CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213176Orig1Orig2s000

PRODUCT QUALITY REVIEW(S)

Recommendation: APPROVAL

NDA 213176
Review #1

Drug Name/Dosage Form	Umbralisib Tablets
Strength	200 mg
Route of Administration	Oral
Rx/OTC Dispensed	R_x
Applicant	TG Therapeutics, Inc
US agent, if applicable	n/a

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	1/10/2020	All
Amendment (SD)	01/24/2020	Process/Facilities
Amendment (SD)	01/27/2020	DS
Amendment (SD)	02/03/2020	DS, Process/Facilities
Amendment (SD)	03/05/2020	DP, DS
Amendment (SD)	03/19/2020	DP, DS
Amendment (SD)	04/14/2020	DP, DS
Amendment (SD)	04/17/2020	DS
Amendment (SD)	06/15/2020	Process/Facilities
Amendment (SD)	07/07/2020	DP
Amendment (SD)	07/13/2020	DS
Amendment (SD)	07/14/2020	DS, Process/Facilities
Amendment (SD)	07/21/2020	DS, Biopharm
Amendment (SD)	09/11/2020	Process/Facilities

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Kabir Shahjahan	Ali Al Hakim
Drug Product	Yang Nan	Anamitro Banerjee
Process and Facilities	Byeongtaek Oh	Bogdan Kurtyka
Microbiology	n/a	n/a
Biopharmaceutics	Qi Zhang	Om Anand
Regulatory Business Process Manager	Rabiya Haider	n/a
Application Technical Lead	Sherita McLamore	n/a
Laboratory (OTR)	n/a	n/a
Environmental	Yang Nan	Anamitro Banerjee

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type III		(b) (4)	n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA
	Type III			n/a	No Review	Adequate information provided in the NDA

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	116762	Development of umbralisib tosylate
IND	(b) (4)	Development of umbralisib tosylate
IND		Development of umbralisib tosylate

2. CONSULTS

N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

OPQ recommends **APPROVAL** of NDA 213176 UKONIQ (umbralisib) tablets, 200 mg. As part of this action, OPQ grants a 36-month expiration period for the drug product when stored at "20°C to 25°C (68°F to 77°F) excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature]." There are no outstanding issues and no post-approval quality agreements to be conveyed to the applicant.

II. Summary of Quality Assessments

A. Product Overview

NDA 213176 was submitted for UKONIQ (umbralisib) tablets, 200 mg in accordance with section 505(b)(1) of the Food, Drug and Cosmetic Act. Umbralisib is a once daily, orally bioavailable dual inhibitor of phosphoinositide-3-kinase (P13K) delta and casein kinase 1 epsilon (CK1ε) that is indicated for the treatment of marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen and for relapsed or refractory Follicular Lymphoma (FL) who have received at least (b) (4) prior systemic therapies. Umbralisib is an NME that was granted Orphan Designation for the treatment of nodal, splenic and extranodal marginal zone lymphoma (MZL) (March 2016) and Breakthrough Therapy Designation for MZL (January 17, 2019. The applicant was granted a rolling review and requested accelerated approval for treatment of adult patients with:

- •Marginal Zone Lymphoma (MZL) who have received at least one prior anti CD20-basedregimen.
- •Relapsed or refractory Follicular Lymphoma (FL) who have received at least (b) (4) prior systemic therapies

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 in this application (original submission and in responses to information requests), OPQ considers all review issues adequately addressed and potential risks to patient safety, product efficacy, and product quality mitigated appropriately. Accordingly, OPQ recommends APPROVAL of NDA 213176 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 20ºC to 25ºC (68ºF to 77ºF).

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of adult patients with marginal zone lymphoma (MZL) who have received at least one prior anti-CD20-based regimen
Duration of Treatment	until disease progression or until unacceptable toxicity.
Maximum Daily Dose	800 mg
Alternative Methods of Administration	None

B. Quality Assessment Overview

Drug Substance

Umbralisib tosylate is a small chiral BCS class II molecule that is manufactured as a single enantiomer. It is freely soluble in dimethyl sulfoxide, soluble in methanol, and practically insoluble in water.

Umbralisib tosylate drug substance is synthesized (b) (4) by Alembic Pharmaceuticals Limited at a typical batch size of (b) (4) (b) (4) (b) (4).
The proposed commercial synthesis the fourth-generation process used through its development; however, the overall manufacturing route and intermediates remained unchanged in all generations.

