CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213176Orig1Orig2s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	January 14, 2021
To:	Natasha Kormanik, MSN, RN, OCN Senior Regulatory Project Manager **Division of Hematologic Malignancies 2 (DHM2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Ruth Mayrosh, PharmD Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nisha Patel, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	UKONIQ (umbralisib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 213176
Applicant:	TG Therapeutics, Inc.

1 INTRODUCTION

On June 15, 2020, TG Therapeutics, Inc. submitted for the Agency's review Part 2 of 2 for a Rolling Submission of an original New Drug Application (NDA) 213176 for UKONIQ (umbralisib) tablets. The proposed indications for UKONIQ (umbralisib) tablets are for the treatment of adult patients with:

- marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen.
- follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies.

On October 23, 2020 the Agency determined a Medication Guide is necessary to ensure safe and appropriate use of UKONIQ (umbralisib) tablets.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Hematologic Malignancies 2 (DHM2) on June 16, 2020 and June 15, 2020, respectively, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for UKONIQ (umbralisib) tablets.

2 MATERIAL REVIEWED

- Draft UKONIQ (umbralisib) tablets MG received on June 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 11, 2021.
- Draft UKONIQ (umbralisib) tablets Prescribing Information (PI) received on June 15, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on January 11, 2021.
- Approved ZYDELIG (idelalisib) comparator labeling dated October 19, 2020.
- Approved COPIKTRA (duvelisib) comparator labeling dated September 26, 2019.
- Approved IMBRUVICA (ibrutinib) comparator labeling dated August 7, 2020.
- Approved ALIQOPA (copanlisib) comparator labeling dated February 12, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more

accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

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SHAWNA L HUTCHINS
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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: January 13, 2021

To: Natasha Kormanik, Regulatory Project Manager
Division of Hematologic Malignancies 2 (DHM2)

Stacy Shord, Associate Director for Labeling, DHM2

From: Nisha Patel, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Trung-Hieu (Brian) Tran, Team Leader, OPDP

Subject: OPDP Labeling Comments for UKONIQ™ (umbralisib) tablets, for oral use

NDA: 213176

In response to DHM2's consult request dated June 15, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original NDA submission for UKONIQ™ (umbralisib) tablets, for oral use (Ukoniq).

Labeling: OPDP has no comments on the proposed PI received by electronic mail from DHM2 on January 11, 2021.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Nisha Patel at (301) 796-3715 or nisha.patel@fda.hhs.gov.

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NISHA PATEL
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	December 2, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 213176
Product Name and Strength:	Ukoniq (umbralisib) tablet, 200 mg
Applicant/Sponsor Name:	TG Therapeutics
OSE RCM #:	2020-289-2
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

TG Therapeutics submitted a revised container label on December 2, 2020 for Ukoniq (umbralisib) tablet under NDA 213176. We reviewed the revised container label for Ukoniq (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that were made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Kane D. Label and Labeling Review for Ukoniq (NDA 213176). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 20. RCM No.: 2020-289-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON DECEMBER 2, 2020

- Container Label

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/s/

DEVIN R KANE
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HINA S MEHTA
12/03/2020 04:32:52 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	November 20, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 213176
Product Name and Strength:	Ukoniq (umbralisib) tablet, 200 mg
Applicant/Sponsor Name:	TG Therapeutics
OSE RCM #:	2020-289-1
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 PURPOSE OF MEMORANDUM

TG Therapeutics submitted a revised container label on November 18, 2020 for Ukoniq (umbralisib) tablet under NDA 213176. We reviewed the revised container labels for Ukoniq (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that were made during a previous label and labeling review.[a]

2 CONCLUSION

The revised bottle container label is unacceptable from a medication error perspective. We note that the statement "Recommended Dose: See Prescribing Information" is not present on the container label. We provide a recommendation below for the Applicant.

3 RECOMMENDATIONS FOR TG THERAPEUTICS

We recommend the following be implemented prior to approval of this NDA:

A. Bottle Container Label

[a] Kane, D. Label and Labeling Review for Ukoniq (NDA 213176). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 OCT 19. RCM No.: 2020-289-1.

1. We note the statement “Recommended Dose: See Prescribing Information” is missing from the revised container label. We recommend revising the container label to include this statement.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON NOVEMBER 18, 2020

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/s/

DEVIN R KANE
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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 19, 2020
Requesting Office or Division:	Division of Hematologic Malignancies 2 (DHM 2)
Application Type and Number:	NDA 213176
Product Name, Dosage Form, and Strength:	Ukoniq (umbralisib) tablet, 200 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	TG Therapeutics
FDA Received Date:	January 10, 2020 and June 15, 2020
OSE RCM #:	2020-289
DMEPA Safety Evaluator:	Devin Kane, PharmD
DMEPA Team Leader:	Hina Mehta, PharmD

1 REASON FOR REVIEW

TG Therapeutics submitted NDA 213176 Ukoniq (umbralisib) tablet on January 10, 2020 and June 15, 2020 as a rolling submission. Ukoniq is proposed for the treatment of adult patients with marginal aone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen or adults with follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies. We evaluated the proposed Ukoniq prescribing information (PI), bottle container label, and patient information sheet for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

TG Therapeutics submitted a 505(b)(1) application to obtain marketing approval of Ukoniq tablets. We performed a risk assessment of the proposed prescribing information (PI), container label, and patient information for Ukoniq to determine whether there are deficiencies that may lead to medication errors and other areas of improvement. Upon discussion with the review team it was determined the patient information sheet should be a Medication Guide and should be reviewed as such.

Our evaluation of the proposed PI, container label and medication guide for Ukoniq identified areas of vulnerability that may lead to medication errors. We recommend clarity on the "do not chew" statement in the PI to include the information that the tablet should not be crushed or cut as well. We also recommend clarity on dosage from and strength and information on storage excursions. For the container label we recommend prominence of the established

name and strength. In addition, we recommend revisions to the Rx only statement, expiration date, and inclusion of medication guide statement to improve clarity. We provide our recommendations below for the Division in Section 4.1 and the Applicant in Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

Our evaluation of the proposed Ukoniq prescribing information (PI), bottle container label, and medication guide identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant. We ask that the Division convey Section 4.2 in its entirety to TG Therapeutics so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR DIVISION OF HEMATOLOGIC MALIGNANCIES 2 (DHM 2)

A. Highlights of Prescribing Information

1. Dosage and Administration

a. The recommended dose statement only advises the patient not the chew the tablet. We recommend revising this statement to include other ways the tablet may be broken. Revise to "do not crush, cut or chew the tablets".

