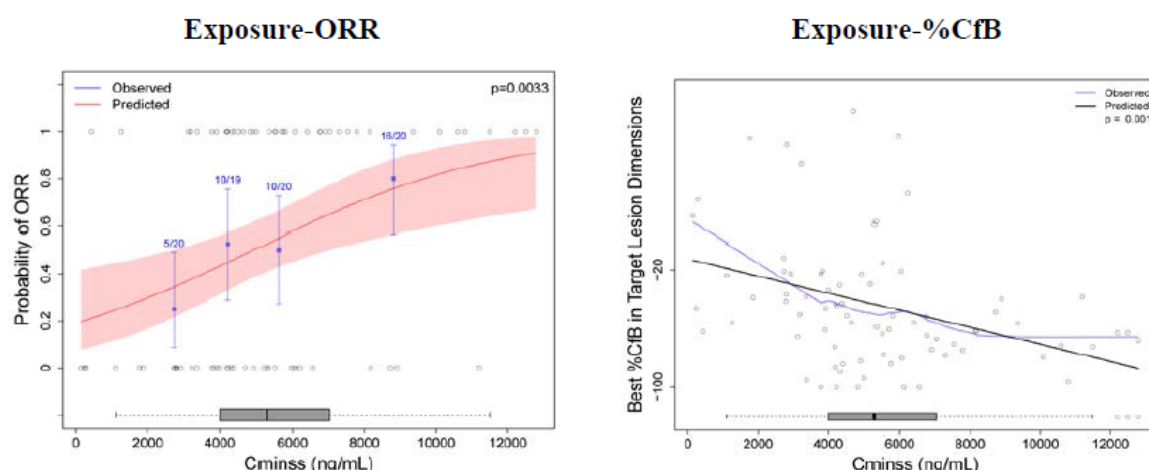
Abbreviations: %CfB=percent change from baseline; CI=confidence interval; DOR=duration of response; NE=not evaluable; ORR=objective response rate; PFS=progression-free survival; QD=once daily; TTR=time to response.

Note: All subjects had PFS data. Missing records for ORR and best %CfB in target lesion dimensions are reflected in N. For ORR, values reflect the count and percentage of subjects in the analysis set. For TTR and DOR, values reflect the median value determined using Kaplan-Meier analysis and 90% CI in those subjects who experienced ORR.

Source: Applicant's population PK and PK/PD study report

The Applicant also conducted multivariate analysis for ORR, TTR and %CfB in target lesion dimensions. The results showed that in addition to exposures, subjects with ECOG score ≥ 1 have significantly reduced probability of ORR; non-White subjects have significantly increased probability of achieving TTR of 5 months; subjects with ECOG score ≥ 1 have reduced response relative to the typical subject with ECOG score=0.

Figure 11: Relationships between exposure-ORR and exposure-%CfB responses in FL population



Abbreviations: %CfB=percent change from baseline; Cminss=minimum concentration at steady state; FL=follicular lymphoma; ORR=objective response rate

Note: Horizontal boxplot below shows the exposure distribution for the 800 mg dose group. The p-value is for the slope of the logistic (left panel) or linear (right panel) fit.

Source: Applicant's population PK and PK/PD study report

Table 49: Model predicted ORR by dose group in FL population

Umbralisib Dose (mg QD)	Model-Predicted Mean ORR (%) Estimate (90% CI)
400	37.4 (26.6, 50.5)
600	47.1 (37.2, 57.2)
800	56.1 (46.2, 65.1)
1000	64.0 (53.1, 73.0)
1200	70.7 (58.2, 79.7)

Abbreviations: CI=confidence interval; Cminss=minimum concentration at steady state; FL=follicular lymphoma; ORR=objective response rate; QD=once daily.

Note: Simulations were based on all subjects in the exposure-ORR analysis set and used subject-specific exposures. The 90% CI was based on model uncertainty and exposure variability.

Source: Applicant's population PK and PK/PD study report

Table 50: Model predicted %CfB in target lesion dimensions by dose group in FL population

Umbralisib Dose (mg QD)	Model-Predicted Mean %CfB Estimate (90% CI)
400	-30.5 (-41.2, -19.6)
600	-38.9 (-47.9, -29.9)
800	-47.3 (-56.9, -38.4)
1000	-55.7 (-68, -44.7)
1200	-64.1 (-79.7, -50.2)

Abbreviations: %CfB=percent change from baseline in target lesion dimensions; CI=confidence interval;
FL=follicular lymphoma; QD=once daily.

Note: Simulations were based on all subjects in the exposure-%CfB analysis set and used subject-specific exposures.
The 90% CI was based on model uncertainty and exposure variability.

