CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218944Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA OPQ Review and Evaluation

NDA 218944
Review # 01

OPQ RECOMMENDATION: APPROVAL

Drug Substance Retest Period: Revumenib citrate retest period of (b) (4) months when stored (b) (4)

FDA Assessment: Retest date of (b) (4) months may be granted when stored (b) (4)

Drug Product Expiration Dating Period: Revumenib tablets expiration dating period of 24 months when stored at controlled room temperature: 20°–25°C (68°–77° F)

FDA Assessment: An expiration dating period of 24 months may be granted when stored at the proposed storage conditions.

Recommended Storage condition: Store tablets 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]

[Applicant will complete this section.]

Drug Name/Dosage Form	Revumenib / Tablets
Strength	25, 110, 160 mg (free base equivalents)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Indication	Revumenib is indicated for the treatment of adult and pediatric patients with relapsed or refractory acute leukemias with a KMT2A rearrangement
Applicant	Syndax Pharmaceuticals
US agent, if applicable	N/A

[FDA will complete these sections.]

Submit Date(s)	January 26, 2024
Received Date(s)	January 26, 2024
PDUFA Goal Date	September 26, 2024
Division/Office	Division of Hematology Malignancies 1/Office of Oncologic Diseases

FDA assessment is indicated in colored fonts

Review Completion Date	July 8, 2024
Established Name	Revumenib Tablets
(Proposed) Trade Name	
Pharmacologic Class	Menin Inhibitor
Recommendation on Regulatory Action	Approval

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Seq0007	*12-15-2023*	*All (CMC Assessment Aide)*
Seq0019	*02-27-2024*	Drug Product
Seq0021	*03-04-2024*	*Biopharmaceutics*
Seq0032	*03-28-2024*	*Quality*
Seq0044	*04-22-2024*	*Biopharmaceutics*
Seq0053	*05-29-2024*	*OPMA*
Seq0058	*06-13-2024*	*Drug Product*
Seq0073	*07-24-2024*	*OPMA*
Seq0074	*07-25-2024*	*Drug Product/DMEPA*
Seq0082	*10-04-2024*	*CMC/Clinical*
Seq0083	*10-11-2024*	*Drug Product and Labelling*
Seq0086	*10-17-2024*	*Drug Substance and OPMA*
Seq0087	*10-24-204*	*Drug Substance and OPMA*
Seq0088	*10-29-2024*	*Drug Product and Biopharmaceutics*
Seq0092	*11-06-2024*	*OPMA*
Seq0094	*11-06-2024*	*Drug Product and DMEPA*
Seq0098	*11-12-2024*	*OPMA*
Seq0100	*11-12-2024*	*Drug Product/DMEPA*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Rajan Pragani	Hari Sarker
Drug Product	Rajiv Agarwal	Shalini Anand
Manufacturing	Diane Goll	Meng Zhaoyang
Biopharmaceutics	Gerlie Geiser	Anitha Govada
Regulatory Business Process Manager	Dahlia Walters	
Application Technical Lead	Shalini Anand	
ORA Lead	n/a	
Environmental	Rajiv Agarwal	Shalini Anand

ORBIS Partner Agency Quality Review Team (To be redacted for FOIA)

Agency	PRIMARY REVIEWER	SECONDARY REVIEWER
HC Canada		
HSA Singapore		
TGA Australia		
Swissmedic Switzerland		

RELATED/SUPPORTING DOCUMENTS

DMFs:

[Applicant will complete]				[FDA will complete]	
DMF #	**Type**	**Holder**	**Item Referenced**	**Status**	**Comments**
(b) (4)	IV		(b) (4)	Active	Adequate, Compatible with the drug product
	III			Active	Adequate, Compatible with the drug product
	III			Active	Adequate, Compatible with the drug product
	III			Active	Adequate, Compatible with the drug product
	III			Active	USP testings are performed
	III			Active	CRC, Compatible with the drug product
	III			Active	USP testings are performed

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

[Applicant will complete this section.]

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	142,693	IND to support development of revumenib, a small molecule inhibitor of the menin-MLL1 interaction for treatment of adult and pediatric

		patients with relapsed or refractory acute leukemias with a KMT2A rearrangement
NDA	(b) (4)	(b) (4)

CONSULTS

No consult was initiated.

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Evaluation of the Quality Information

[Applicant to provide link to the data in m3 sections as appropriate]

DIFFERENCES IN M3 MODULE IN SUBMISSIONS TO DIFFERENT AGENCIES

None. The first application submission for Revumenib is to the US.