B. Prescribing Information

1. Section 2: Dosage and Administration

a. As currently presented, Section 2.1 Recommended Dosage states the recommended dose is 800 mg taken orally (b) (4). We recommend revising this statement to read "The recommended dose of Uknoiq is 800 mg orally once daily at approximately the same time" in order to prevent confusion.

b. Section 2.1 states that the tablets should be swallowed whole and not chewed. We recommend including that the patient should not crush or cut the tablets in addition to not chewing the tablets. Revise statement to read "Swallow tablets whole with food. Do not crush, cut or chew the tablets".

2. Section 3: Dosage Forms and Strengths

a. We recommend revising for clarity the dosage from statement. Revise to read "Tablets: 200 mg, green film-coated, oval-shaped with "L474" on one side and nothing on the other side.".

C. Medication Guide

1. Under the heading "How Should I Take Ukoniq" the patient information sheet currently states that Ukoniq tablets should not be chewed. We recommend expanding that statement to include "Do not crush, cut or chew the tablets."
2. As currently presented, the storage requirements statement does not include the allowable temperature excursions. We recommend including the approved temperature excursions to align with the prescribing information (PI).

4.2 RECOMMENDATIONS FOR TG THERAPEUTICS

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).
2. As currently presented the strength is not prominently displayed on the container label. We recommend revising the strength statement to increase readability.
3. As currently presented the net quantity is in close proximity to the drug product strength and can lead to confusion. Relocate the net quantity statement away from the product strength, such as to the bottom of the principal display panel. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement.
4. Decrease the prominence of the statement "Rx Only" by debolding it as it appears more prominent than the established name on the principal display panel. In addition, we recommend using the same size font for the entire statement.
5. As currently presented, the expiration date is provided in DD-MMM-YYYY format using alphabetical characters. We recommend that the expiration date appears in YYYY-MM-DD format is only numerical characters are used or in YYYY-MMM-DD is alphabetical characters are used to represent the month.
6. As currently presented, the proposed container label contains the statement (b) (4). We recommend removing this statement from the container label as it is not needed.
7. We note based upon discussion with the review team it was determined the patient information sheet should be a Medication Guide and should be reviewed as such. Per 21 CFR 208.24(d), please revise the container label to prominently

display the statement “Dispense the enclosed Medication Guide to each patient” on the principle display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Ukoniq received on June 15, 2020 from TG Therapeutics.

Table 2. Relevant Product Information for Ukoniq	
Initial Approval Date	N/A
Active Ingredient	umbralisib
Indication	For the treatment of adult patients with: • Marginal Zone Lymphoma (MZL) who have received at least one prior anti-CD20-based regimen. • Relapsed or refractory follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies.
Route of Administration	Oral
Dosage Form	tablet
Strength	200 mg
Dose and Frequency	800 mg orally, once daily
How Supplied	Supplied in white opaque round HDPE bottles containing 120 green, film coated, oval shaped tablets of 200 mg umbralisib. Tablets are debossed with "L474" on one side and plain on the other side. (b) (4) (b) (4). Bottles are capped with a 38 mm child resistant polypropylene closure with heat sealed peel-able foil liner.
Storage	Store tablets at 68°F to 77°F (20°C to 25°C). Excursions permitted between 59°F and 86°F (15°C and 30°C) [see USP Controlled Room Temperature]. (b) (4)

APPENDIX G.LABELS AND LABELING

G.1List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error data, we reviewed the following Ukoniq labels and labeling submitted by TG Therapeutics.

- Bottle Container label received on June 15, 2020
- Medication Guide (image not shown) received on June 15, 2020, available from \\cdsesub1\evsprod\nda213176\0008\m1\us\m1-14-1-3-patient-information-sheet.pdf
- Prescribing Information (Image not shown) received on June 15, 2020, available from \\cdsesub1\evsprod\nda213176\0008\m1\us\m1-14-1-3-draft-uspi.pdf

G.2Label and Labeling Images

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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CLINICAL INSPECTION SUMMARY

Date	September 16, 2020
From	Anthony Orencia M.D., F.A.C.P., Medical Officer Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
To	Maryam Yazdy, M.D., Medical Officer Candis Morrison, Ph.D., C.R.N.P., Clinical Analyst Nicholas Richardson, D.O., M.P.H., Team Leader Nicole Gormley, M.D., Acting Director Natasha Kormanik, M.S.N., R.N., Regulatory Project Manager Division of Hematology Malignancies 2 Office of Oncologic Diseases
NDA	213176
Applicant	TG Therapeutics, Inc.
Drug	Ukoniq™ (umbralisib)
NME	Yes
Division Classification	Dual inhibitor of phosphoinositide 3-kinase delta and casein kinase 1 epsilon (antiproliferator and antitumorigenic)
Proposed Indication	Treatment of adult patients with marginal zone lymphoma who have received at least one prior anti-CD20-based regimen, and follicular lymphoma who have received at least (b) (4) lines of prior therapy.
Consultation Request Date	July 22, 2020 (Priority Review)
Summary Goal Date	November 15, 2020
Action Goal Date	December 15, 2020
PDUFA Date	February 15, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigators (Felipe Samaniego, M.D. and Nilanjan Ghosh, M.D.) and the sponsor TG Therapeutics, Inc. were inspected in support of NDA 213176.

Based on the inspections, the study data derived from Drs. Samaniego's and Ghosh's clinical sites are considered reliable. Sponsor's oversight of the clinical trial and quality of conducting this study were adequate. The audited study data submitted to the Agency appear acceptable in support of this application and proposed indication, in compliance with Good Clinical Practice.

II. BACKGROUND

Umbralisib is a dual inhibitor of phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase 1 epsilon (CK1ε). Inhibition of both kinases is anti-proliferative and promotes an anti-tumorigenic microenvironment.