The drug substance manufacturing process is described in sufficient detail (b) (4) (b) (4) (b) (4). The applicant provided adequate justification for the suitability of the proposed control strategy for the drug substance manufacturing process. The drug substance was investigated for polymorphism and the data indicated that umbralisib tosylate does not exhibit polymorphic behavior

The drug substance is stored (b) (4) (b) (4)

(b) (4) the specifications and acceptance criteria for the drug substance are consistent with ICH Q6A and are adequate to ensure the quality of the drug substance as it relates to the safety and efficacy of the drug product. The applicant proposed acceptance criterion of ≤ (b) (4) (b) (4), which is not listed in ICH Q3C. Based on informal consult with pharm/tox reviewer Dr. Simon Williams, the OPQ review team concluded that the proposed (b) (4) limit is acceptable. All analytical methods are described in adequate detail and are appropriate for their intended use. All validation parameters - system suitability and system precision, specificity, linearity, range, precision, accuracy, ruggedness, robustness, and stability of solutions are provided in the NDA.

Batch analyses were included for sixty-two drug substance batches. All batches were within the proposed specification and are acceptable.

The applicant provided up to 24 months of long term (25℃/60%RH) and 6-month accelerated (40℃/75%RH) stability data for three registration batches of the drug substance. Thirty-six months of long-term data was also provided for one supportive drug substance batch. The stability data for the registration batches demonstrated no notable changes after up to 24 months under long term storage condition. The applicant requested (b) (4) month retest for drug substance. The provided stability data and stress testing supports the proposed retest of (b) (4) months for the drug substance (b) (4) (b) (4) and may be granted.

Drug Product

The drug product, UKONIQ (umbralisib) tablets, 200 mg, is an immediate-release, non-enteric, film-coated tablets for oral administration. The drug product formulation includes the active (200 mg umbralisib free base, equivalent to 260.20 mg umbralisib tosylate) together with compendial excipients that are commonly used in solid oral dosage forms (hydroxypropyl betadex, croscarmellose sodium, microcrystalline cellulose, hydroxypropyl cellulose, magnesium stearate, and (b) (4)). The tablet coating contains Hypromellose 2910 (b) (4), titanium dioxide, triacetin, polydextrose, (b) (4) PEG 8000, FD&C Yellow, FD&C Blue and iron oxide. The drug product is presented as a green film-coated, oval-shaped tablet, debossed with "L474" on one side and plain on the other. The formulation contains no novel excipients and each of the excipients are below the maximum potency as reported in the IIG. Detailed descriptions of the quantitative and qualitative drug product formulation are provided in the submission.

The drug product is manufactured by Alembic Pharmaceuticals Ltd, of India at a commercial batch size of (b) (4) which corresponds to (b) (4) tablets. The drug product manufactured (b) (4) (b) (4) in standard processing equipment with clearly defined CPPs and IPCs. The applicant demonstrated the suitability of the manufacturing process for the drug product at the proposed commercial scale. The description of the manufacturing process includes appropriate in-process controls and operating parameters and is described in sufficient detail to support the approval of this NDA.

The drug product specifications include appearance, identification, uniformity of dosage units, assay, related substances, dissolution, microbial limits (b) (4). The applicant included a risk assessment for elemental impurities as per ICH Q3D/USP <232> and provided justification for the omission of tests for residual solvents (complies with USP<467> option 1). The results of the risk assessment were acceptable and therefore a test for an elemental impurity in the drug product release specifications was not proposed and is not required. The final drug product specifications are consistent with ICH Q6A and are based on batch analyses,

manufacturing capability, and stability data. The drug product specifications are adequate to establish the drug product identity, potency and purity and provide adequate controls to ensure the quality of the drug product through the product expiry. The proposed specifications and acceptance criteria for the drug product, together with controls for impurities in the drug substance are adequate to ensure that the critical quality attributes of this product are well controlled.

In support of the proposed 36-month expiry, the applicant included 24 months of long term (25°C/60% RH) and 6 months of accelerated (40°C/75% RH) data for three commercial scale batches of the drug product packaged in the intended commercial packaging (120-count white opaque round 150 cc HDPE bottles with a 38 mm polypropylene cap with a heat seal peelable foil liner). All primary stability batches were manufactured at the commercial site according to the proposed commercial manufacturing process. Stability studies were executed in accordance with the ICH 1A and Q1B; and the available stability data shows consistency over time and supports the proposed expiry. Therefore, based on the 24 months of primary stability data and the supportive stability data included in this application for UKONIQ (umbralisib) tablets, 200 mg, TG Therapeutics, Inc proposed and the FDA accepts the expiration dating period of **36 months** for the drug product when stored at controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

NDA 213176 is recommended for approval from a drug product and drug process perspective.