1. EXECUTIVE SUMMARY

Summary of Rationale for Recommendation:

a. The applicant provided sufficient information to assure the identity, strength, purity, and quality of the proposed drug product. All associated manufacturing, testing, packaging facilities were deemed acceptable. Based on the OPQ review team's evaluation of the information provided in the submission, OPQ recommends APPROVAL of NDA 218944 for REVUFORJ (revumenib) tablets.

b. ***Is the overall recommendation in agreement with the individual discipline recommendations?*** *Yes*

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology – Adequate

Life Cycle Considerations:
None

2. APPLICATION BACKGROUND

Revumenib is a first-in-class, potent, orally available, small molecule inhibitor of the binding of both histone-lysine N-methyltransferase 2A enzyme (KMT2A) fusion proteins and wild-type KMT2A to menin. The interaction of KMT2A fusion proteins with menin is a critical driver of the leukemic transcription program in *KMT2A* rearranged (*KMT2A*r) leukemia, inclusive of both ALL and AML subtypes; therefore, disruption of this interaction represents a unique therapeutic opportunity in this population with high unmet need. Despite great advances in the understanding of targetable biological mechanisms

underlying acute leukemia, the current treatment options are not optimized for patients with a *KMT2A*r (Marks 2013) and are generally ineffective for relapsed/refractory (R/R) AML and ALL (Heuser 2020, Richard-Carpentier 2021). The Sponsor considers that the topline results of the interim analysis (IA) from the pivotal Study SNDX-5613-0700 *KMT2A*r cohorts, demonstrate clear potential for revumenib to provide substantial improvement over available therapies in adult and pediatric patients with R/R acute leukemia with a *KMT2A*r.

Revumenib was granted orphan drug designation on 21 Apr 2020 (ODD #: DRU-2020-7345) and Fast Track Designation on 24 Jun 2021 (Reference ID: 4815990). Revumenib received Breakthrough Therapy Designation for the treatment of adult and pediatric patients with R/R acute leukemia harboring a *KMT2A*r on 30 Nov 2022 (Reference ID: 5086239). The Sponsor submitted a Diversity Plan for the NDA on 27 Jun 2023 (SN0298) and a Real-Time Oncology Review (RTOR) request on 13 Sep 2023 (SN0323). RTOR was granted in the pre-NDA meeting held 20 Oct 2023.

3. SUMMARY OF CMC SPECIFIC PRESUBMISSION AGREEMENTS

The Applicant's Position:

During the course of revumenib development Syndax has sought FDA feedback in several development areas. The table below lists chemistry, manufacturing and control (CMC) topics and agreements that were discussed in either CMC meetings or meetings requested by other disciplines. Meetings are listed in reverse chronological order.

Table: Revumenib CMC Meetings and Questions

Date	Meeting/ Submission	CMC Question Topic	Response
20 Oct 2023	Type B Pre-NDA Meeting Minutes (Reference ID: 5265866)		(b) (4)
20 Oct 2023	Type B Pre-NDA Meeting Minutes (Reference ID: 5265866)	Drug Product for Commercial Launch	(b) (4)
20 Oct 2023	Type B Pre-NDA Meeting Minutes	Tablet Formulation	

Date	Meeting/ Submission	CMC Question Topic	Response
	(Reference ID: 5265866)		is comparable between the capsule and tablet formulation.
20 Oct 2023	Type B Pre-NDA Meeting Minutes (Reference ID: 5265866)	[redacted] (b) (4)	
19 May 2023	Type B Pre-NDA Content and Format Written Responses (Reference ID: 5177161)	NDA Structure	Agreement with the plan to submit a full Module 2.3 and 3.2.S in the revumenib tablet NDA [redacted] (b) (4) (2) NDA Module 3.2.S. Full revumenib drug product sections will be provided for tablets [redacted] (b) (4)
19 May 2023	Type B Pre-NDA Content and Format Written Responses (Reference ID: 5177161)	Executed Batch Records in NDA	Agreement on the approach of submitting one executed batch record for each revumenib drug product tablet strength (25, 110, and 160 mg free base equivalents) [redacted] (b) (4) with the NDA is acceptable. However, include a summary of batch records for additional batches manufactured.
19 May 2023	Type B Pre-NDA Content and Format Written Responses (Reference ID: 5177161)	[redacted] (b) (4)	
10 Apr 2023	Type B CMC Preliminary Meeting Comments (Reference ID: 5151397)	RSMs	Agreement that based on the submitted information, the proposal to designate [redacted] (b) (4) as regulatory starting materials is acceptable.
10 Apr 2023	Type B CMC Preliminary	Drug Product Primary	Agreement on the proposal of submitting 6-months long term accelerated stability