Source: Applicant's population PK and PK/PD study report

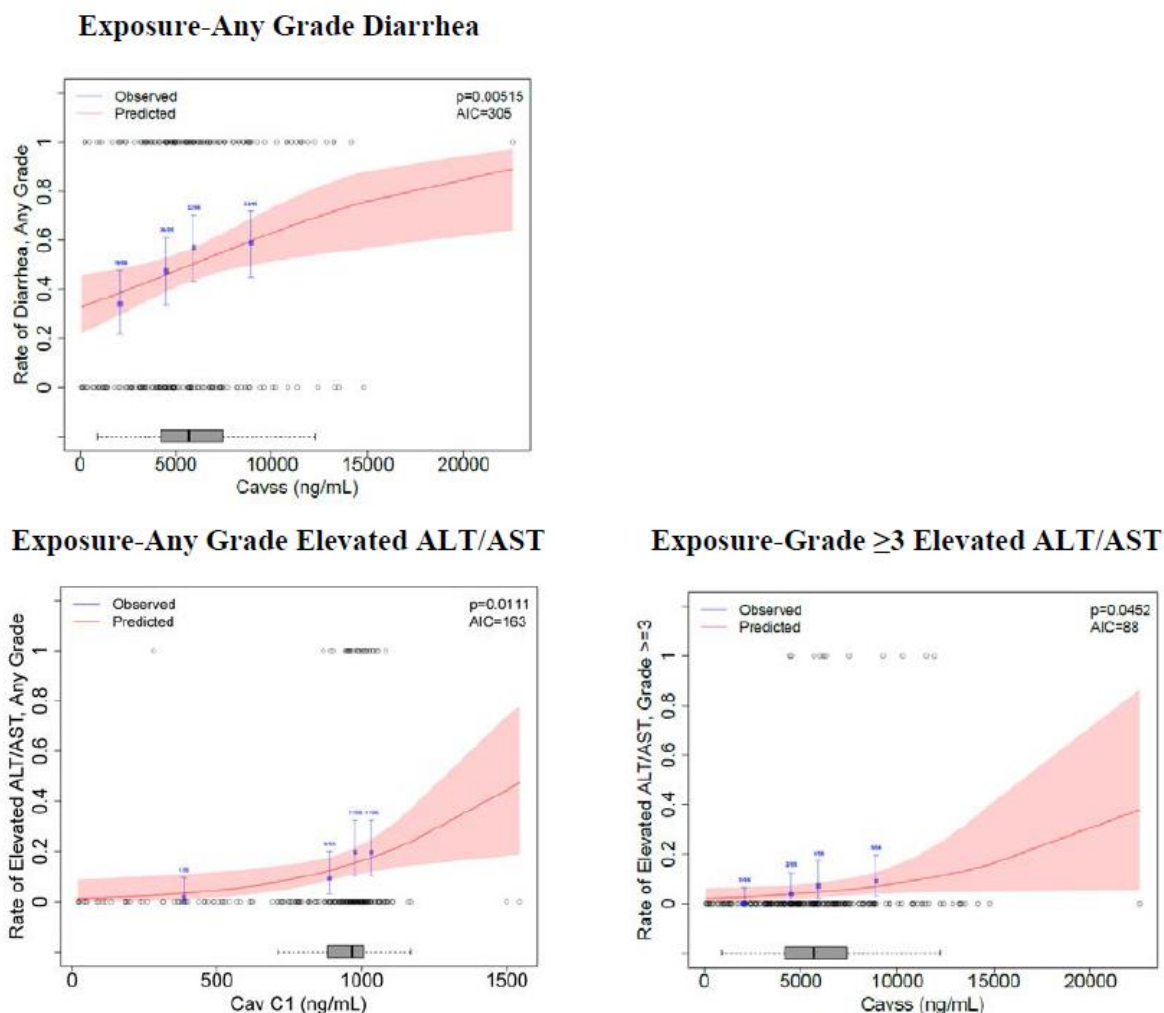
Reviewer's comments:

The Applicant's E-R analyses for efficacy are acceptable. The positive E-R relationships for ORR and %CfB in FL population indicated that higher dose than the recommended 800 mg will provide better efficacy. However, this interpretation is limited as only a small number of patients received doses other than 800 mg QD.

3. E-R Analyses for Safety

The exposure-safety dataset included 223 subjects (N=83 from Study 101 and N=140 from Study 205). Of the safety-endpoints evaluated, the AESI with an incidence rate $\geq 10\%$ were diarrhea, elevated ALT/AST, rash, neutropenia, pneumonia, and anemia. Among these AESI, only diarrhea (any grade) and elevated ALT/AST (any grade and Grade ≥ 3) were statistically correlated with umbralisib exposure (**Figure 12**).

Figure 12: Relationships between exposure and diarrhea or elevated ALT/AST



Abbreviations: AIC=Akaike information criterion; ALT=alanine aminotransferase; AST=aspartate aminotransferase; Cav C1=Cycle 1, Day 1 average concentration; Cavss=average concentration at steady state. Note: Horizontal boxplot below shows the exposure distribution for the 800 mg dose group. The p-value is for the slope of the logistic regression fit.

Source: Applicant's population PK and PK/PD study report

For any grade diarrhea, following the covariate analysis, a statistically significant effect of sex on the intercept of the relationship was identified and retained in the final model. For C_{avg} -any grade elevated ALT/AST, following the covariate analysis, statistically significant effects of ECOG and MZL on the slope of the relationship were identified and retained in the final model. No E-R relationships were identified for any grade rash, neutropenia, anemia, thrombocytopenia and pneumonia.

Reviewer's comment:

The Applicant's E-R analyses for safety are acceptable. The positive E-R relationships for diarrhea and elevated ALT/AST indicated that increasing the dose in MZL/FL population may lead to higher incidence of adverse events.

4. Integrated E-R Analyses

The Applicant conducted simulation to predict the probability of key efficacy and safety endpoint rates for doses ranging from 400 to 1200 mg QD in MZL and FL populations (**Table 51**). For exposure-efficacy analysis for FL population, detail refers to Pharmacometrics Review in Appendix in FL Assessment Aid. **Figure 13** shows the relative change in event rates relative to the 800 mg QD dose.

For MZL population, similar ORR was projected at different doses, higher rates of diarrhea and ALT/AST elevation were predicted at higher doses. For FL population, there was a substantial reduction in ORR and tumor shrinkage projected at doses lower than 800 mg QD. On the other hand, any grade and Grade ≥ 3 diarrhea was projected to modestly increase by $<30\%$, while any grade and Grade ≥ 3 elevated ALT/AST were projected to increase by 62% and 32% for the 1000 mg QD dose, and by 131% and 72% for the 1200 mg QD dose.

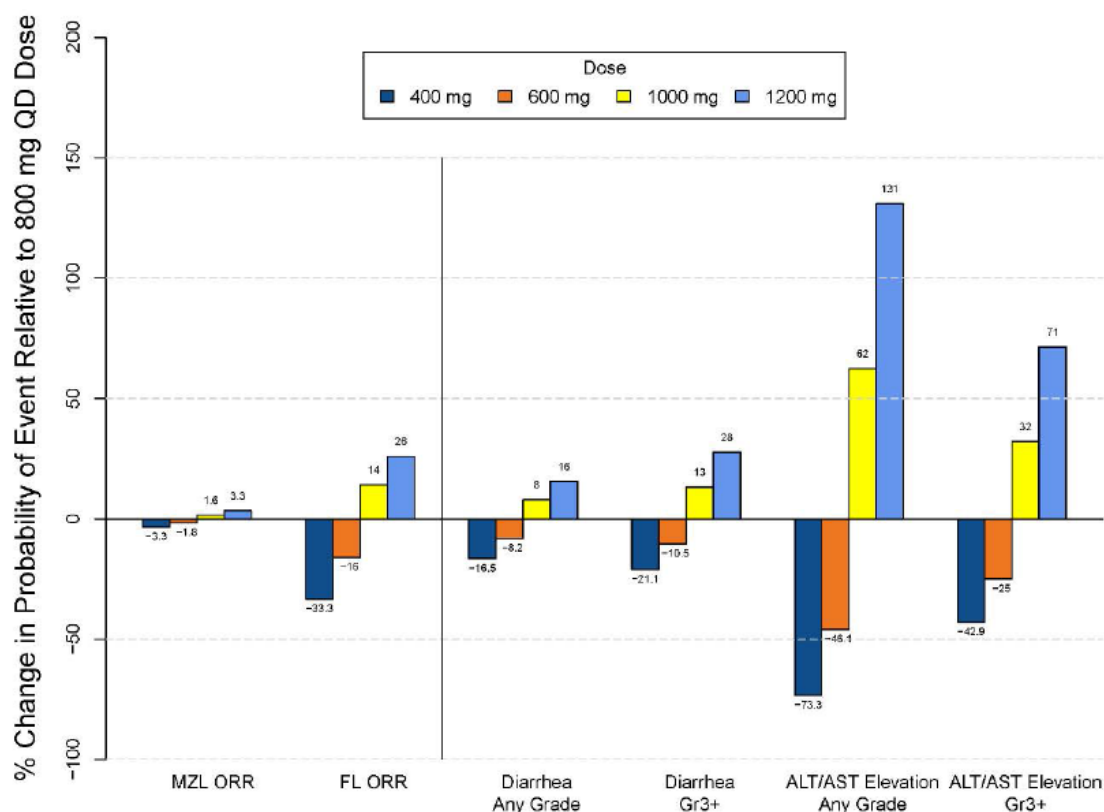
Table 51: Model-projected probabilities of key efficacy and safety endpoints by dose group