Biopharmaceutics

The biopharmaceutics review focused on the acceptability of the proposed in vitro dissolution method and acceptance criterion for the routine quality control testing of the proposed drug product at batch release and on stability. The dissolution method included a USP Apparatus 1 (Baskets, 10 mesh) at 100 RPM in 900 mL of 0.05M Phosphate Buffer with 0.5% sodium lauryl sulfate at 37°C. The proposed dissolution acceptance criterion was Q (b) (4) % in 45 minutes. The dissolution method and acceptance criterion are acceptable as QC method for batch release and stability testing of the drug product.

The proposed to-be-marketed Umbralisib Tablets, film coated, 200 mg have the same formulation and manufacturing site as the batches used in the pivotal clinical study. Accordingly, bridging between the clinical formulation and commercial product was not needed.

NDA 213176 is recommended for approval from biopharmaceutics perspective.

Facilities

This application includes 4 sites and all sites were listed as ready for inspection:

- **Alembic Pharmaceuticals Limited (API Unit-III) (FEI 3007501748)-** Manufacture, release and stability testing of umbralisib tosylate
- **Alembic Pharmaceuticals Limited (Formulation Division) (FEI 3004956904)** – Testing of umbralisib tosylate for elemental impurities, manufacture of umbralisib tablets, testing and release of umbralisib tablets, packaging of umbralisib tablets
- (b) (4) Packaging of umbralisib tablets
- **TG Therapeutics, Inc. (FEI NOT LISTED)-** Lot release for umbralisib tablets

All facilities were deemed acceptable for the responsibility listed in the application. NDA 213176 is recommended for approval from the facilities perspective.

Environmental Assessment

The applicant provided a claim for categorical exclusion and a statement of no extraordinary circumstances under 21 Code of Federal Regulations (CFR) Sections 25.31(e) and a statement of no extraordinary circumstances 21 CFR 25.15(d).

The request for categorical exclusion is granted.

C. Special Product Quality Labeling Recommendations (NDA only)

n/a

D. Final Risk Assessment (see Attachment)

Included at the beginning of the drug product review.

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	UKONIQ	Adequate
Established name(s)	Umbralisib	Adequate
Route(s) of administration	Oral	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Tablets: 200 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	The drug product tablets are not scored.
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)		The drug product is tablet, no special instruction for product preparation is needed.

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

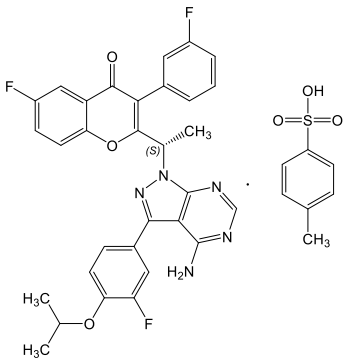
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Tablet	Adequate
Strength(s) in metric system	200 mg	Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Refer to section 11.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	UKONIQ is a green, film-coated, oval-shaped, 200-mg tablet (b) (4) with "L474" on one side and plain on the other.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk	N/A	

package and imaging bulk package.		

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	UKONIQ (umbralisib)	Adequate
Dosage form(s) and route(s) of administration	UKONIQ tablets are for oral administration.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Each tablet contains 200 mg of umbralisib free base equivalent to 260.2 mg of umbralisib tosylate with the following inactive ingredients: microcrystalline cellulose, hydroxypropyl betadex, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, titanium dioxide, polydextrose, hypromellose 2910, triacetin, FD&C Blue no. 1, polyethylene glycol 8000, FD&C yellow no. 5, and ferric oxide yellow.	The active ingredient is a tosylate salt, 200 mg is the amount of free base. The naming practice for the strength 200 mg follows the USP Salt Policy per FDA Guidance. This is adequate.
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	See above	Compendial excipient names follow USP/NF. The drug product coating film (b) (4) contains FD&C Yellow No. 5. Email was sent on September 25, 2020 to clinical division about specific warnings for this excipient per 21 CFR 201.20 and warning language is included in the labeling.