The submitted application was to support a single agent umbralisib from the Phase 2 pivotal trial UTX-TGR-205 (UNITY-NHL) for the treatment of marginal zone B-cell lymphoma and follicular lymphoma.

A single study, Study UTX-TGR-205, forms the basis for the regulatory decision-making process for this application. Study Protocol UTX-TGR-205 is entitled "A Phase IIb Randomized Study to Assess the Efficacy and Safety of the Combination of Ublituximab + TGR-1202 with or without Bendamustine and TGR-1202 Alone in Patients with Previously Treated Non-Hodgkin's Lymphoma".

Study UTX-TGR-205

Study UTX-TGR-205 was a 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 indolent non-Hodgkins lymphoma (iNHL), mantle cell lymphoma (MCL), and diffuse large B cell lymphoma (DLBCL). Subjects were enrolled into one of several cohorts: marginal zone lymphoma (MZL), follicular lymphoma (FL), small lymphocytic leukemia (SLL), mantle cell lymphoma, or DLBCL, in accordance with the tumor type and disease characteristics.

Study treatments were administered on an outpatient basis with all treatments in 4-week (28 day) cycles.

The primary study objective was to assess the efficacy as measured by overall response rate (ORR) of the following: umbralisib alone, umbralisib plus ublituximab, and in select non-Hodgkin lymphoma (NHL) subtypes, umbralisib plus ublituximab plus bendamustine. A supplementary study objective was to assess the efficacy as measured by progression-free survival (PFS) and duration of response.

The primary efficacy endpoint was overall response rate (ORR) defined as the percent of subjects who achieved complete response [CR] or partial response [PR], based on the International Working Group (IWG) Revised Response Criteria for Malignant Lymphoma modified as described in the Lugano classification. The best clinical response as well as disease progression were determined by the Independent Central Radiology Group (ICRG), also referred to as Independent Review Committee (IRC). Efficacy was also assessed as progression-free survival (PFS) and duration of treatment response.

The first subject enrolled on June 9, 2016. The data cutoff for safety analysis was September 1, 2019. The data cut-off for treatment efficacy analysis was November 30, 2019.

There were 82 sites in the Unites States (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).

The enrolled patients comprised this group stratification:
Umbralisib: 275 subjects (69 subjects with marginal zone B cell lymphoma, 131 subjects with follicular lymphoma, 23 subjects with mantle cell lymphoma, 30 subjects with DLBCL, and 22 subjects with small lymphocytic leukemia).

Umbralisib in combination with ublituximab (U2): 147 subjects (17 subjects with marginal zone B cell lymphoma, 41 subjects with follicular lymphoma, 23 subjects with mantle cell lymphoma, and 66 subjects with DLBCL).

Rationale for Site Selection
DHM2 requested an audit of two domestic clinical sites with the highest number of enrolled patients. Sponsor's oversight of this study was also assessed during this inspection.

III. RESULTS (by site)

1. **Felipe Samaniego, M.D./ Site HOB**
   Department of Lymphoma/Myeloma - Unit 429
   M.D. Anderson Cancer Center
   1515 Holcombe Blvd.
   Houston, TX 77030

   Inspection dates: August 10 to 14, 2020

   A total of 30 subjects were screened and 24 study patients were enrolled at the site. There were 15 subjects who received study treatment discontinued: 9 patients discontinued due to disease progression, four study subjects withdrew due to adverse events, and one patient withdrew due to unspecified reasons. The study is ongoing.

   Source documents were reviewed for study eligibility, review/approval, monitoring, test article accountability, concomitant medication, and adverse event/serious adverse event reporting; radiology documents such as imaging. Records review of the 30 screened subjects indicated that the eligibility criteria for enrollment were met. There were no limitations during conduct of the clinical investigation.

   The primary efficacy raw data endpoint was verifiable at the study site for investigator-assessed treatment response. Progression-free survival and duration of treatment response raw data was verifiable at the study site. There was no under-reporting of adverse events.

2. Nilanjan Ghosh, M.D./ Site CLA
Levine Cancer Institute
1021 Morehead Medical Drive
Charlotte, NC 28204

Inspection dates: August 25 to 27, 2020

A total of 23 subjects consented for the study, and a total of 19 study subjects were enrolled and randomized. There were 16 study patients who received treatment but discontinued, due to confirmed disease progression (10 patients) and withdrawal by clinical study investigator (six patients: two unconfirmed Progressive Disease, three adverse events and one in order to change treatment). Three study subjects remain on treatment in this ongoing study.

Source documents were reviewed for study eligibility, informed consent, Institutional Review Board (IRB) review/approval, monitoring, test article accountability, concomitant medication, delegation of authority, primary efficacy endpoint, and adverse event/serious adverse event reporting. Records review of the 19 enrolled and randomized subjects indicated that the eligibility criteria for enrollment were met. The inspection also covered a review of the source worksheets, laboratory results, ECGs, echocardiogram reports, and electronic medical records.

Source documents were verified against the case report forms and sponsor data line listings. There were no limitations during conduct of the clinical site inspection.

The primary and secondary efficacy raw data endpoints were verifiable at the clinical site. This site data audit verified available treatment response investigator site assessments without significant discrepancies noted.

Two non-serious adverse events (ulcer like lesion on nostril [Subject (b) (6)] and bilateral lower extremity edema [Subject (b) (6)]) were not reported in subjects' electronic case reports forms. The clinical investigator added these two adverse events in the subjects' eCRFs after they were identified during the inspection. There was no under-reporting of serious adverse events.

3. TG Therapeutics, Inc.
4909 Western Blvd Ste 114
Raleigh, NC 27606-1772

Inspection dates: August 11 to 18, 2020

This onsite inspection assessed TG Therapeutics, Inc.'s responsibilities concerning its oversight of randomized Study UTX-TGR-205. No previous CDER history of inspection of this sponsor was recorded.