Umbralisib Dose (mg QD)	Model-Predicted Rate (%) Estimate (90% CI)					
	ORR-MZL	ORR-FL	Diarrhea Any Grade	Diarrhea Grade ≥ 3	Elevated ALT/AST Any Grade	Elevated ALT/AST Grade ≥ 3
400	55.0 (35.8, 73.1)	37.4 (26.6, 50.5)	43.9 (37.1, 51.2)	6.0 (3.5, 10.3)	4.4 (1.6, 12)	3.2 (1.6, 6.5)
600	55.9 (41.1, 70.1)	47.1 (37.2, 57.2)	48.3 (42.5, 54.1)	6.8 (4.4, 10.6)	8.9 (5.3, 14.9)	4.2 (2.5, 7.4)
800	56.9 (43.2, 69.8)	56.1 (46.2, 65.1)	52.6 (46.4, 58.2)	7.6 (5.1, 11.9)	16.5 (12.3, 22.2)	5.6 (3.4, 9.5)
1000	57.8 (41.5, 71.6)	64.0 (53.1, 73.0)	56.8 (49.1, 63.3)	8.6 (5.4, 14.6)	26.8 (17.7, 39.6)	7.4 (4.3, 13.1)
1200	58.8 (37.9, 74.7)	70.7 (58.2, 79.7)	60.8 (51.3, 68.3)	9.7 (5.3, 18.3)	38.1 (21, 59.3)	9.6 (4.9, 18.3)

Abbreviations: ALT=alanine transaminase; AST=aspartate transaminase; CI=confidence interval; FL=follicular lymphoma; MZL=marginal zone lymphoma; ORR=objective response rate; QD=once daily.

Source: Applicant's population PK and PK/PD study report

Figure 13: Percent change in key efficacy and safety endpoints relative to 800 mg QD, stratified by dose group in MZL and FL population



Source: Applicant's population PK and PK/PD study report

Reviewer's comment: Based on the Applicant's simulation, a lower dose in MZL population may provide better safety profile while maintaining efficacy. However, there is no efficacy data available at doses lower than 800 mg QD in the MZL patients to discern that. For FL population, while the reduced efficacy at lower doses, and increased risk of diarrhea and ALT/AST elevation at higher doses appear to support the proposed 800 mg QD regimen, these projections were potentially limited by small number of subjects at doses outside of 800 mg in the E-R analysis dataset, particularly for efficacy.

In conclusion, the Applicant developed a PPK model that reasonably described the PK behavior of umbralisib in MZL and FL patients. The PK of umbralisib following oral administration was adequately described by a three-compartment model combined with first- and zero-order absorption after a lag time and first-order elimination. Flat E-R relationships were observed for MZL population while positive E-R relationships were identified for ORR, TTR and %CfB in target lesion dimensions in FL population, with potential uncertainties due to limited number of subjects at doses outside of 800 mg QD. Positive E-R relationships were observed for diarrhea and elevated ALT/AST.

19.4.3. Physiologically Based Pharmacokinetic (PBPK) Modeling Analysis

Executive Summary

The objective of this review is to evaluate the adequacy of the applicant's physiologically based pharmacokinetic (PBPK) analyses to evaluate

- the inhibitory potential of umbralisib on the pharmacokinetics (PK) of substrates of CYP2C8, CYP2C9 and CYP2C19
- the inhibitory and induction potential of umbralisib on the PK of midazolam, a sensitive CYP3A substrate

The Division of Pharmacometrics has reviewed the PBPK analyses report (R_TGT/1/B) submitted with NDA 213176, responses to FDA's information requests (IRs) submitted on July 24th and 31st, 2020, and the modeling supporting files, and concluded that the effects of umbralisib on CYP3A, CYP2C8, CYP2C9 and CYP2C19 could not be confidently predicted using the PBPK modeling approach. The potential of drug-drug interactions (DDIs) of umbralisib with substrates of these enzymes cannot be ruled out.

Background

The proposed umbralisib dosing regimen is 800 mg once daily with food. The maximal dose examined is 1200 mg once daily with food. Following oral administration of umbralisib (b) (4) once daily under the fed condition, umbralisib AUC and C_{max} increased approximately dose proportionally across the dose range of 200-mg to 1000-mg on cycle 1 day1 (C1D1) and C2D1, and steady-state was achieved by C3D1. Umbralisib had a long half-life (166 h) and its accumulation ratio ranged from 5.2 to 11.3 for $AUC_{0-\infty}$ and 2.8 to 5.9 for C_{max} across the doses from 200- to 1200-mg.

Umbralisib was determined in vitro to be an inhibitor and inducer of CYP3A, and an inhibitor of CYP2C8, CYP2C9 and CYP2C19. The applicant intended to use a PBPK modeling approach to evaluate the potential of drug interactions of umbralisib with the substrates of these CYP enzymes. Refer to the Clinical Pharmacology review section for detail information on umbralisib regarding its ADME properties, in vitro and clinical studies used in PBPK modeling.