Date	Meeting/ Submission	CMC Question Topic	Response
	Meeting Comments (Reference ID: 5151397)	Stability Batch Data	data from three registration stability drug product batches of each drug product and strength at the time of NDA submission with an agreement to provide the additional stability data as soon as possible during the review cycle, preferably within 30 days of the initial NDA submission.
10 Apr 2023	Type B CMC Preliminary Meeting Comments (Reference ID: 5151397)	[redacted] (b) (4)	
10 Apr 2023	Type B CMC Preliminary Meeting Comments (Reference ID: 5151397)	DMF References	[redacted] (b) (4)
10 Apr 2023	Type B CMC Preliminary Meeting Comments (Reference ID: 5151397)	Tablet Dissolution Method	According to the FDA 2018 Dissolution Guidance, if the drug product meets the eligibility requirements as per the Guidance, a standard method using 500 mL of 0.1N HCl should be implemented because it reflects the acidic gastric condition where the drug is mainly dissolved and absorbed. Your proposal to test n=6 tablets for routine testing with an additional 6 tablets if Stage 2 testing is required appears reasonable.
16 Dec 2022 06 Mar 2023	1.11.1 Quality Information Amendment – SNDX-5613 Tablets Dissolution Development Report (IND 142,693 SN 0218) General Advice Letter for IND 142693 SNDX-	Tablet Dissolution Method	Based on our review of the dissolution method development information and data provided in the submissions dated 12/16/2022 and 02/06/2023, we consider that the proposed dissolution medium of [redacted] (b) (4) is not adequate for revumenib dissolution testing. We request you follow the recommendations of the FDA's 2018-Dissolution Guidance and implement the following standard dissolution method: USP Apparatus 2 (Paddle) with sinker, 50 rpm, 500 ml of

Date	Meeting/ Submission	CMC Question Topic	Response
	5613 (Reference ID: 5137115)		0.1N HCl, 37°C, for the dissolution testing of your proposed drug product. We also request that you continue collecting complete multi-point dissolution profile data (n=12, individual, mean, standard deviation, figures, sampling timepoints: 15, 20, 30, and 45 minutes) for the pivotal PK/clinical and registration batches of your proposed drug product throughout the stability program.
06 Jun 2022	Type C Guidance Preliminary Meeting Comments (Reference ID: 4988982)	Drug Product Primary Stability Batch Data	Agreement on the approach of submitting 9 months of drug product stability data at the time of filing and then providing 12 months long term stability data on registration batches during the review of the NDAs (but no later than 3 months prior to the PDUFA date) and considering data when assessing drug product expiry.
06 Jun 2022	Type C Guidance Preliminary Meeting Comments (Reference ID: 4988982)	RSMs	Based on the provided information, the proposal to designate (b) (4) as starting materials for the manufacture of SNDX-5613 monocitrate monohydrate drug substance appears to be reasonable; however, additional information is necessary to assess the acceptability of the proposed starting materials.
06 Jun 2022	Type C Guidance Preliminary Meeting Comments (Reference ID: 4988982)	Drug Product Primary Stability Batch Scale	Agreement on a tablet registration batch scale of (b) (4) / batch using the representative process and equipment intended for commercial manufacture.
13 Jun 2022	Type C Guidance Preliminary Meeting Comments (Reference ID: 4994946)	Tablet Dissolution Method	The proposed dissolution methods for the Capsules and Tablets are not acceptable at this time. Recommend using the standard dissolution method and acceptance criterion of Q= (b) (4)% at 30 minutes following the FDA guidance for industry: *Dissolution Testing and Acceptance Criteria for Immediate-Release Solid Oral Dosage Form Drug Products Containing High Solubility Drug Substance* (2018).

Date	Meeting/ Submission	CMC Question Topic	Response
15 Jul 2021	Type C Guidance Written Responses (Reference ID: 4826163)	Change to Tablet Formulation	To support dose selection for the proposed new tablet formulation, you should conduct a pilot evaluation of the new tablet formulation in a cohort of patients who are currently receiving the capsule formulation. You should compare exposures after administration of each formulation and use the collected data to justify dose selection for new patients starting treatment with the tablet formulation in Study SNDX-5613-0700.

The FDA's Assessment: ***Consistent with FDA's records***

4. ENVIRONMENTAL ASSESSMENT

The Applicant's Position:

Syndax Pharmaceuticals claims that the proposed New Drug Application (NDA) for revumenib qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist. The following information is provided to support this exclusion:

Amount Produced for Direct Use

(b) (4)

- KMT2Ar ALL: (b) (4)

(b) (4)

Expected Introduction Concentration Calculation

EIC-aquatic (ppb) = A x B x C x D

A= (b) (4) kg/year produced for direct use (as active moiety)

B= 1/ liters per day entering publicly owned treatment works. A value of 1.214×10^{11} liters/day was used.