		The excipients used in tablets and those in coating film (b) (4) should be separated and organized alphabetically. Recommend Applicant to revise the excipients as follows: *Each tablet contains 200 mg of umbralisib free base equivalent to 260.2 mg of umbralisib tosylate. The tablets also contain inactive ingredients: croscarmellose sodium, hydroxypropyl betadex, hydroxypropyl cellulose, microcrystalline cellulose and magnesium stearate.* *The tablet coating film consists of FD&C Blue No. 1, FD&C Yellow No. 5, ferric oxide yellow, hypromellose 2910, polydextrose, polyethylene glycol 8000, titanium dioxide and triacetin*. The Applicant accepted the above suggestions.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	

Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	UKONIQ (umbralisib) is a specific and orally bioavailable inhibitor of phosphoinositide 3 kinase delta (PI3Kδ) and casein kinase 1epsilon (CK1ε).	Adequate
Chemical name, structural formula, molecular weight	The active pharmaceutical ingredient is umbralisib tosylate, which is a white to light brown powder with the molecular formula $C_{38}H_{32}F_3N_5O_6S$ and a molecular weight of 743.75 g/mol. Umbralisib tosylate is freely soluble in dimethyl sulfoxide, soluble in methanol, and practically insoluble in water. The chemical name for umbralisib tosylate is *(S)*-2-(1-(4-amino-3-(3-fluoro-4-isopropoxyphenyl)-1*H*-pyrazolo [3, 4-d] pyrimidin-1-yl)-ethyl)-6-fluoro-3-(3-fluorophenyl)-4*H*-chromen-4-one 4-methylbenzenesulfonate and has the following structure: 	Adequate

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)		No other important physical properties such as pKa or pH are listed in the label. Recommendation: *Include the pKa or pH value of the drug substance in Section 11.* The Applicant included "The ionization constant (pKa) of umbralisib tosylate is 2.71." in response dated December 12, 2020; the response is acceptable.

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Tablets	Adequate
Strength(s) in metric system	200 mg	Adequate

Available units (e.g., bottles of 100 tablets)	Each bottle contains 120 tablets (30-day supply).	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Green, film-coated, oval-shaped tablets debossed with “L474” on one side and plain on the other	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor’s Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	N/A	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”		No desiccant is used in container closer system.
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	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	Adequate

	Room Temperature]. (b) (4)	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”		Drug product doesn’t contain latex; no latex is used in drug product container closer system.
Include information about child-resistant packaging	White opaque round 150cc high density polyethylene (HDPE) bottle capped with a 38 mm child resistant polypropylene closure with heat sealed peelable foil liner.	Adequate

1.2.5 Other Sections of Labeling

Assessor’s comment: Regarding FD&C Yellow No. 5, refer to section 11.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	Distributed and Marketed by: TG Therapeutics, Inc. Edison, NJ 08837	There is no street address for the company; a comment was issued to the Applicant by Labeling Division to request for street address per 21 CFR 201.1 and 21 CFR 201.100(e). In response dated December 07, 2020, the Applicant provided street address, 343 Thornall Street, Suite 740.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

CMC related information in Patient Information is the same as in USPI. Refer to the above evaluation for details.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

[redacted]

3.2 Carton Labeling

Only the draft labeling for the bottle is provided. There is no carton mentioned in container closure system. The following review is for the bottle labeling.

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	UKONIQ	Adequate
Dosage strength	200 mg	Adequate
(b) (4) [redacted]		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Each tablet contains 200 mg umbralisib free base equivalent to 260.2 mg of umbralisib tosylate.	Adequate
Net contents (e.g. tablet count)	120 Tablets	Adequate

“Rx only” displayed on the principal display	Yes	Adequate
NDC number	NDC 73150-200-12	Adequate
Lot number and expiration date	Yes, included.	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	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]. Keep out of reach of children.	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	TG Therapeutics, Inc.	Adequate
Medication Guide (if applicable)	N/A	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available		

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

None

Overall Assessment and Recommendation:

The Applicant has made all the updates as requested. The labeling is adequate from CMC perspective.

Primary Labeling Assessor Name and Date: Yang Nan, Ph.D.

Secondary Assessor Name and Date (and Secondary Summary, as needed): Anamitro Banerjee, Ph.D., Branch Chief

Yang Nan

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Anamitro Banerjee

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CHAPTER VI: BIOPHARMACEUTICS

NDA Number	213176; 505 b (1)-NME
Assessment Cycle Number	1
Drug Product Name/ Strength	UKONIQ™ (umbralisib) Tablets 200 mg[1]
Route of Administration	Oral (800 mg orally once daily with food)
Applicant Name	TG Therapeutics, Inc.
Therapeutic Classification/ OND Division	Oncology OND/DHM2
Associated INDs	IND 116762 (Phase 1 study TGR-1202-101) IND (b) (4) (pivotal Phase 2b study UTX-TGR-205)
Proposed Indication	UKONIQ is a kinase inhibitor indicated 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. Accelerated approval was granted for MZL and FL based on overall response rate. Continued approval for these indications may be contingent upon verification and description of clinical benefit in a confirmatory trial.
Primary Reviewer	Qi Zhang, Ph.D.
Secondary Reviewer	Om Anand, Ph.D.
Assessment Recommendation	***Adequate***