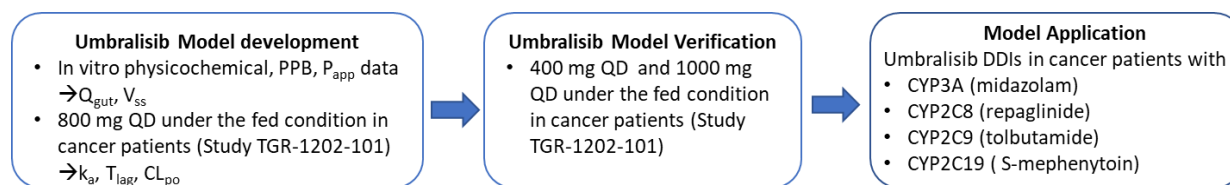
Methods

All simulations were performed using the PK/PD Profiles mode in the Simcyp® Simulator (Version 18 Certara, Sheffield, UK). A scheme of the PBPK simulation strategy is shown in Figure 14, which summarizes the studies used for model development and verification, and model applications in DDI predictions with CYP substrates. The model structure, model optimization and final model parameters for the umbralisib PBPK model are summarized in Table 52. For prediction of DDIs with umbralisib as a perpetrator, Simcyp library substrate files of midazolam, repaglinide, tolbutamide, S-mephenytoin were used without any modifications. All simulations were completed using the sim-Healthy Volunteer population aged 20-50 years with 50% female subjects under the fed condition. All DDI simulations were

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conducted after 168 days of hypothetical QD umbralisib administration to ensure a maximum systemic umbralisib exposure for DDI prediction.

Figure 14: PBPK Modeling and simulation strategy



Source: This flow chart was generated by the reviewer.

Table 52: Final input parameters for umbralisib in its PBPK model

PARAMETER	Umbralisib	Reference
Physicochemical and Blood Binding		
MW (gm/mol)	571.5	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
logP _{ow}	5.52	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
Compound type	Monoprotic base	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
pKa	2.71	PDR TGR 1202 Tablets, draft_26 Sept - Pharmaceutical Development Report
B:P	0.78	Predicted by Simulator
f _{up}	0.003	Mean of (5 μM) 12F158-rhiz - Human plasma protein binding, (2 μM) DMPK-5264-PB-01 - Preclinical and human plasma binding
Absorption		
Model	First Order	Fit-for-purpose
P _{app} (x10 ⁻⁶ cm/s)	6.59	OPT-2017-164: 10 μM TGR-1202 + 3 μM elacridar A → B in P-gp expressing MDCK
P _{eff,man} (x10 ⁻⁶ cm/s)	0.825	Predicted by Simulator
f _{gut}	1.00	Fit-for-purpose assumption – worst-case scenario for perpetrator DDI prediction objective
Q _{gut} (L/hours)	5.56	Predicted by Simulator
k _a (hours ⁻¹)	0.99	Parameter Estimation (ka-flag-full-pbpbk.pwkwz)
T _{lag} (hours)	0.77	Parameter Estimation (ka-flag-full-pbpbk.pwkwz)
f _s	1.00	Fit-for-purpose assumption
Distribution		
Model	full PBPK	Fit-for-purpose
V _{ss} (L/kg) Method 2	60.5	Method 2 estimate resulted in improved fit over Method 1 (12.0 L/kg)
Elimination		
Model	Global Clearance	Fit-for-purpose
CL _{oral} (L/hours)	6.3	54% of oral clearance calculated from dose and AUC _{0-24h} on C2D1 (11.6 L/hours) in TGR-1202-101 800 mg DP containing micronized DS in fed subjects
Interaction		
CYP2C8 K _i (μM)		(b) (4)
CYP2C9 K _i (μM)		
CYP2C19 K _i (μM)		
CYP3A4 K _i (μM)		
CYP2C8 f _{u,mic}		
CYP2C9 f _{u,mic}		
CYP2C19 f _{u,mic}		
CYP3A4 f _{u,mic}		
CYP3A4 EC ₅₀ (μM)		
Calibrated CYP3A4 Ind _{max}		
CYP3A4 f _{u,app}		

Abbreviation: PDR = Pharmaceutical Development Report

Source: Table 3.26 in the PBPK report (R_TGT/1/B)