C= year/ 365 days

D= 10^9 ug/kg (conversion factor)

EIC-aquatic (ppb) = (b) (4) x (1/1.214 x 10^{11} liters/day) x 1 year/365 days) x 10^9 ug/g

EIC-aquatic (ppb) = (b) (4) ppb

The FDA's Assessment: ***Adequate***

Syndax Pharmaceuticals claims that the proposed New Drug Application (NDA) for revumenib qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist. ***Granted***

Following information was received from the EA assessment team via. email dated 01/30/2024- Since the API is not a hormone and its production is only (b) (4) kg/yr (EIC (b) (4) ppb), according to the EA screening tool Screening Tool for Environmental Assessments, Categorical Exclusions, and Other Actions. The drug product reviewer can just accept the claim of CE.

5. FACILITIES

Drug substance manufacturing, packaging and testing facilities are listed below and also located in Module 3.2.S.2.1:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
(b) (4)			

Tablet drug product manufacturing, packaging and testing facilities are listed below and also located in Module 3.2.P.3.1:

---------- [Applicant to fill] ----------			[FDA to fill]
Site/address	**FEI/DUNS**	**Responsibility**	**Recommendation**
[redacted] (b) (4)			TCM Approve - Based on Previous History
			LCP Approve - Based on Previous History
			LMN Approve - Based on Previous History
			TCM Approve - Based on Previous History
			NEC (NEN) No Evaluation Necessary

The FDA's Assessment: ***Adequate***

Facilities are approved based on prior history, file review and district recommendation.

111 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

8. BIOPHARMACEUTICS

a. BCS Classification

Applicant to fill:
BCS Classification: BCS III

FDA assessment (FDA to fill):
Acceptable

Information to support the BCS Class I designation request, if applicable.
Link: Page#:

Drug Substance Solubility: *High*
The solubility of revumenib monocitrate monohydrate (formerly referred to as SNDX-5613, SNDX-50613 or VTP-50613) (b) (4) drug substance in various pH media is at least 23 mg/mL at 37°C (as shown in Table 2 of 3.2.S.1). The highest single dose of revumenib tablets is 270 mg (provided by combining one tablet each of the 110 mg and 160 mg strengths), which when solubilized in 250 mL produces a theoretical drug concentration of 1.08 mg/mL (i.e., substantially lower than the drug concentrations that could be achieved in various pH media).

As shown in Table 1 and Table 2 of the SN-21 IR Response, both developmental revumenib salt forms (i.e., citrate and (b) (4)) are highly soluble per BCS criteria, and are both stable in 0.1N HCl for 24 hours.

(b) (4)

Drug Substance Permeability: *Not High*
The absolute bioavailability or revumenib oral tablets was not determined because of the lack of a revumenib formulation intended for intravenous administration.

Human Mass Balance Study
Note that per the Clinical Pharmacology Reviewer, definitive conclusions about oral bioavailability of revumenib cannot be made from the conducted mass balance study

results because the mean total recovery of radioactivity in urine + feces from 4 patients had a reported range of 70% to 86%. Specifically, following a single (276 mg) dose of 100 µCi [^{14}C]-revumenib (oral solution), [and multiple oral 276 mg doses of non-radiolabeled revumenib as oral capsules or 50 mg/mL "F1" or "F2" oral solution every 12 hours], 76.1% of the radioactive dose was recovered in urine (27.2%) and feces (48.9%) of cancer patients within 240 hours (SNDX-5613-0705).

In Vitro Caco-2 Permeability Study

Based on the results of the Caco-2 permeability study (21SYNDP1), FDA confirmed the Applicant's conclusion that revumenib could not be classified as highly permeable drug substance, per BCS criteria. Specifically, at nominal drug concentrations of 17.5 µM, 175 µM, and 1.75 mM [equivalent to 1%, 10%, and 100% of a 276 mg (free base) dose in 250 mL], the Apical-to-Basolateral P_{app} values of revumenib were lower than that measured for the co-dosed high permeability internal standard (minoxidil). Additionally, the calculated efflux ratios (greater than 2.0 at all drug concentrations) suggest that revumenib is a substrate of a drug efflux transporter (although may not be necessarily P-glycoprotein, based on the Clinical Pharmacology Reviewer's assessment of the additional results from the MDCK II study).

Drug Product Dissolution: *Very Rapid in Various pH Media*

Using standard dissolution method conditions for drug products containing highly soluble drug substances (i.e., 500 mL of 0.1N HCl; paddle at 50 rpm), all three revumenib citrate tablet strengths exhibited very rapid dissolution (at least 85% dissolves within 15 minutes (refer to Figure 2 of 2.7.1). Very rapid dissolution was also observed (b) (4) as shown in Figure 10 of the briefing package submitted in IND 142693/SN-247.

a. Dissolution Test

As per feedback from the Division of Biopharmaceutics (IND 142,693 [SN0218]) on the Dissolution Development report (Reference ID: 5151397) the media was changed from a (b) (4) to 0.1N HCl. Comparison of dissolution profiles on fresh and aged tablet samples demonstrates the media change did not affect dissolution profile, Module 3.2.P.2.2.3. The acceptance criterion has been set (b) (4) Revumenib citrate meets the criteria for a highly soluble drug substance and is formulated in an immediate release drug product form therefore (b) (4) discriminatory studies were not conducted.