Assessment Summary:

The Applicant, TG Therapeutics, is seeking approval of the proposed UKONIQ™ (umbralisib) Tablets, 200 mg for the treatment of adult patients with marginal zone lymphoma (MZL) and follicular lymphoma (FL). Umbralisib is a novel inhibitor of phosphoinositide 3-kinase delta (PI3Kδ) and casein kinase 1 epsilon (CK1ε). The proposed Umbralisib Tablet is an immediate release, green film coated tablet containing 200 mg umbralisib (free base). The clinical program in support of this NDA includes an ongoing pivotal Phase 2b study (UTX-TGR-205), an ongoing Phase 2 study (TGR-1202-202), and a first-in-human, dose escalation, Phase 1 study (TGR-1202-101).

The Biopharmaceutics review is focused on evaluation of (i) the adequacy of the proposed dissolution method and acceptance criterion, (ii) bridging throughout the drug product development, and (iii) risk assessment.

1) **Dissolution Method and Acceptance Criterion**

[1] 200 mg of umbralisib free base equivalent to 260.2 mg of umbralisib tosylate

Per agreement under IND (b) (4) meeting dated August 13, 2018, the dissolution method was redeveloped (b) (4) (b) (4). Based on the totality of the information and data provided [complete dissolution at 45 minutes, method's discriminating ability against critical process parameters, and relevant Biopharmaceutics considerations (control of API particle size, and Tmax is not critical], the dissolution method proposed by the Applicant in the current submission, using 0.05 M phosphate buffer pH 6.8 with 0.5% sodium lauryl sulphate and acceptance criterion of Q = (b) (4)% at 45 minutes, for the drug product batch release and stability testing are acceptable.

Approved Dissolution Method and Acceptance Criterion for UKONIQ™ (umbralisib) Tablets, 200 mg				
Apparatus	**Speed**	**Medium**	**Volume/Temp**	**Acceptance Criterion**
USP Apparatus 1 (Basket, 10 mesh)	100 rpm	0.05 M phosphate buffer pH 6.8 with 0.5% sodium lauryl sulphate	900 mL/37°C	Q(b) (4)% in 45 minutes

2) Bridging Throughout Product Development

The proposed to-be-marketed Umbralisib Tablets, film coated, 200 mg have the same formulation and manufacturing site as the batches used in the pivotal clinical study [Phase 2b Study UTX-TGR-205]. Thus, bridging between the clinical formulation and commercial product is not needed.

3) Biopharmaceutics Risk Assessment

The initial risk deemed dissolution as "Moderate" from a Biopharmaceutics standpoint, because the drug substance has low solubility. The Applicant has included drug substance particle size acceptance criterion. Additionally, the Tmax (4 hours) of Umbralisib is not considered critical regarding treatment effect or disease control for the proposed indication. The risk can be further mitigated with the implementation of the dissolution specification for the proposed drug product.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Original Submission	01/10/2020
Response to Information Request	07/21/2020

Concise Description of Outstanding Issues (List bullet points with key information and update as needed):

None.

Recommendation:

From a Biopharmaceutics perspective, NDA 213176 for UKONIQ™ (umbralisib) Tablets, 200 mg is recommended for APPROVAL.

B.1 BCS DESIGNATION

Assessment: *A BCS designation is not requested nor required.*

The Applicant claimed that umbralisib tosylate is a BCS Class 2 drug with low solubility and high permeability because umbralisib tosylate exhibits low solubility (over pH range of 1 to 7.4) and high permeability based on a MDCK-MDR1 cell assay.

Solubility: Umbralisib tosylate was identified as a single crystal form (Form 1) and it has been used in clinical supplies and registration stability batches. The Applicant submitted the solubility data (**Table 1**) for umbralisib tosylate at different pH values and varying surfactant concentrations.