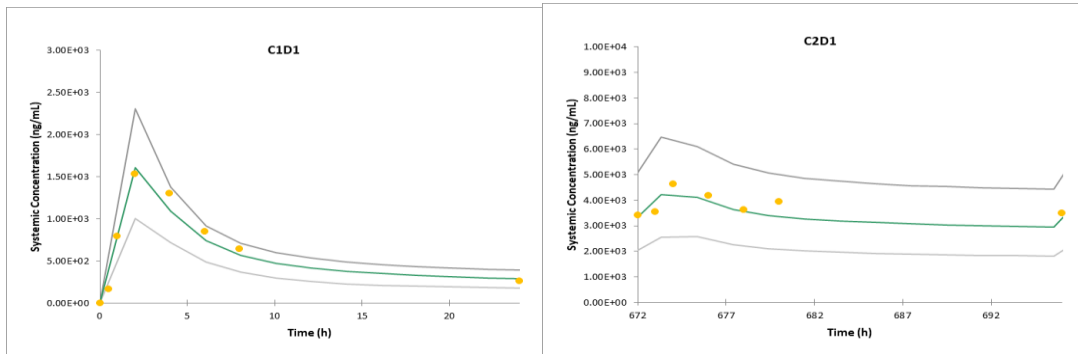
Results

1. Can the PBPK model adequately describe the PK profiles of umbralisib?

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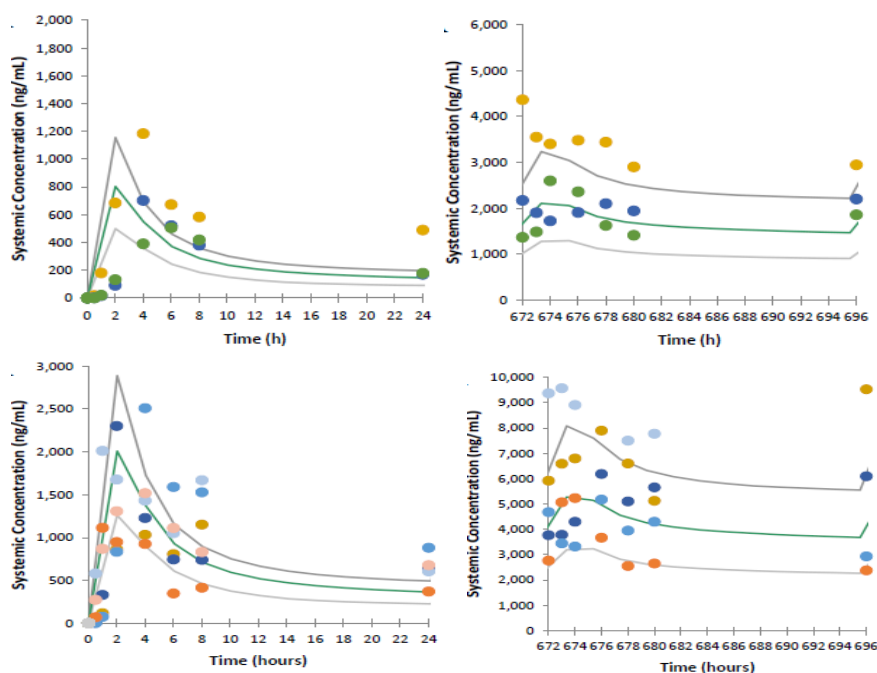
Yes, the PBPK model of umbralisib described umbralisib PK following administration of multiple doses of umbralisib in cancer patients (Figures 15 - 16 and Table 53).

Figure 15: Mean simulated (green lines) and observed (dots) PK profiles of umbralisib following 800 mg of umbralisib once daily in cancer patients (TGR-1202-101) on C1D1 (left) and C2D1 (right)



Source: Figure 4-1-1 and Figure 4-1-2 in the PBPK report (R_TGT/1/B). The grey lines represent the 5th and 95th percentiles of the total simulated population PK.

Figure 16: Predicted mean (green lines) and observed (dots) PK profiles following 400- (upper pane) and 1000-mg (lower panel) umbralisib once daily in cancer patients (TGR-1202-101) on C1D1 (left) and C2D1 (right).



Source: Figure 4-2-1 to Figure 4-2-4 in the PBPK report (R_TGT/1/B)

Table 53: Predicted and observed PK parameters following multiple doses of umbralisib once daily in cancer patients (TGR-1202-101) on C1D1 and C2D1

Dose (mg)		C1D1			C2D1		
		T _{max} (h)	C _{max} (ng/ml)	AUC _{0-24h} (h*ng/ml)	T _{max} (h)	C _{max} (ng/ml)	AUC _{0-24h} (h*ng/ml)
800	observed	2.1 (2-3.6)	1830 (23)	14200 (11)	3.9 (2.1-23)	4920 (50)	68700 (64)
	simulated	1.9 (1.2-2.9)	1610 (24)	13200 (19)	1.9 (1.3-2.9)	4360 (28)	76000 (33)
	sim/obs	0.9	0.88	0.93	0.49	0.89	1.11
400	PopPK	4 (4-6)	750 (45)	8830 (42)	0.0 (0-2.1)	2910 (37)	53200 (31)
	predicted	1.9 (1.2-2.9)	806 (24)	6600 (19)	1.9 (1.3-2.9)	2180 (28)	38000 (33)
	pred/obs	0.48	1.07	0.75	ND	0.75	0.71
1000	PopPK	3 (0.9-7.8)	1680 (36)	20700 (39)	4 (2-4)	6920 (36)	126000 (50)
	predicted	1.9 (1.2-2.9)	2020 (24)	16500 (19)	1.9 (1.3-2.8)	5440 (28)	95000 (33)
	pred/obs	0.63	1.2	0.8	0.48	0.79	0.75

C_{max} and AUC_{0-24h}: Geometric mean; T_{max}: median

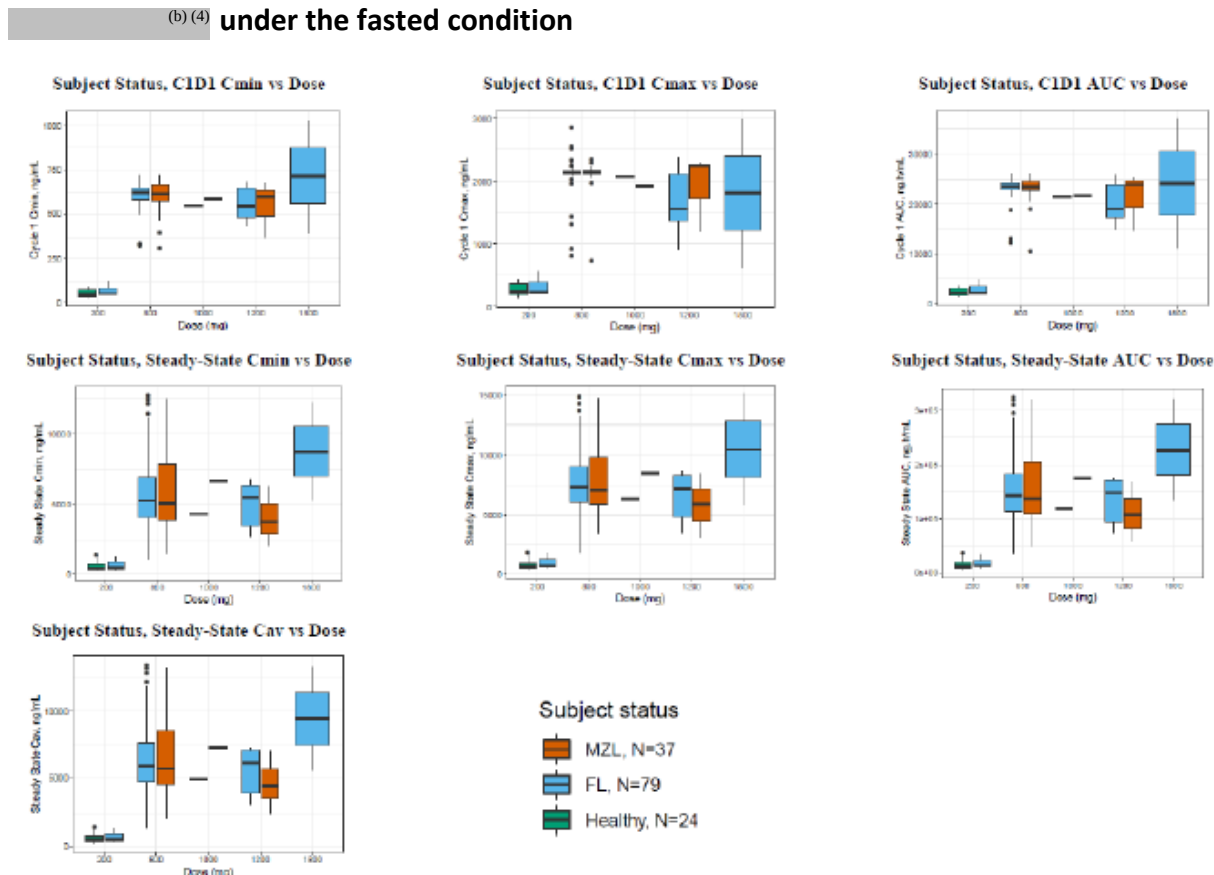
Source: the PBPK report (R_TGT/1/B)