USP Apparatus	Paddle Rotation Speed	Medium Volume	Temperature	Medium	Acceptance Criterion
Apparatus 2 (paddles)	50 rpm	500 mL	37°C	0.1 N HCl	Q= (b) (4)% at 30 minutes

FDA Comment: **Dissolution Method - *Adequate***

(b) (4)

FDA Comment: **Dissolution Acceptance Criterion - *Acceptable***

The proposed dissolution acceptance criterion (Q = (b) (4)% at 30 minutes (b) (4) Per the Applicant, all batches of revumenib tablets have met the proposed dissolution acceptance criterion after Stage 1 testing of six dosage units during release and stability testing.

Of note, all the pivotal clinical lots exhibited very rapid dissolution (i.e., at least 85% dissolved within 15 min) using the standard dissolution method for highly soluble drug substances/products. Refer to Table 3 of the SN-21 IR Response.

Additionally, as discussed above, the revumenib drug substance exhibits high solubility, per BCS criteria. Per the proposed labeling (and as confirmed by the CDER QT-IRT), revumenib can cause QT interval prolongation. To mitigate the QT prolongation risk, FDA recommended additional precautionary measures (e.g., monitoring and correction of serum electrolyte abnormalities prior to and during use, contraindicated use in patients with QTc >450 msec; frequent monitoring of patients with known cardiac risks and patients on concomitant QT prolonging drugs or strong CYP3A4 inhibitors) in the labeling.

Dissolution on Stability

As indicated above, the standard dissolution method for drug products containing highly soluble drug substances was adopted (per FDA recommendation) after primary stability testing had been initiated. Thus, majority of the currently available dissolution on stability data of the revumenib citrate oral tablets were generated using the penultimate dissolution method (using (b) (4) . Since based on dissolution methods bridging data, the dissolution profile of a stability sample is lower in (b) (4) medium than in the final dissolution medium (0.1N HCl) with all other dissolution method parameters being the same, a primary stability batch that was shown to conform to dissolution testing (Q = (b) (4) at 30 minutes, by USP Stage 1 testing/n=6) using the penultimate dissolution method is

expected to also conform to the same (i.e., final proposed commercial) dissolution acceptance criterion by USP Stage 1 testing when using final dissolution method.

During 12 months of long-term and 6 months of accelerated stability testing, there was no significant storage-dependent changes in dissolution of the primary registration stability batches of the drug product, and the product conformed to the proposed dissolution acceptance criterion (Q = (b) (4) % at 30 min).

Based on the provided stability data, the Drug Product Reviewer agrees with the proposed expiration dating period of the proposed tablets (packaged in 30-count HDPE bottles with (b) (4) desiccant) of 24 months when stored under USP Controlled Room Temperature conditions.

	Applicant to fill:	FDA assessment: N/A
The dissolution method is discriminating for:		
i) Particle size distribution (PSD) Link[1]:	Not applicable	Not applicable Page#:
ii) Polymorph/solid state form Link[1]:	Not applicable	Not applicable Page#:
iii) Formulation variations Link[1]:	Not applicable	Not applicable Page#:
iv) Manufacturing process variations Link[1]:	Not applicable	Not applicable Page#:
v) Other (specify): Link[1]:	Not applicable	Not applicable Page#:

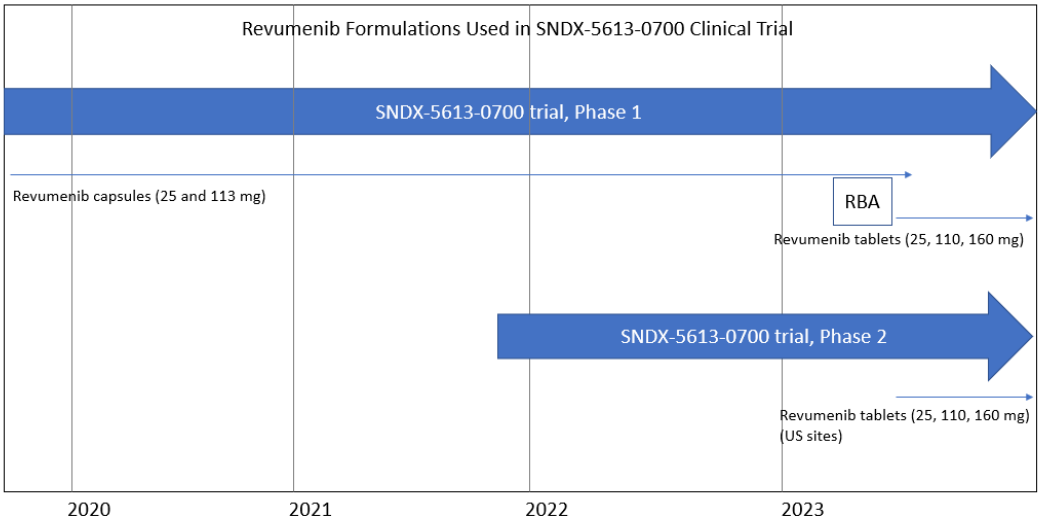
[1]The applicant to provide link to the appropriate section in the submission. FDA reviewer may update the link as needed