Selection process and responsibility of various Contract Research Organizations, vendors,

and clinical trial management services were reviewed during this sponsor inspection: (a) (b) (4) was responsible for site monitoring, data management, and safety databases, (b) Alembic Pharmaceuticals Limited provided investigational product manufacturing services, (c) (b) (4) provided management of study supplies including storage services, (d) (b) (4) was responsible for interactive response technology and study randomization services, and (e) (b) (4) was contracted for independent evaluation and analysis of medical imaging data.

The inspection included a review of the organizational charts, investigator agreements, transfer of obligations, financial disclosures with the sponsor, study master file, assessment of selection of clinical study site investigators, and selection of clinical study monitors and their training records. Standard operating procedures were evaluated, principally concerning clinical site monitoring, data collection, and handling of adverse event data.

TG Therapeutics conducted monitoring activities including pre-site selection, site initiation, and interim monitoring visits. There has not been any site close out visits.
Eight study sites were selected for review of monitoring visit reports for study protocol adherence and compliance: (1) Site CLA (Dr. Ghosh, South Carolina), (2) Site HOB (Dr. Samaniego, Texas), (3) Site BPA (Dr. Berard, Connecticut), (4) Site CFA (Dr. Hodson, Cambridge, U.K.), (5) Site CIA (Dr. Islas-Ohlmayer, Ohio), (6) Site DAB (Dr. Rizvi, Texas), (7) Site KNB (Dr. Kambhampati, Missouri) and (8) Site WHA (Dr. Agajanian, California). Clinical study conduct in these clinical investigative sites and sponsor trial oversight were found to be appropriate.

No underreporting of significant adverse events (SAEs) to the Agency was noted. FDA did not encounter any barriers during the sponsor site audit. In general, study procedures, record-keeping and reporting procedures were adequate.

{See appended electronic signature page}
Anthony Orencia, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Min Lu, M.D., M.P.H.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}
Kassa Ayalew, M.D., M.P.H.
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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/s/

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 213176
Submission Number	008
Submission Date	6/15/2020
Date Consult Received	6/15/2020
Drug Name	Umbralisib
Indication	Marginal Zone Lymphoma (MZL) who have received at least one prior anti-CD20-based regimen
Therapeutic dose	800 mg once daily (QD) with food
Clinical Division	DHM2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This review responds to your consult dated 6/15/2020 regarding the sponsor's QT evaluation. We reviewed the following materials:

- Previous IRT reviews under IND 116762 dated 04/13/2018 and 05/30/2019 in DARRTS (Link)
- TGR-1202-102 clinical study report and concentration-QT analysis report (Submission 0008)
- Proposed labeling (Submission 0008)
- Highlights of Clinical Pharmacology and Cardiac Safety (Submission 0009)

1 SUMMARYQ

Although no large mean increases in the QTc interval (i.e., > 20 msec) of umbralisib was detected in this QT assessment, the umbralisib exposure observed is lower than the exposure reported by the population PK model. It's not clear to us why this study had lower exposure. Additional QT assessment may be needed to characterize the effect of umbralisib on the QTc interval following completion of OCP's assessment. Refer to section 2.1 for further discussion.

The effect of umbralisib was evaluated in the monotherapy treatment cohort (Cohort S, n=32) of an open-label study (TGR-1202-102) in patients with advanced cancer who had relapsed from or were refractory to various types of solid tumors. The highest dose evaluated was 1200 mg QD which is the maximum tolerated dose. The data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that umbralisib is associated with large mean increases in the QTc interval (see Table 1 for overall result). The results from this analysis are supported by the available nonclinical data (section 3.1.2), by-timepoint analysis (section 4.3), and categorical analysis (section 4.4).

Table 1: The Point Estimates and the 90% CIs

Actual Treatment	Cycle	Number of Subjects	Umbralisib (ng/mL)	ΔQTCF (msec)	90.0% CI (msec)
Umbralisib 800 mg QD	2	8	3,633.5	2.2	(-4.0 to 8.4)
Umbralisib 1200 mg QD	2	5	4,172.1	1.9	(-5.0 to 8.8)
Umbralisib 800,1200 mg QD	2	7	4,367.8	1.8	(-5.3 to 8.9)

1.1 RESPONSES TO QUESTIONS POSED BY SPONSOR

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

In this study, the geometric mean Cmax on Cycle 2 Day 1 is 4012 ng/mL (n=20). The mean Cmax reported in the proposed label is 4920 ng/mL (i.e., observed data from Study TGR-1202-101 in 3 subjects) which is approximately 23% higher but not too concerning. In contrast, the mean Cmax predicted by the population pharmacokinetics model is 6327 ng/mL which is approximately 58% higher.

It's not clear to us why this study had lower exposure. It appears that different batches of drug substances (different manufacturing processes and particle sizes) were used in this study, the study population was different from the targeted patient population, and the bioanalytical method (method ID: MET126, plasma concentration) was different from that was used in the Phase 2 study (UTX-TGR-205) included in the population PK analysis (method ID: MET193, serum concentration). It was noted that the sponsor's population PK report suggested significant effect by study ID on bioavailability. As the pharmacometrics reviews and clinical pharmacology reviews are ongoing, we defer the relevance of these variations to the clinical pharmacology review team.

If OCP finds the value reported by the population PK model to be correct, we have concerns extrapolating conclusions from this QT assessment study to the higher exposure range. Additional QT assessment, either as a dedicated QT study or as a sub-study in a Phase 2/3 clinical trial, may be recommended if the therapeutic exposure is determined to be substantially higher than what was observed in this QT study.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to Submission 0008 (link) from the IRT. Our changes are highlighted (addition, ~~deletion~~). Our changes are for suggestions only and we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

(b) (4)

Reviewer's comment:

- *If the therapeutic exposure at the 800 mg QD dose is not substantially higher than what is observed in the QT assessment, we propose the above edits to the label.* (b) (4) (b) (4) *Without an appropriate placebo control and a positive control or high exposure to establish assay sensitivity, we are reluctant to conclude a lack of clinically relevant effect on the QTc interval.*
- *If the therapeutic exposure at the 800 mg QD dose is substantially higher than what was observed in the study, we propose to remove any QT-related language in section 12.2 of the product label and recommend a PMR for further QT assessment.*

3 SPONSOR'S SUBMISSION

3.1 OVERVIEW

3.1.1 Clinical

TG Therapeutics is developing umbralisib for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen or follicular lymphoma (FL) who have received at least (b) (4) prior systemic therapies. The recommended dose of umbralisib is 800 mg taken orally (four 200 mg tablets) once daily at approximately the same time with food.