Additional comments:

The multiple-dose PK data from the 800-mg umbralisib cohort (n=3) in Study TGR-1202-101 were used to build and optimize the umbralisib PBPK model during the model development. (b) (4) drug product was given under the fed condition in this study. Figures 15 - 16 and Table 53 show that the model could reasonably well recover umbralisib plasma concentrations in cancer patients, and the estimated exposures (C_{max} and AUC_{0-24h}) were mostly within 25% of the values observed or estimated from population PK (PopPK) analysis.

It should be noted that the applicant developed the PBPK model of umbralisib to predict DDI in cancer patients. However, all simulations were performed using the default sim-Healthy Volunteer population model. To apply the simulation results, there are two underlying assumptions. One is that umbralisib PK in healthy subjects is similar to that in cancer patients. This assumption may be supported by umbralisib PK at 200-mg dose in healthy subjects (TRG-1202-PK101) and cancer patients (TGR-1202-101) as shown in Figure 17. The second assumption is that there is no difference in enzyme abundance or activity of CYP3A and CYP2Cs between healthy subjects and cancer patients. This is the case for sim-Healthy Volunteer population and sim-Cancer population models. However, there are evidences that CYP enzyme abundance or activity may be altered in cancer patients (Coutant DE 2015; Schwenger H 2018). Therefore, the simulation results should be interpreted with caution.

Figure 17: PK parameters following oral administration of a single dose of 200-mg umbralisib under the fasted condition



Source: Figure 4-4, the population PK analysis (TGTX-PMX-UMBRAISIB-1100-001)

2. Can PBPK analyses predict the effects of umbralisib on the pharmacokinetics of CYP substrates?

No, the PBPK analyses are inadequate to predict the complex inhibitory and induction effects on CYP3A, and the effects of umbralisib on the PK of the substrates of CYP2C8 (repaglinide), CYP2C9 (tolbutamide) and CYP2C19 (S-mephenytoin) due to the uncertainties about in vitro to in vivo extrapolation.

(b) (4)

(b) (4)

Source: the reviewer's analysis

Conclusions

The effects of umbralisib on CYP3A, CYP2C8, CYP2C9 and CYP2C19 cannot be confidently predicted using the PBPK modeling approach. The potential of drug-drug interactions of umbralisib with substrates of these enzymes cannot be ruled out.

References

1. Austin RP et al. The influence of nonspecific microsomal binding on apparent intrinsic clearance, and its prediction from physicochemical properties. *Drug Metab Dispos* 2002;30(12):1497-503
2. Cheng Y, Prusoff WH. Relationship between the inhibition constant (K_i) and the concentration of inhibitor which causes 50 per cent inhibition (I₅₀) of an enzymatic reaction. *Biochem Pharmacol* 1973; **22**(23):3099-3108.
3. Coutant DE et al. Understanding Disease–Drug Interactions in Cancer Patients: Implications for Dosing Within the Therapeutic Window. *Clin Pharm Ther* 2015; 98 (1): 78-86
4. Schwenger H et al. Harnessing Meta-analysis to Refine an Oncology Patient Population for Physiology-Based Pharmacokinetic Modeling of Drugs. *Clin Pharm Ther* 2018; 103 (2): 271-280

19.5. Grouped Preferred Terms Used in Safety Analyses Conducted by FDA

The FDA's Assessment:

The following table presents the FDA grouped preferred terms used for the safety analyses with this application.

FDA Grouped PT	Included in Grouping	Not Included
Abdominal pain	All PTs containing "abdominal pain", Abdominal discomfort, Abdominal tenderness, Epigastric discomfort, Gastrointestinal pain	
Anemia	All PTs containing "anemia", RBC count decreased, hemoglobin decreased	
Atrial fibrillation or flutter	Atrial fibrillation, Atrial flutter, Cardiac flutter	

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FDA Grouped PT	Included in Grouping	Not Included
Bruising	All PTs containing “bruise,” “contusion,” or “ecchymosis”	Petechiae, Purpura, Increased tendency to bruise
Cardiac arrhythmias	High-level group term, “Cardiac arrhythmias”	
Cardiac failure	All PTs containing “cardiac failure”, Congestive cardiomyopathy, Cardiomyopathy, Left ventricular failure, Cor pulmonale, Cardiopulmonary failure	
Chest pain	Chest discomfort, Chest pain, Angina pectoris	Noncardiac chest pain
Colitis	Colitis, Colitis microscopic, Colitis ulcerative, Colitis erosive, Enterocolitis, Enterocolitis hemorrhagic	Enteritis, Enterocolitis viral
Cough	All PTs containing “Cough”	
Cytomegalovirus infection	Cytomegalovirus infection, Cytomegalovirus viremia	
Diarrhea	Diarrhea, Diarrhea hemorrhagic, Defecation urgency	Post procedural diarrhea
Diarrhea or colitis	All terms under FDA’s grouping of “Diarrhea” and “Colitis”	
Dizziness	All PTs containing “Dizziness” or “Vertigo”	
Dyspnea	All PTs containing “Dyspnea”	
Edema	Edema, Generalized edema, Face edema, Swelling face, Peripheral swelling, Swelling, Edema peripheral, Fluid overload, Fluid retention, Pulmonary edema, Acute pulmonary edema, Pulmonary congestion	Edema blister, Localized sites of edema or swelling (e.g., Localized edema, Lip edema, Nasal edema, Periorbital edema, Eye swelling, breast edema, testicular edema)
Fatigue	Asthenia, Fatigue, Lethargy	
Febrile neutropenia	Febrile neutropenia, Febrile bone marrow aplasia, Neutropenic infection, Neutropenic sepsis* * Note: Neutropenic sepsis is counted under both the “febrile neutropenia” and “sepsis” PTs	
Gastroenteritis	Gastroenteritis and specific types (e.g. viral), Enterocolitis viral	Gastroenteritis radiation, Gastritis
Gastrointestinal hemorrhage	All PTs containing “Gastrointestinal hemorrhage”, Gastric hemorrhage, Gastric ulcer hemorrhage, Large intestinal ulcer hemorrhage, Hematochezia, Hematemesis, Intestinal hemorrhage, Intestinal hemorrhage, Melena, Hemorrhoidal hemorrhage, Rectal hemorrhage, Small intestinal hemorrhage	
Headache	All PTs containing “headache”, Migraine	