FDA Comment:

Note that because revumenib is a highly soluble drug substance (per BCS criteria), and the proposed drug product exhibits 'very rapid dissolution' when tested under the standard dissolution method conditions recommended in the 2018 FDA Guidance, there is no expectation that the dissolution method would be discriminating for quality attributes including drug substance particle size distribution (DS PSD). Thus, from the Biopharmaceutics perspective, the DS PSD tolerance limit should preferentially be based on historical batch data, mainly from the clinical lots. Table 2 of the IR Response in SN-21, Table 1 and Table 7 of 3.2.S.4.4 (as well as the table provided in Section 6.d.ii above) show that the d_{90} of the ingoing DS lots used in manufacture of the clinical trial materials is up to (b) (4) µm; considering that the drug substance is highly soluble per BCS criteria, the proposed drug substance d_{90} (NMT (b) (4) µm, by Laser Diffraction) is reasonable. Regarding DS polymorphic forms, relative solubility data are not available; however, as described in Section 8.a above, identification of the correct API polymorphic form is part of the proposed DS QC specifications, and the Applicant provided justification to support the stability of the desired Form (b) (4) during drug product manufacture and storage. *The final determination regarding the adequacy of the proposed DS PSD and DS polymorphic form controls is deferred to the Drug Substance Reviewer. As well, the acceptability of the Applicant's proposed finished product QC specifications (which does*

not include API polymorphic form testing) will be determined by the Drug Product Reviewer.

b. Bridging Throughout Drug Product Development (Formulation, Process, or Site Change)



Revumenib capsules utilize (b) (4) salt form, tablets utilize citrate salt form
RBA= Relative Bioavailability Study (n=9)
Additionally, capsule and tablet drug products in vitro dissolution profiles were comparable (Module 3.2.P.2.2.1).

Link: Page#:

Initial development of revumenib utilized (b) (4), which was formulated in capsules. Capsule drug product was used extensively in trial SNDX-5613-0700. Drug substance salt form was then changed to the monocitrate monohydrate form (referred to as revumenib citrate) (b) (4) At the same time the drug product form was changed to immediate release tablets. Revumenib tablets were compared to revumenib capsules in a relative bioavailability study performed in patients and exposures were found to be comparable, Module 2.7.1. As noted in the Type B Pre-NDA Meeting Minutes (Reference ID: 5265866) FDA stated the currently available data appears to support that revumenib pharmacokinetics is comparable between the capsule and tablet formulation. Additionally, data is provided in the NDA for formulation PK comparisons by non-compartmental analysis and PopPK analyses.

The FDA's Assessment:

Bridging to the Final To-Be-Marketed Revumenib Citrate Tablet: ***Adequate***

As shown in the Applicant's figure above, the proposed commercial formulation/process was used by the proposed commercial drug product manufacturer (b) (4) to produce the revumenib *citrate tablet* lots (that were packaged in the proposed commercial container closure system) used in the primary stability studies (and introduced into the pivotal clinical trial). Refer to Table 3 and Figure 1 to Figure 3 of the SN-21 IR Response. The tablets with the final commercial image were used in the pivotal clinical and primary registration stability studies.

The batch size ((b) (4) tablets) of the primary registration (and majority of the pivotal clinical) lots of the revumenib citrate tablets is approximately (b) (4) of the proposed commercial scale ((b) (4) tablets). Tablet batches manufactured to date have ranged from (b) (4) tablets to (b) (4) tablets. Based on the dissolution profile data provided in the IR Response (SN-44), regardless of batch size and strength, the revumenib citrate tablets exhibited very rapid dissolution (at least 85% within 15 min) using the standard dissolution method for highly soluble drug substances (in 0.1N HCl), as well using the developmental dissolution method (b) (4) which indicates that the proposed manufacturing scale up does not impact product performance. Additionally, the Process Reviewer confirmed that the provided data were adequate to support batch scale up.