Previously the sponsor submitted an ECG analysis plan based on the results from Cohort S (monotherapy cohort) of study TGR-1202-102. Cohort S in study TGR-1202-102 was an open-label, multiple dose treatment in 32 cancer patients. Study drug was self-administered with food on an out-patient basis. ECG data were collected at screening, 4-hour postdose on C1D1 and C2D1. The primary analysis was concentration-QTc analysis based on QTcF. The proposal was found to be reasonable to characterize the QT prolongation potential of umbralisib. The IRT noted limitations in PK/ECG sampling schedule and ECG quality, and recommended that the sponsor perform by-time point analysis and categorical analysis. Whether the data excludes a large mean effect at the proposed therapeutic dose of 800 mg QD remained a review question (previous IRT review under IND 116762 dated 05/30/219 in DARRTS).

The sponsor provided a concentration-QTc analysis report in the current submission. The proposed therapeutic dose and primary analysis method remained the same. The sponsor used ECG data derived from a computer-assisted method with manual adjudication for the analysis. The reviewer used ECG data with fully automatic reading for the analyses. Patients in the initial enrollment started umbralisib treatment at 1200 mg QD dose and reduced the dose to 800 mg QD after protocol amendment. Patients receiving either 800 or 1200 mg QD dose are labeled as the "800 mg QD" (N=11) or "1200 mg QD" (N=14) group. Patients receiving both 800 and 1200 mg QD doses during the entire treatment

period are labeled as the "800,1200 mg QD" group (N=7); dose reduction may or may not occur in the first two cycles.

Highlight of clinical pharmacology: According to the sponsor's proposed label, the pharmacokinetics of the umbralisib are characterized by an absorption phase that has a Tmax of 4 hours after repeated dosing. Accumulation at steady state after the 800 mg QD dose is abou (b) (4)-fold for AUC and (b) (4)-fold for Cmax. The terminal elimination half-life is about (b) (4). Umbralisib is minimally metabolized by CYP isozymes and there are no major plasma metabolites. A radiolabeled dose of 800 mg showed that 81% of the dose was recovered in feces with 17% as unchanged drug, and with 3% in urine. High fat meal increases umbralisib exposure by approximately 2-fold. Mild and moderate renal impairment increases Cmax by approximately (b) (4). CYP3A4 inhibitors, acid-reducing agent, age, sex, race, and mild hepatic impairment do not substantially increase umbralisib Cmax (i.e. <25% increase). The effects of severe renal, or of moderate and severe hepatic impairment, are not known.

3.1.2 Nonclinical Safety Pharmacology Assessments

An in vitro hERG channel study was performed on a whole-cell voltage-clamp setup with mammalian cells expressing the hERG potassium channel. The IC50 was determined to be >100 μM, the highest concentration solubility permitted. In comparison, at the to be marketed dose of 800 mg in humans, the estimated Cmax of total drug (bound and unbound) at steady state is of 7 μM, which resulted in a safety margin of >10-fold.

Reviewer's comment: *Plasma binding is 99.7% at 2 μM and 99.8% at 5 μM. Assuming a free fraction of 1%, the ratio between the highest concentration tested (100 μM, 28.3% inhibition) and free Cmax (<0.07 μM) is >1000-fold. The ratio would be >900-fold with an estimated $C_{max,ss}$ of 6327 ng/mL and a molecular weight of 571.5 g/mol.*

Additionally, evaluation of in vivo cardiovascular safety was incorporated into the 28-day, 13-week and 26-week GLP repeat-dose toxicity studies in beagle dogs at various timepoints pre-treatment, during the treatment period and during the recovery period. A six lead (I, II, III, aVR, aVL, aVF) ECG examination was conducted on all animals for each study at the scheduled timepoints and measurements during the treatment period were conducted approximately 1 to 2 hours following dose administration. In all evaluations, there were no treatment-related quantitative or qualitative differences between HR, RR, PR interval, QRS duration or QT/QTcV interval values in the treated groups compared to the control groups. The highest dose evaluated in beagle dogs with no changes in ECG parameters was 500 mg/kg/day (HED of 19,400 mg/day in 70 kg human).

3.2 SPONSOR'S RESULTS

3.2.1 By Time Analysis

The primary analysis for umbralisib was based on exposure response analysis. Please see section 3.2.3 for additional details.

Reviewer's comment: *The sponsor observed slight (uncertain) upward trend from C1D1-04H to C2D1-04H on QTcF (without adjusting baseline, combined all dosage groups). Please see Section 4.3 for details of non-parametric summary of ΔQTcF.*

3.2.1.1 Assay Sensitivity

Not applicable as there is no positive control.

3.2.1.1.1 QT Bias Assessment

Not applicable.

3.2.2 Categorical Analysis

There were no significant outliers per the sponsor's analysis for QTc (i.e., > 500 msec or > 60 msec over baseline. There were outliers for HR (<45 or >100 beats/min), PR (>220 msec) and QRS (>120 msec) per the sponsor's analysis.

Reviewer's comment: *The sponsor's categorical analysis included C1D1 pre-dose data, did not considered percentage of change from baseline, and used core-lab ECG measurements. Therefore, sponsor's counts for HR and QRS outliers are higher than counts in reviewer's analysis. Please see Section 4.4 for details.*

3.2.3 Exposure-Response Analysis

The sponsor conducted linear mixed effect modeling using ΔQTcF as the dependent variable, intercept, concentration, time, and age as fixed effect covariate, and included random effect on intercept, concentration slope and intercept-concentration interaction. The concentration-ΔQTcF slope was 0.00002 [msec/(ng/ml)] with a p-value of 0.984. The predicted ΔQTcF at the geometric mean Cmax at the 800 mg QD dose is 3.6 msec (90% CI: -3.1 to 10.2 msec).