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FDA Grouped PT	Included in Grouping	Not Included
Hemorrhage	All PTs containing “hemorrhage” or “hemorrhagic”, all PTs contained in FDA’s “Gastrointestinal hemorrhage” grouping, Menorrhagia, Hemarthrosis, Hemoptysis, Hematuria, Epistaxis	Petechiae, Purpura, FDA’s grouping for “Bruising”
Hemorrhage intracranial	Includes but is not limited to: Hemorrhage intracranial, Subdural hematoma, Subdural hemorrhage, Cerebral hemorrhage, Hemorrhagic stroke, Subarachnoid hemorrhage	
Hepatitis	All PTs containing “hepatitis”, Hepatocellular injury, Hepatotoxicity, Drug-induced liver injury, Liver injury	FDA’s “Transaminase elevation” grouping, PTs containing “Hepatic failure”, Hepatic encephalopathy
Herpesvirus infection	High-level group term, “Herpes viral infection”	
Hyperbilirubinemia	Blood bilirubin increased, Hyperbilirubinemia, Jaundice	
Hypertension	Hypertension, Essential hypertension, Blood pressure increased, Blood pressure systolic increased	
Hypotension	Hypotension, Diastolic hypotension, Orthostatic hypotension, Blood pressure decreased	
Leukocytosis ^a	Leukocytosis, Hyperleukocytosis, White blood cell count increase	
Lower respiratory tract infection	All PTs containing “bronchitis” or “lower respiratory tract infection”, Bronchiolitis, Lung infection	Bronchiectasis
Musculoskeletal pain	Back pain, Musculoskeletal chest pain, Noncardiac chest pain, Musculoskeletal pain, Musculoskeletal discomfort, Myofascial pain syndrome, Neck pain, Pain in extremity, Myalgia, Spinal pain	Arthralgia, Musculoskeletal stiffness
Myocardial ischemia or infarction	Acute myocardial infarction, Myocardial ischemia, Angina unstable, Troponin increased, Acute coronary syndrome, Myocardial infarction, Coronary artery stenosis or occlusion	Angina pectoris
Nausea	Nausea, Retching	Procedural nausea
Neutropenia	Neutropenia, Neutrophil count decreased, Granulocytopenia	Febrile neutropenia
Nonmelanoma skin cancer	Squamous cell carcinoma of skin, Basal cell carcinoma, Bowen's disease, Basosquamous carcinoma, Lip squamous cell carcinoma	
Pneumonia	All PTs containing “pneumonia”, including within another word (e.g. bronchopneumonia), Bronchopulmonary aspergillosis, Lung infiltration, Lung consolidation	Lung infection
Pneumonitis	Pneumonitis, Acute respiratory distress syndrome, Interstitial lung disease, Respiratory tract inflammation	

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FDA Grouped PT	Included in Grouping	Not Included
Rash	All PTs containing “rash”, all PTs containing “dermatitis” except as noted, Drug eruption, Drug reaction with eosinophilia and systemic symptoms, Erythema, Erythema multiforme, Generalized erythema, Toxic skin eruption, Palmar erythema, Palmoplantar keratoderma, Palmar-plantar erythrodysesthesia syndrome, Skin reaction, Skin toxicity, Stevens-Johnson syndrome, Toxic epidermal necrolysis	All PTs containing “Eczema”, Dermatitis atopic, Actinic keratosis, Folliculitis, Urticaria, Lichen planus, Herpes dermatitis, Acarodermatitis, Vaccination site rash, Photodermatosis
Renal insufficiency	All PTs containing “renal failure” or “nephropathy”, Acute kidney injury, Blood creatinine increase, Creatinine renal clearance decreased, Glomerular filtration rate decreased, Renal impairment, Hypercreatinemia, Chronic kidney disease	
Respiratory tract infection	Respiratory tract infection + specific types (e.g. respiratory tract infection viral, respiratory syncytial virus infection, influenza, Haemophilus infection, Human metapneumovirus, Influenza like illness, Sinobronchitis	Upper respiratory tract infection, Lower respiratory tract infection
Sepsis	All PTs containing “Bacteremia” or “Sepsis”, including within another word (e.g. urosepsis) Septic shock * Note: Neutropenic sepsis is counted under both the “febrile neutropenia” and “sepsis” PTs	
Supraventricular tachycardia	High-level term, “Supraventricular arrhythmias”	
Thrombocytopenia	Thrombocytopenia, Platelet count decreased	Immune thrombocytopenic purpura
Thrombosis or thromboembolism	All PTs containing “thrombosis” except as noted, Peripheral embolism, Pulmonary embolism	Superficial thrombosis, Embolic cerebral infarction
Transaminase elevation	Alanine aminotransferase increased, Aspartate aminotransferase increased, Alanine aminotransferase, Aspartate aminotransferase, Transaminase increased, Hypertransaminasemia, Hepatic enzyme increased	PTs under FDA’s “Hepatitis” grouping, PTs containing “hepatic failure”, Hepatic function abnormal
Upper respiratory tract infection	All PTs containing “upper respiratory tract infection,” “sinusitis,” “laryngitis,” “tonsillitis,” or “pharyngitis,” including within another word (e.g. nasopharyngitis), all PTs containing “rhinitis” except as noted, Rhinovirus infection, Human rhinovirus test positive, alpha hemolytic streptococcal infection	Rhinitis allergic
Urinary tract infection	All PTs containing “cystitis” or “urinary tract infection”, Pyelonephritis, Kidney infection	
Ventricular arrhythmia	High-level term, “Ventricular arrhythmias and cardiac arrest”	

FDA Grouped PT	Included in Grouping	Not Included
Xerosis	Dry skin, Dry eye, Dry mouth, Xerosis	

^a Grouping for other lab-related AEs is similar, e.g., hyperglycemia = hyperglycemia + blood glucose increased, hypokalemia = hypokalemia + blood potassium decreased, lymphopenia = lymphopenia + lymphocyte count decreased