Table 1: Solubility of Umbralisib Tosylate in Different Media

Media	Solubility (mg/mL)
0.1N HCl	0.16
Acetate buffer pH 4.5	<0.01
Buffer pH 5.5	<0.01
Phosphate buffer pH 6.8	<0.01
Phosphate buffer pH 7.4	<0.01
Water	0.015
Water + 0.5% SLS	0.22
Water + 1.0% SLS	5.77
Water + 1.5% SLS	14.23
Water + 2.0% SLS	20.07
Water + 0.5% Polysorbate 80	0.23
Water + 1.0% Polysorbate 80	0.45
Water + 1.5% Polysorbate 80	0.62
Water + 2.0% Polysorbate 80	0.82
0.1N HCl + 0.5% SLS	0.31
0.1N HCl + 1.0 % SLS	1.83
0.1N HCl + 1.5 % SLS	3.87
Simulated gastric fluid (pH=1.2)	0.13
Simulated intestinal fluid (pH=6.8)	<0.01
0.05 mol/L Phosphate Buffer pH 6.8 + 0.25% SLS	1.18
0.05 mol/L Phosphate Buffer pH 6.8 + 0.5% SLS	1.93
0.05 mol/L Phosphate Buffer pH 6.8 + 1.0% SLS	2.69
0.05 mol/L Phosphate Buffer pH 6.8 + 1.5% SLS	5.01
0.05 mol/L Acetate Buffer pH 4.5 + 0.25% SLS	0.12
0.05 mol/L Acetate Buffer pH 4.5 + 0.5% SLS	2.44
0.05 mol/L Acetate Buffer pH 4.5 + 1.0% SLS	8.47
0.05 mol/L Acetate Buffer pH 4.5 + 1.5% SLS	14.53

Source: Module 3.2.P.2.1, Table 3.
Abbreviations: SLS=sodium lauryl sulfate.

The solubility data are consistent with the indicated BCS class of the drug substance, as the solubility is 0.16 mg/mL in 0.1 N HCl, < 0.01 mg/mL at higher pHs, and 0.015 mg/mL in water, whereas the minimum required solubility is 3.2 mg/mL in 250 mL for the single 800 mg-dose. The solubility increases in the presence of surfactants, e.g., 1.93 mg/mL in 0.05 M phosphate buffer with 0.5% SLS, in the proposed dissolution medium.

Permeability: The apparent permeability (Papp) values were measured with the absorptive (apical to basolateral) permeability of 2.22, 9.30, and 3.53×10^{-6} cm/sec and secretory (basolateral to apical) permeability of 2.14, 6.85, and 1.09×10^{-6} cm/sec, using 1 µM, 10 µM, and 100 µM umbralisib tosylate, respectively.

Note that the absolute bioavailability and relative bioavailability of umbralisib have not been determined. According to the labeling, approximately 81% of the dose was recovered in feces (17% unchanged) and 3% in urine (0.02% unchanged) following a single radiolabeled dose of umbralisib 800 mg to healthy subjects.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERION

Assessment: *Adequate*

Drug Product: The proposed 200 mg Umbralisib Tablets are green film-coated, oval shaped, debossed tablets containing active ingredient umbralisib tosylate 260.2 mg, (b) (4) microcrystalline cellulose and croscarmellose (b) (4), hydroxypropyl cellulose (b) (4), magnesium stearate (b) (4). The drug product is manufactured by (b) (4) (b) (4). The drug product is dissolving in 45 minutes using the proposed dissolution method.

Dissolution Method Development: (b) (4) (b) (4)