The proposed commercial drug substance manufacturer (b) (4) produced the active pharmaceutical ingredient used to manufacture the registration stability batches and the (pivotal) clinical batches of revumenib citrate tablets (refer to Table 2 of 3.2.S.2). Per the Applicant (and as confirmed by the Drug Substance Reviewer), throughout development, (b) (4) for the production of revumenib citrate drug substance batches for nonclinical, clinical and stability study use. Additionally, in SN-86, the Applicant confirmed that all ingoing drug substance lots [i.e., regardless of tablet strength], conformed to the proposed commercial drug substance QC specifications.

REVIEWER NOTE (Bridging of Proposed To-Be-Marketed Drug Product to Other Clinical Developmental Formulation(s): ***Refer to Clinical Pharmacology Review for assessment of the adequacy of the clinical (PK) bridge between the two salt forms/dosage forms of revumenib ((b) (4) capsule versus citrate tablet).***

The salt form of revumenib was changed from (b) (4) to citrate (b) (4) so the tablet dosage form was developed. Based on internal discussions of the NDA review team, it appears that steady-state PK data (as well as clinical efficacy and safety data) are available from a total of 50 patients enrolled in clinical trials to support characterization of revumenib citrate tablets. Note that in the Type B Pre-NDA meeting minutes dated 4/5/2023, the Applicant confirmed that relative BA data to bridge the two salts/dosage forms from 12 patients will be included in the NDA. Per the Applicant, based on the relative bioavailability (RBA) results of the

pivotal Phase I/II SNDX-5613-0700, the dose-normalized (parent and major metabolite/M1) PK and safety (including ECG) profiles of the capsule and tablet formulations are comparable thereby justifying the formulation switch after pivotal clinical trial initiation (refer to Figure 6 and Figure 7 of 2.7.1). *The Clinical Pharmacology (and Clinical) Reviewers will evaluate the supporting clinical data in the NDA to confirm that PK (as well as efficacy and safety) is comparable between the revumenib* (b) (4) *capsule and revumenib citrate tablet formulations that were used in the pivotal Phase 1/2 clinical trial (SNDX-5613-0700).*

c. Biowaiver Request

The Applicant's Position:

The NDA does not contain a biowaiver request.

[To the Applicant: Explain the reasons why biowaiver is not needed for the proposed drug product. If biowaiver request is made, provide information to support the biowaiver request, if applicable (compositional proportionality, PK linearity, comparative dissolution profiles with f2 analysis)]

Link: Page#:

A biowaiver is not requested. Data for the PK and safety of revumenib in capsule, tablet, and oral solution formulations will be provided in the NDA. These data will include formulation PK comparisons by non-compartmental analysis and PopPK analyses.

The FDA's Assessment: ***Adequate***

In the Biopharmaceutics IR Response in SN-21, the Applicant confirmed that the pivotal Phase 1/2 clinical trial used the 110 mg and 160 mg strengths of the proposed revumenib tablets; to date, only one patient has used the 25 mg strength of revumenib citrate tablets.

The biowaiver request for the 25 mg strength is **granted** based on the following supporting information: (1) This lower strength is (b) (4) (b) (4) compositionally proportionally and (2) like the two higher tablet strengths, is also very rapidly dissolving (>90% released within 15 minutes) (b) (4) Based on available dissolution profile data showing very rapid dissolution for the highest strength (160 mg) tablet (b) (4) dissolution is not anticipated to be any slower in (b) (4) medium for the lowest strength (25 mg) tablet. For the compositions of the three strengths of the revumenib citrate tablet, refer to Table 2 of 3.2.P.2. For the comparative dissolution profiles of the three tablets strengths generated using the final proposed QC dissolution method, refer to Figure 1 to Figure 3 of the SN-21 IR Response).

REVIEWER NOTE (regarding Alternative Mode of Tablet Administration):
For patients who are not able to swallow the whole tablets, an option is to crush the tablets and disperse in water prior to administration via an oral syringe.

In SN-0088, the Applicant provided (and the Drug Product Reviewer confirmed the acceptability of the) data to demonstrate satisfactory in-use stability, delivered dose recovery, and compatibility of the aqueous dispersion of the oral tablets. Additionally, it was reported that (i) after 5 minutes of preparing the aqueous dispersion in 10 mL water, (b) (4) % of the entire revumenib will be in solution in this aqueous dispersion when prepared at a recommended dose range of 25 mg to 270 mg, and (ii) the final pH (b) (4) of the tablet dispersion is the same as those of the F1 and F2 oral solutions that were also used in the pivotal clinical trial.

Of note, (1) the labeling recommends that the tablets should be taken with a cup of water, (2) in nonclinical toxicology studies, the toxicity of revumenib drug substance in solution administered via oral gavage was assessed (refer to the IB v. 6.0), and (3) in the pivotal clinical trial, various oral solution formulations (i.e., F1/F2 (b) (4) were used to administer revumenib.