NDA 213176 (Original 1 & 2)/Umbralisib				
Assessment Aid Signatures				
DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Simon Williams, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☐ Approved
	Signature: Simon Williams -S Digitally signed by Simon Williams -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Simon Williams -S, 0.9.2342.19200300.100.1.1 2001572753 Date: 2021.01.30 10 25 46 -05'00'			
Nonclinical Team Leader	Brenda Gehrke, PhD	OOD/DHOT	Sections: 5	Select one: ☒ Authored ☒ Approved
	Signature: Brenda Gehrke -S Digitally signed by Brenda Gehrke -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Brenda Gehrke -S, 0.9.2342.19200300.100.1.1 0012062023 Date: 2021.01.30 10 33 45 -05'00'			
Nonclinical Team Division Director	Haleh Saber, PhD	OOD/DHOT	Sections: 5, 14	Select one: ☐ Authored ☒ Approved
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Clinical Pharmacology Reviewer	Edwin Chow, PhD	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☐ Approved
	Signature: Edwin C. Chow -S Digitally signed by Edwin C. Chow -S DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Edwin C. Chow -S, 0.9.2342.19200300.100.1.1 2001621378 Date: 2021.01.25 10 54 28 -05'00'			
Clinical Pharmacology Team Leader	Ruby Leong, PharmD	OCP/DCPI	Sections: 6, 19.4	Select one: ☒ Authored ☒ Approved
	Signature: Ruby Leong -S3 Digitally signed by Ruby Leong -S3 DN c US, o U.S. Government, ou HHS, ou FDA, ou People, cn Ruby Leong -S3, 0.9.2342.19200300.100.1.1 2000548953 Date: 2021.01.25 10 34 12 -05'00'			
Clinical Pharmacology TBPK Reviewer	Ying-Hong Wang, PhD	OCP/DPM	Sections: 6,19.4	Select one: ☒ Authored ☐ Approved
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Clinical Pharmacology TBPK Team Leader	Xinyuan Zhang, PhD	OCP/DPM	Sections: 6, 19.4	Select one: ☐ Authored ☒ Approved
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Clinical Pharmacology Division Director	Brian Booth, PhD	OCP/DCPI	Sections: 6, 15, 19.4	Select one: ☐ Authored ☒ Approved
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Pharmacometrics Reviewer	Ruojing Li, PhD	OCP/DPM	Sections: 4, 19.4	Select one: ☒ Authored ☐ Approved
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Pharmacometrics Team Leader	Lian Ma, PhD	OCP/DPM	Sections: 4, 19.4	Select one: ☒ Authored ☒ Approved
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Clinical Reviewer	Candis Morrison, PhD, CRNP	OOD/DHMI	Sections: 2, 3, 4, 7, 8, 9, 10, 12, 13, 19	Select one: ☒ Authored ☐ Approved
	Signature: Candis Morrison -S Digitally signed by Candis Morrison -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1 2001366518, cn=Candis Morrison -S Date: 2021.01.29 13:56:24 -0500			
Clinical Reviewer	Maryam Sarraf Yazdy, MD	OOD/DHMI	Sections: 2, 3, 4, 7, 8, 9, 10, 12, 13, 19	Select one: ☒ Authored ☐ Approved
	Signature: Maryam Sarraf Yazdy -S Digitally signed by Maryam Sarraf Yazdy -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=2002210276, cn=Maryam Sarraf Yazdy -S Date: 2021.02.03 11:28:17 -0500			
Associate Director for Labeling	Elizabeth Everhart, MSN, RN, ACNP	OOD	Sections: 11	Select one: ☒ Authored ☒ Approved
	Signature: Elizabeth E. Everhart -S Digitally signed by Elizabeth E. Everhart -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=2000363858, cn=Elizabeth E. Everhart -S Date: 2021.01.28 10:31:5 -0500			
Statistical Reviewer	Laura Fernandes, PhD	OB/DBIX	Sections: 7, 8	Select one: ☒ Authored ☐ Approved
	Signature: Laura Fernandes -S Digitally signed by Laura Fernandes -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1 1300389006, cn=Laura Fernandes -S Date: 2021.02.03 12:33:53 -0500			
Statistical Team Leader	Yu-Te Wu, PhD	OB/DBIX	Sections: 7, 8, 16	Select one: ☒ Authored ☒ Approved
	Signature: Yute Wu -S Digitally signed by Yute Wu -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yute Wu -S, 0.9.2342.19200300.100.1.1 1300389006, cn=Yute Wu -S (Affiliate) Date: 2021.01.29 13:41:23 -0500			
Biostatistics Division Director	Thomas Gwise, PhD	OB/DBIX	Sections: 7, 8, 16	Select one: ☐ Authored ☒ Approved
	Signature: Thomas E. Gwise -S Digitally signed by Thomas E. Gwise -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1 1300369224, cn=Thomas E. Gwise -S Date: 2021.02.03 12:33:53 -0500			
Cross-Disciplinary Team Leader (CDTL)	Nicholas Richardson, DO, MPH	OOD/DHMI	Sections: All	Select one: ☒ Authored ☒ Approved
	Signature: Nicholas C. Richardson -S Digitally signed by Nicholas C. Richardson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.23 2.19200300.100.1.1=2002010136, cn=Nicholas C. Richardson -S Date: 2021.02.03 13:33:23 -0500			

Clinical Division Director	Nicole Gormley, MD	OOD/DHMII	Sections: All	Select one: ☐ Authored ☐ Approved
	Signature: Nicole J. Gormley -S Digitally signed by Nicole J. Gormley -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1 0012754803, cn=Nicole J. Gormley -S Date: 2021.02.04 12:13:35 -0500			
Office Signatory	Marc Theoret, MD	OOD	Sections: All	Select one: ☐ Authored ☒ Approved
	Signature: See appended signature page below			
OOD: Office of Oncologic Diseases				
DHOT: Division of Hematology, Oncology, Toxicology				
OCP: Office of Clinical Pharmacology				
DPM: Division of Pharmacometrics				
DTPM: Division of Translational and Precision Medicine				
DCPI: Division of Cancer Pharmacology I				
OB: Office of Biostatistics				
DBIX: Division of Biometrics IX				
DHMII: Division of Hematologic Malignancies II				

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

/s/

NATASHA L KORMANIK
02/05/2021 07:40:19 AM

NICHOLAS C RICHARDSON
02/05/2021 07:44:11 AM

MARC R THEORET
02/05/2021 09:12:36 AM

My signature indicates that I have considered the FDA assessments and recommendations included in this Review in determining the regulatory action.