Reviewer's comment: *The reviewer's analysis showed numerical differences compared to the sponsor's analysis. They are not affecting the conclusion that umbralisib does not cause large mean increases on the QTc interval in the studied exposure range.*

3.2.4 Cardiac Safety Analysis

In monotherapy group, treatment-emergent SAEs were reported in 8 subjects (25%) and 1 subject (Subject (b) (6)) died due to SAE (hepatic failure). For 1 subject (Subject (b) (6)), umbralisib dosing was discontinued due to an SAE (embolic stroke).

There were no cardiac TEAEs in the monotherapy arm. One subject has an ACS event with combination therapy.

An AE of QT prolonged was reported in 1 subject on Day 15 in the umbralisib + nab-paclitaxel + gemcitabine group. The AE resolved on Day 36 and was considered not related to umbralisib.

Reviewer's comment: *None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.*

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The sponsor used QTcF for the primary analysis, which is acceptable as no large increases or decreases in heart rate (i.e., |mean| < 10 beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Waveforms of digitized ECGs from Cohort S were uploaded to the ECG warehouse, but analysis quality couldn't be determined due to the limitation of the digitization. Paper ECGs, automatic readings were also submitted. Overall ECG acquisition and interpretation in this study appears acceptable. The reviewer used ECG data with fully automatic reading for the primary analyses.

4.2.2 QT Bias Assessment

Not applicable.

4.3 BY TIME ANALYSIS

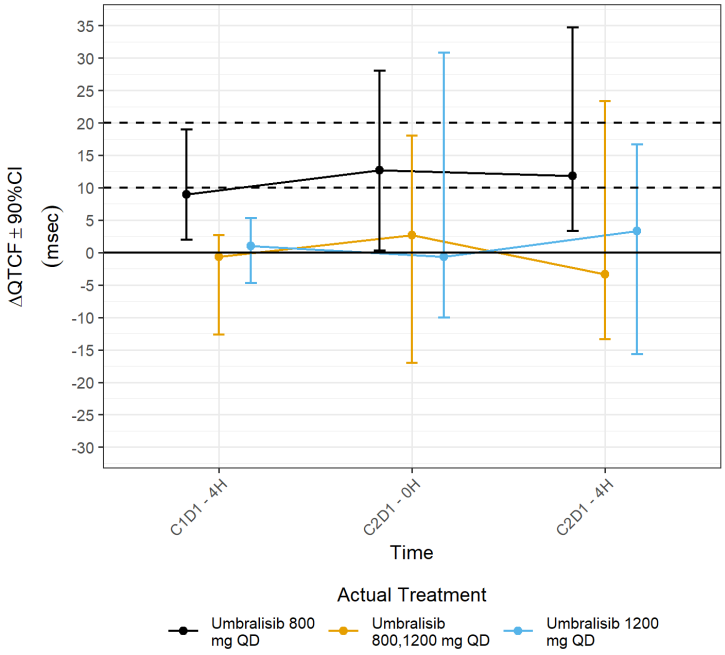
The analysis population used for the by-time analysis included all subjects with a baseline and at least one post-dose ECG. Results below are displayed by dosage sequence. Fourteen subjects received only 1200 mg QD, and only 6 subjects remained at C2D1-0H. Eleven subjects received only 800 mg QD, and only data from 5 subjects were available at C2D1-0H. Therefore, the width of confidence intervals for these two groups are larger at timepoints C2D1-0H and C2D1-4H in Figure 1 to Figure 5.

The statistical reviewer evaluated the ΔQTcF time trend using non-parametric statistics.

4.3.1 QTc

Figure 1 displays the time profile of ΔQTcF for different treatment groups.

Figure 1: Median and 90% CI of ΔQTcF Time Course (unadjusted CIs).



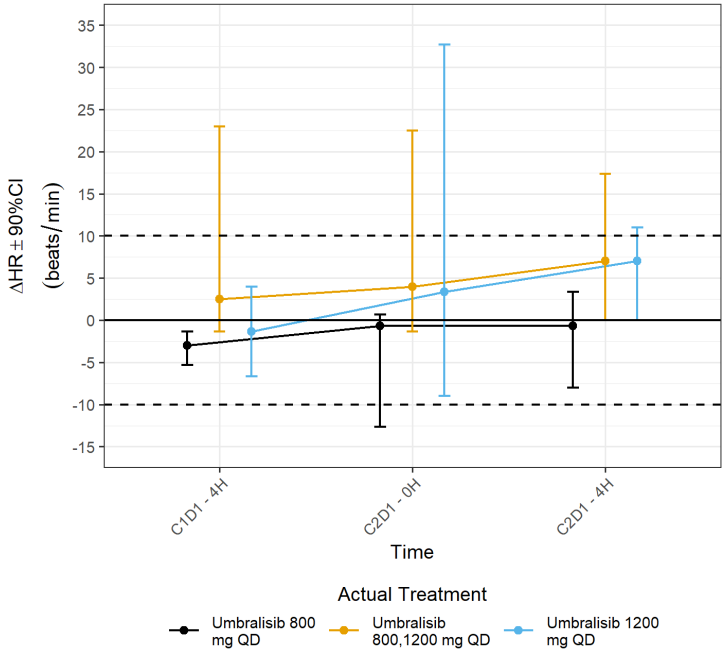
4.3.1.1 Assay sensitivity

Not applicable.

4.3.2 HR

Figure 2 displays the time profile of ΔHR for different treatment groups.

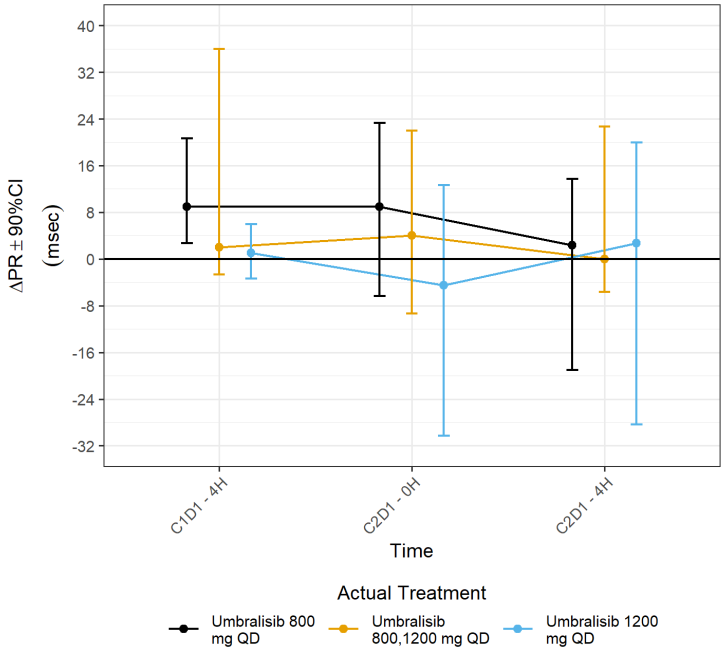
Figure 2: Median and 90% CI of ΔHR Time Course



4.3.3 PR

Figure 3 displays the time profile of ΔPR for different treatment groups.