Based on the nonclinical data, the FDA Review Team has no additional concerns about use of crushed tablet in water for oral administration of revumenib.

Thus, from the Biopharmaceutics perspective, the totality of the available data/information support the alternative administration of revumenib oral tablets as an aqueous dispersion in water. A dedicated BE study is not required to support labeling of this alternative mode of administration for revumenib tablet.

d. Data to Support IVIVC and/or PBBM Modeling, If Applicable.

[To the Applicant: Provide summary of the objective of the model, model development and validation, and outcome. Insert additional text, graphs, and table here to support the information provided above as necessary]

Link: Page#:

Not applicable.

The FDA's Assessment: ***Not Applicable***

PBPK modeling and Population PK modeling were performed by the Applicant to address revumenib's drug-drug interaction potential and dosage selection. The modeling results will be assessed by the Clinical Pharmacology Reviewers.

9. LABELING

USPI

Highlights: Adequate

Section 2 (if relevant): Adequate

(b) (4)

(b) (4)

Section 3 Dosage Forms and Strengths: Adequate

(b) (4)

Section 11 Description: Adequate

If the following excipients used in the drug product, include warning/declaration in the USPI:

- FD&C Yellow No.5 or No.6, as a color additive (21 CFR 201.20) is not used.
- Phenylalanine, as a component of aspartame (21 CFR 201.21) is not used.
- Sulfites (21 CFR 201.22) is not used.

1 Page(s) of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Section 16 How Supplied/Storage and Handling*: *Adequate

(b) (4)

Manufacturer Information (Name and Address): Provided: Adequate

(b) (4)

Container/Carton Label *Adequate*

11 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Final Risk Assessments

[FDA will complete this section.]
To the Review Team: *Keep the appropriate Table; delete the rest*

DRUG SUBSTANCE

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Starting Material Design	• Impurities • Chirality • Assay • Identity	Medium		Low	
Manufacturing process	• Chemical transformations • Control of Materials • In-process controls • Critical process parameters • Control of Raw materials/reagents • Isolated intermediates • Starting materials/ICH Q11 • Impurities • Residual Solvents • Chirality • Particle Size	Medium		Low	
ID/Characterization	• Structural characterization • Physicochemical characterization • Chirality • Polymorphic form	Low		Low	
Impurities	• Impurities/ICH M7,Q3A, S9	Low		Low	
Residual solvents	• Impurities ICH Q3C	Choose an item.		Low	
Elemental impurities	• Impurities ICH Q3D • Residue on ignition	Low		Low	
Stability	• Appearance • Assay • Impurities/ICH Q3A, M7, S9	Low		Low	

	• Water Content • Polymorph • Microbial content				

SOLID ORAL

Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Assay, stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site	Low	(b) (4)	Low	The assay shows little change on stability. No trend is observed.
Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Medium		Low	The assay shows little change on stability. No trend is observed.
Content Uniformity	• Formulation • Container closure • Raw material • Process Parameters • Scale/equipment • Site	Low		Low	The assay shows little change on stability. No trend is observed.
(b) (4)				(b) (4)	
Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	Choose an item.		Low	
Dissolution – BCS (b) (4)	• Formulation • Container Closure • Raw materials • Process parameters • Scale/equipment • Site	Choose an item.		Low	

Recommendation Page

Drug Substance: Approval

Primary Reviewer: Rajan Pragani Date: May 6, 2024
Secondary Reviewer: Hari Sarker Date: October 31, 2024

Drug Product: Approval

Primary Reviewer: Rajiv Agarwal Date: October 29, 2024
Secondary Reviewer: Shalini Anand Date: November 12, 2024

Manufacturing: Approval

Primary Reviewer: Diane Goll Date: July 23, 2024
Secondary Reviewer: Zhaoyang Meng Date: July 23, 2024

Primary Reviewer: Diane Goll Date: November 12, 2024
Secondary Reviewer: Daniel Obrzut Date: November 12, 2024

Biopharmaceutics: Approval

Primary Reviewer: Gerlie Geiser Date: October 31, 2024
Secondary Reviewer Anitha Govada Date: October 31, 2024

Application Technical Lead: Approval

Shalini Anand Date: November 12, 2024

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/

SHALINI ANAND
11/12/2024 04:13:20 PM

HARIPADA SARKER
11/12/2024 07:37:55 PM
DS Review.

RAJIV AGARWAL
11/13/2024 07:37:01 AM

DAVID J CLAFFEY
11/13/2024 08:50:15 AM

DIANE W GOLL
11/13/2024 09:01:32 AM

ZHAOYANG MENG
11/13/2024 09:03:04 AM

GERLIE GIESER
11/13/2024 09:06:32 AM

ANITHA P GOVADA
11/13/2024 11:09:35 AM

DAHLIA A WALTERS
11/13/2024 11:15:49 AM