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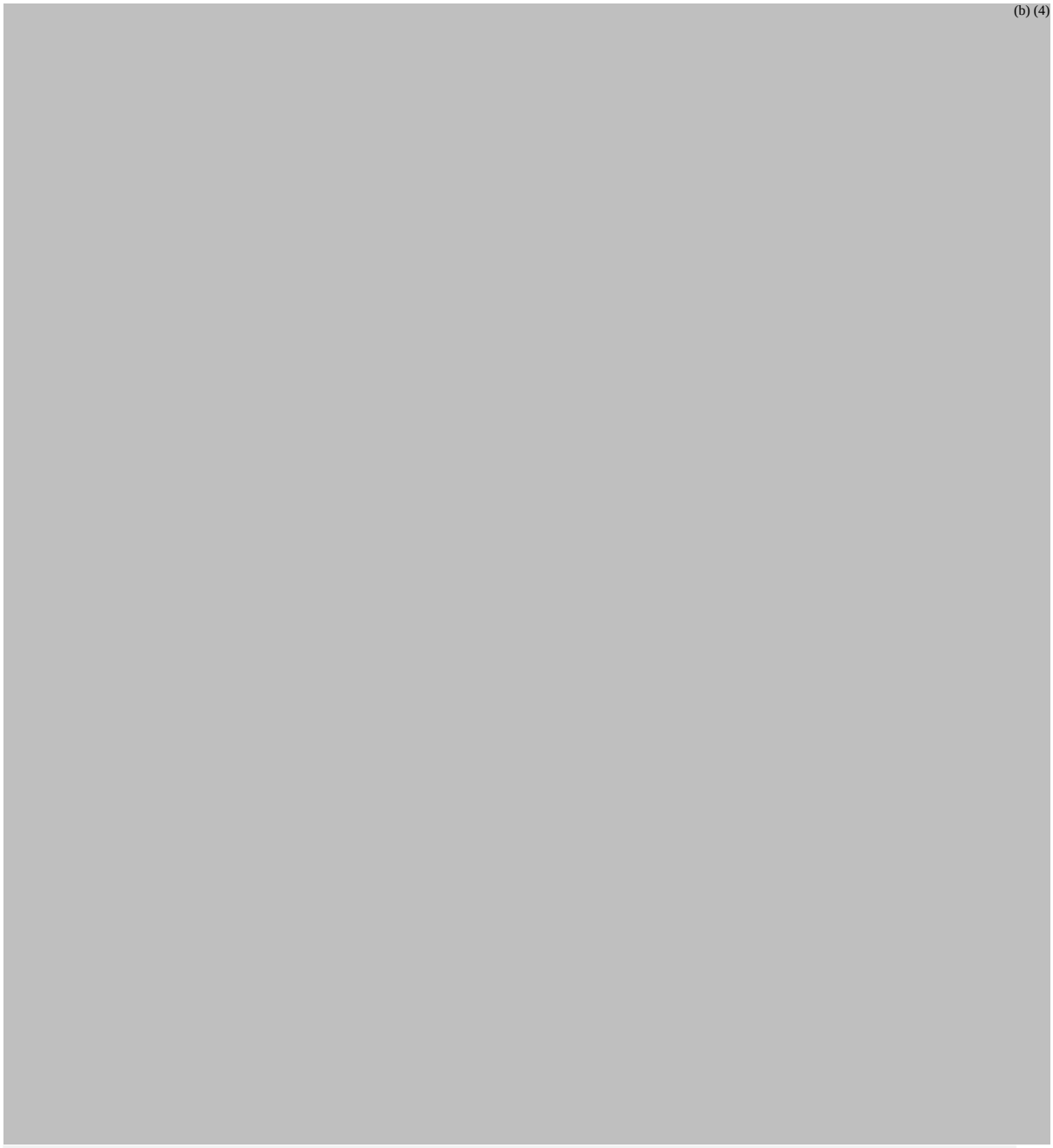


Validation of Dissolution Method: The final dissolution method proposed has been validated with respect to the analytical HPLC method (refer to the Drug Product Review), and the complete dissolution data generated using the proposed dissolution method from the clinical and registration/stability batches demonstrate the repeatability, reproducibility, and robustness of the dissolution of the proposed drug product on a batch-to-batch basis.

Dissolution Acceptance Criterion: The dissolution acceptance criterion of Q=(b) (4)% at 45 minutes is proposed by the Applicant based on the dissolution profiles from 1) investigation of the selection of the dissolution medium and the method's discriminating

ability, and 2) batch release data for most recent three clinical batches (**Figure 9; Table 2**) and long term stability data up to 18 months for the registration/stability batches (6 M, 9 M, and/or 12 M and 18 M) (**Table 3**).

Figure 9: Dissolution Profiles of 3 Recent Clinical Batches at Release

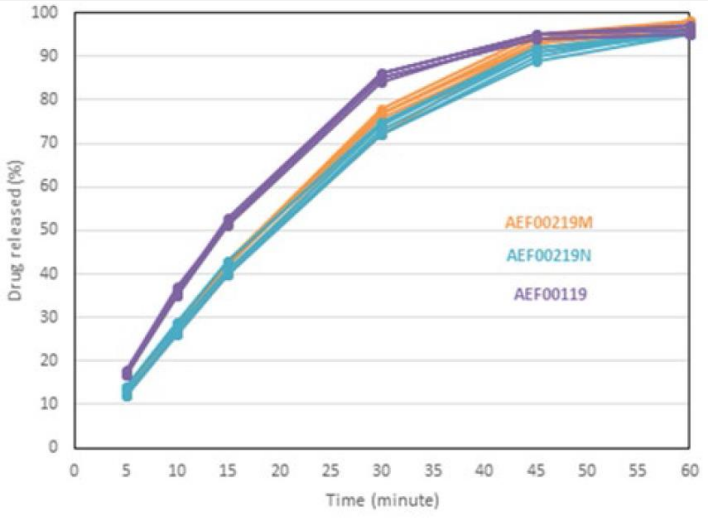


Table 2: Summary of Mean Dissolution Data at Release for 3 Recent Clinical Batches

	Time (minutes)					
	5	**10**	**15**	**30**	**45**	**60**
Minimum Mean % Dissolution	14	29	44	76	92	95
Maximum Mean % Dissolution	15	32	46	80	94	97

Table 3: Summary of Mean Dissolution for Registration Batches after Storage for up to 18 Months