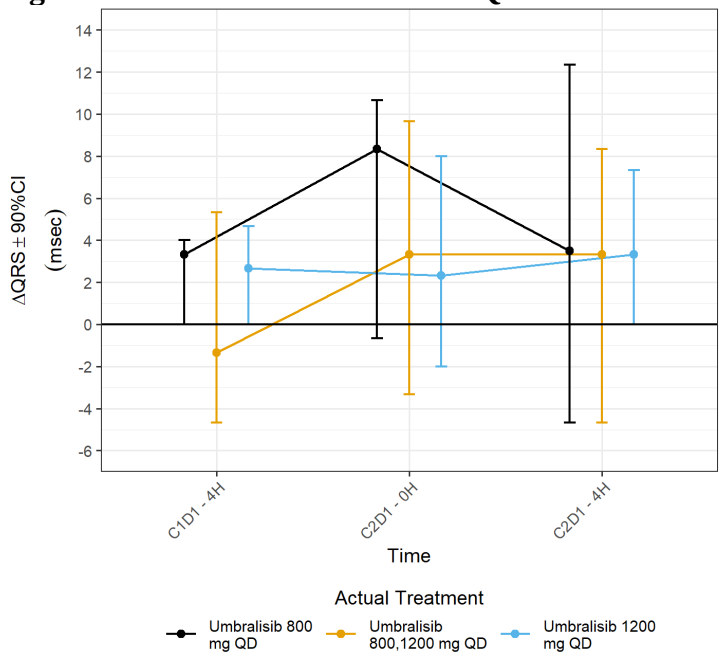
Figure 3: Median and 90% CI of ΔPR Time Course



4.3.4 QRS

Figure 4 displays the time profile of ΔQRS for different treatment groups.

Figure 4: Median and 90% CI of ΔQRS Time Course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements either using absolute values, change from baseline or a combination of both. The analysis was conducted using the safety population and includes both scheduled and unscheduled ECGs.

4.4.1 QTc

No subjects experienced QTcF greater than 480 msec or QTcF change from baseline greater than 60 msec.

4.4.2 HR

Table 2 lists the categorical analysis results for HR. Observed HR values were categorized into less than or equal to 100 beats/min and greater than 100 beats/min groups.

Table 2: Categorical Analysis for HR

Actual Treatment	Total (N)		Value <= 100 beats/min		Value > 100 beats/min	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Umbralis b 800 mg QD	11	35	11 (100.0%)	35 (100.0%)	0 (0%)	0 (0%)
Umbralis b 800,1200 mg QD	7	26	5 (71.4%)	24 (92.3%)	2 (28.6%)	2 (7.7%)
Umbralis b 1200 mg QD	14	40	12 (85.7%)	38 (95.0%)	2 (14.3%)	2 (5.0%)

4.4.3 PR

Table 3 lists the categorical analysis results for PR (less than 200 msec; between 200 and 220 msec and above 220 msec with and without 25% increase over baseline). One subject in 800 mg group experienced PR > 220 msec at one timepoint. The subject (b) (6) (b) (6) had a maximum observed PR interval of 249 msec (corresponding to 40% increase over baseline).

Table 3: Categorical Analysis for PR

Actual Treatment	Total (N)		Value <= 220 msec		Value > 220 msec & >= 25%	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Umbralis b 800 mg QD	11	35	10 (90.9%)	34 (97.1%)	1 (9.1%)	1 (2.9%)
Umbralis b 800,1200 mg QD	7	26	7 (100.0%)	26 (100.0%)	0 (0%)	0 (0%)
Umbralis b 1200 mg QD	14	39	14 (100.0%)	39 (100.0%)	0 (0%)	0 (0%)

4.4.4 QRS

No subjects experienced QRS above 120 msec with 25% increase over baseline.

4.5 EXPOSURE-RESPONSE ANALYSIS

Exposure-response analysis was conducted using all subjects with baseline and at least one post-baseline ECG with time-matched PK in Cohort S of study TGR-1202-102.

4.5.1 QTc

The objective of the clinical pharmacology analysis was to assess the relationship between ΔQTcF and the concentration of umbralisib.

Prior to evaluating the relationship between drug concentration and QTc using a linear model, the three key assumptions of the model need to be evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) delay between plasma concentration and ΔQTc and 3) presence of non-linear relationship.

Figure 2 shows the time-course of ΔHR, which shows an absence of significant ΔHR changes. Figure 5 (top) shows a lack of dose response at the two dose levels of umbralisib. Pharmacokinetic fluctuation is low. The lack of dose response is also seen for ΔQTcF-time (Figure 5 bottom). Considering high drug accumulation and low fluctuation in both PK and QTc profiles, it is unlikely that potential delayed effect would significantly impact the concentration-QTc analysis. Figure 6 shows the relationship between drug concentration and ΔQTc and supports the use of a linear model.