	Time (minutes)					
	5	**10**	**15**	**30**	**45**	**60**
Minimum Mean % Dissolution	14	29	44	79	92	94
Maximum Mean % Dissolution	16	33	49	82	94	96

As recommended by the FDA under IND 116762 CMC Type B Meeting 08/13/2018, to bridge the old (b) (4) and new (pH 6.8/0.5% SLS) dissolution methods for stability, dissolution profiles in the 3 media were collected for all the registration batches for new stability time points and will continue to be collected in the 3 media for the rest of the stability program. Note that dissolution of the registration stability batches at all time points in the new medium (pH 6.8/0.5% SLS) meet the proposed specifications of Q= (b) (4) % at 45 minutes, and no significant change in dissolution for long-term stability data up to 18 months tested.

B.3 CLINICAL RELEVANCE OF DISSOLUTION METHOD & ACCEPTANCE CRITERIA *(e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)*

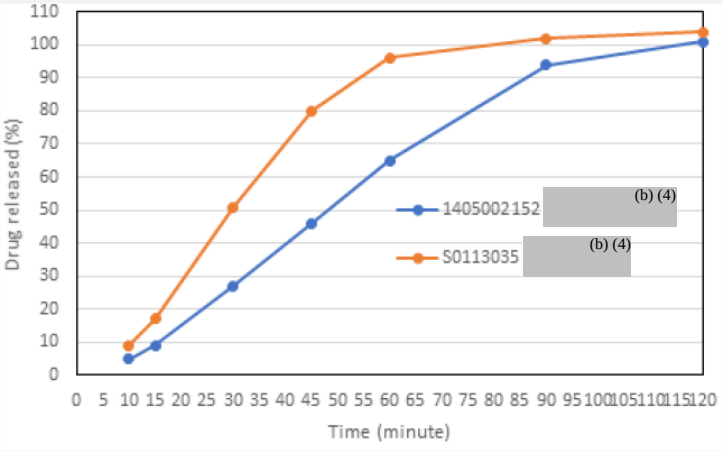
Assessment: ***N/A***

Data Evaluating the PK of Different Formulation Variants: Two formulations containing different particle size drug substance lots were evaluated in the BA PK study (TGR-1202-PK102). One batch (batch #1305005591) was manufactured using (b) (4) The other batch (batch # S0113035) was manufactured using (b) (4). PK results of these two batches are provided in **Table 4**. The systemic exposure (AUC) after administration of the drug product containing (b) (4) umbralisib drug substance was 60% higher than that after administration of the drug product containing (b) (4) umbralisib drug substance. In addition, dissolution profiles of tablets made with (b) (4) drug substance (b) (4) was shown significantly higher than that of (b) (4) (b) (4) drug substance (b) (4) in an acidic dissolution medium (0.1 N HCl with 1% SLS) as tested (**Figure 10**). Therefore, the decision was made to (b) (4) drug substance for further formulation development and clinical batches manufacture, and a three-tier particle size control (b) (4) has been included in the drug substance specification.

Table 4: Human Pharmacokinetic Results for Evaluation of Drug Substance Particle Size in 200 mg Umbralisib Tablets

Pharmacokinetic Parameter	**Tablet batch 1305005591** (b) (4)	**Tablet Batch S0113035** (b) (4)
AUCt (ng*hr/mL)[a]	5914 (33.6)	9440 (26.9)
AUC∞ (ng*hr/mL) [a]	7940 (37.7)	12324 (29.8)
Cmax (ng/mL) [a]	167 (41.7)	372 (35.1)
Tmax (hr)[b]	3.00 (2.00, 6.00)	3.00 (2.00, 4.03)

Figure 10: Dissolution Profiles of Tablets with (b) (4) and (b) (4) Drug Substance in 0.1 N HCl with 1% SLS



B.12 BRIDGING OF FORMULATIONS

Assessment: ***Adequate***

The following changes were made to the 200 mg umbralisib film-coated tablets throughout product development: (b) (4) (b) (4) (b) (4). A list of all the batches manufactured for clinical trials is presented in Table 35 Section 3.2.P.22. The table outlines the changes that were made throughout the development of this product as described above and a comparison between early clinical, pivotal clinical and the commercial (to be marketed) formulation. The specific clinical trials that these batches were used for are summarized in Table 11 Section 2.7.1. The formulation composition of the commercial batches is the same as the most recent 13 clinical batches used in most of the clinical trials. Among the 13 clinical batches, three were registration batches (1705004779, 1705007655 and 1805003844). Therefore, no additional information is needed to bridge the drug product formulations.

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