Figure 5: Time course of drug concentration (top) and QTc (bottom)

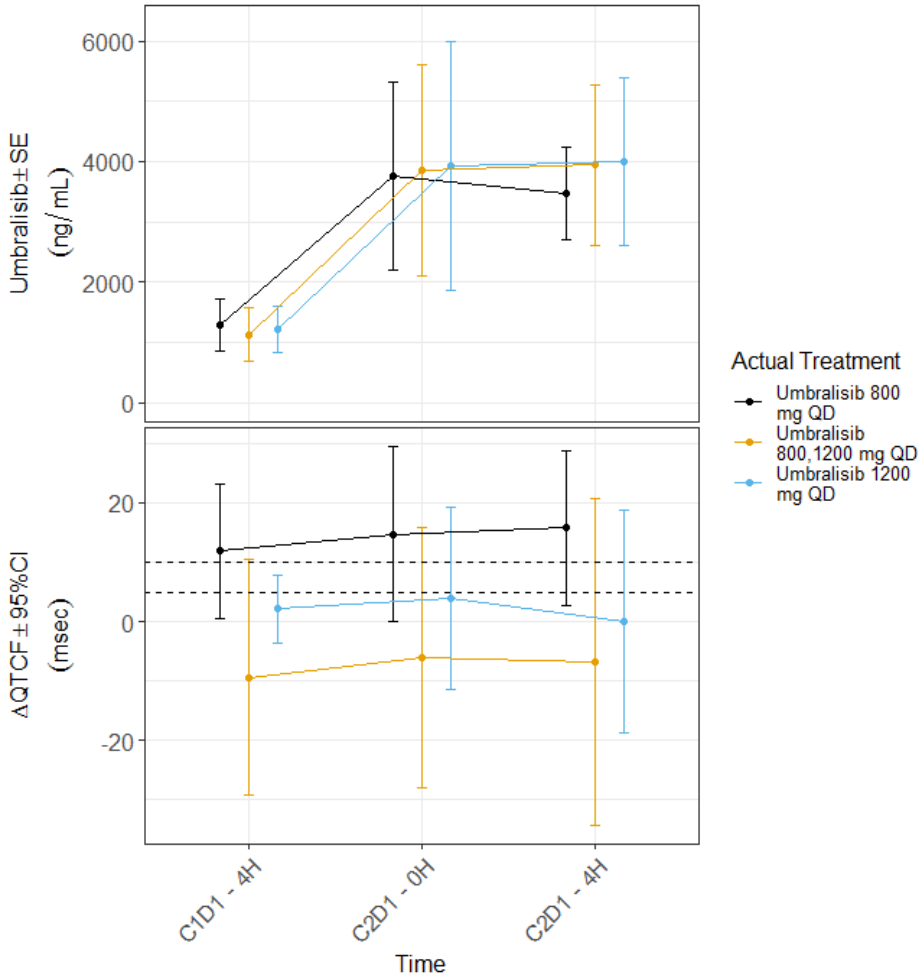
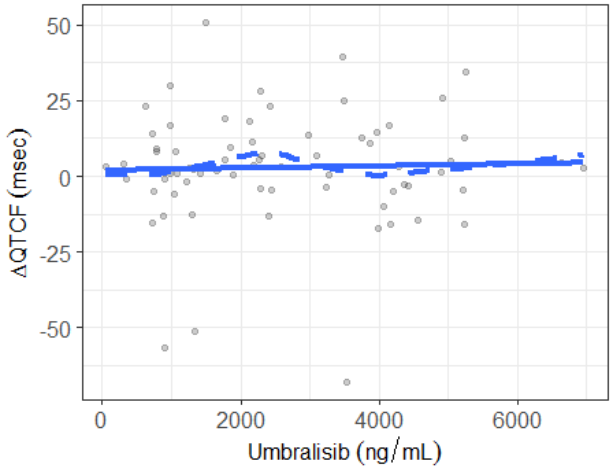
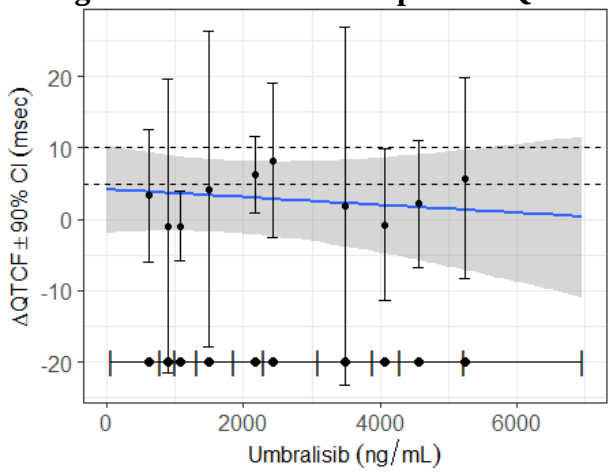


Figure 6: Assessment of linearity of concentration-QTc relationship



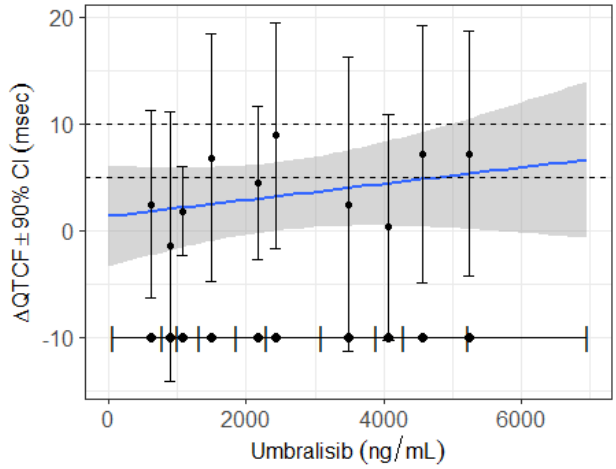
Finally, the linear model (ΔQTcF ~ 1 + CONC + centered baseline, random effect on the intercept and slope) was applied. The goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTc model are provided in Table 1.

Figure 7: Goodness-of-fit plot for QTc



The concentration-QTc analysis using the sponsor ECG reading (i.e. derived from a computer-assisted method with manual adjudication) resulted in a numerically positive slope (0.76 msec per ug/mL; p-value=0.4) (Figure 8). The predicted ΔQTcF (mean [90% CI]) at the observed Cmax value in this study is 4.4 [0.5 to 8.4] msec at 4012 ng/mL. The results support the conclusions from the primary analysis using fully automated ECG reading.

Figure 8: Goodness-of-fit plot for QTc (sponsor's ECG reading)



4.5.1.1 Assay sensitivity

Not applicable

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/s/

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